Pentavalent Rotavirus Vaccine and Prevention of Gastroenteritis Hospitalizations in Australia
Emma J. Field, Hassan Vally, Keith Grimwood and Stephen B. Lambert
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Pentavalent Rotavirus Vaccine and Prevention of Gastroenteritis Hospitalizations in Australia

abstract

OBJECTIVE: A publicly funded, universal infant pentavalent rotavirus vaccine (RV5) program was implemented in Queensland, Australia, in mid-2007. We sought to assess vaccine effectiveness (VE) of 3 doses of RV5 at preventing rotavirus and nonrotavirus acute gastroenteritis (AGE) hospitalizations in the first birth cohort and impact on hospitalizations in all age groups.

METHODS: Hospitalization rates for rotavirus and nonrotavirus AGE in all age groups before and after RV5 introduction were compared. Population vaccine coverage, hospitalization data, and individual vaccination status were obtained from routinely collected, publicly funded state- and nationally based data sets. Data linkage was performed to calculate 3-dose VE for preventing hospitalization in the eligible age group.

RESULTS: RV5 coverage in the first eligible birth cohort was 89.6% for at least 1 dose and 73.1% for 3 doses. Three-dose VE for preventing nonrotavirus AGE hospitalization was 62.3% to 63.9% (any/primary diagnosis) and 89.3% to 93.9% (any/primary diagnosis) for rotavirus hospitalizations. After program implementation, there were immediate and sustained reductions in rotavirus hospitalizations for those who were younger than 20 years and nonrotavirus AGE-coded hospitalizations for those who were younger than 20 years and nonrotavirus AGE-coded hospitalizations for those who were younger than 5 years.

CONCLUSIONS: RV5 is highly effective at preventing rotavirus hospitalizations in a developed country setting, confirming efficacy figures from the pivotal clinical trial. Additional direct and indirect effects are substantial and include reductions in nonrotavirus AGE hospitalizations in vaccinated age groups and rotavirus and nonrotavirus AGE hospitalization rates in older age groups. Pediatrics 2010;126: e506–e512

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KEY WORDS: rotavirus, pentavalent rotavirus vaccine, vaccine effectiveness, screening method

ABBREVIATIONS

AGE—acute gastroenteritis
RV5—pentavalent rotavirus vaccine
RV1—monovalent rotavirus vaccine
VE—vaccine effectiveness
CI—confidence interval
ED—emergency department
QHAPDC—Queensland Hospital Admitted Patient Data Collection
ICD-10-AM—International Classification of Diseases, Tenth Revision, Australian Modification
VIVAS—Vaccine Information and Vaccine Administration System
ACIR—Australian Childhood Immunisation Register
PPV—proportion of the population vaccinated

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Rotavirus is the leading cause of severe acute gastroenteritis (AGE) in early childhood, globally causing >500,000 deaths and 2.4 million hospital admissions each year for children who are younger than 5 years. To combat this disease burden, 2 live oral rotavirus vaccines, RotaTeq (pentavale nt rotavirus vaccine [RV5; Merck Vaccines, Whitehouse Station, NJ]) and Rotarix (monovalent rotavirus vaccine [RV1; GlaxoSmithKline Biologicals, Rixensart, Belgium]), have been developed [RV1; GlaxoSmithKline Biologicals, Rixensart, Belgium]) and Rotarix (monovalent rotavirus vaccine [RV1; GlaxoSmithKline Biologicals, Rixensart, Belgium]), have been developed and shown to be highly efficacious against severe rotavirus disease, including hospitalization (85%–98%), in large clinical trials.\(^2,3\)

Since the introduction of RV5, several studies have reported on its postlicensure use and impact in real-world settings. In the United States, RV5 was introduced in 2006; by 2008, with modest 1-dose coverage of 31% in children who were younger than 2 years, the onset and peak of the 2007–2008 rotavirus season were delayed by 15 and 8 weeks, respectively, and the proportion of fecal specimens that were positive for rotavirus was reduced by 69%.\(^4\) This decline in rotavirus activity persisted into the 2008–2009 season.\(^5\)

A single-center case-control study that was conducted in Houston, Texas, and used a control group that combined children who had rotavirus-negative AGE or acute respiratory infection yielded a 3-dose vaccine effectiveness (VE) of 88% (95% confidence interval [CI]: 68%–96%) against rotavirus-AGE that required hospitalization or emergency department (ED) visits.\(^6\) A nationwide health insurance claim-based, postlicensure study that compared concurrent cohorts of children who received 3 doses of RV5 with those who received 3 doses of diphtheria-tetanus-acellular pertussis and no doses of RV5 provided a VE for preventing ED presentations and hospitalizations as a result of rotavirus and all-cause AGE of 100% (95% CI: 87%–100%) and 59% (95% CI: 47%–68%), respectively;\(^6\) however, the performance of RV5 seems to be setting dependent. A case-control study in Nicaragua, a high-burden, developing country where 1-dose RV5 coverage quickly reached 80%,\(^6\) demonstrated a 3-dose effectiveness of just 46% (95% CI: 18%–64%) at preventing hospitalization or intravenous rehydration.\(^8\) Early evidence from double-blind, randomized, multicenter, placebo-controlled phase III trials in other developing countries supports this concept, with efficacy of 3 doses of RV5 of 64% (95% CI: 40%–79%) and 51% (95% CI: 13%–73%) against severe rotavirus gastroenteritis in Africa and Asia, respectively.\(^9\) The scope for rotavirus vaccines to prevent global diarrhea-related deaths in children was demonstrated in Mexico, where RV1 was introduced in February 2006, reaching 1-dose coverage of at least 74% for children who were aged ≤11 months by December 2007.\(^11\) When comparing median values for 2003 to 2006 with 2008 data, the diarrhea-related mortality rate was reduced by 41% (95% CI: 36%–47%) for children who were aged ≤11 months and by 29% (95% CI: 17%–39%) for those who were aged between 12 and 23 months.\(^11\) The primary aim of this study was to calculate the VE of RV5 at preventing hospitalization in the first annual birth cohort of eligible children in the high 3-dose coverage setting of Queensland, Australia.

**METHODS**

The state of Queensland, Australia, has a population of 4.4 million people and a current annual birth cohort of 63,000.\(^12\) Rotavirus vaccine was added to the Australian universal, publicly funded immunization program for all infants who were born on or after May 1, 2007, with children in a given state or territory offered a full course of either RV1 or RV5.\(^13\) In Queensland, this program commenced on July 1, 2007, with RV5.

**Hospital Admission Data**

The Queensland Hospital Admitted Patient Data Collection (QHAPDC) collects admission data from all public and private hospitals in Queensland.\(^14\) Records from 2000 to 2008 with International Classification of Diseases, Tenth Revision, Australian Modification (ICD-10-AM) codes for AGE including rotavirus (ICD-10-AM codes A00–A09 excluding A02.2, A06.4–A06.8, and K52)\(^15,16\) in the primary or any secondary diagnostic field were extracted from QHAPDC in October 2009. Age group–specific rates of hospitalization in the prevaccine era (mean annual rates for 2000–2006) were compared with 2007 and 2008 figures by calculating rate ratios with 95% CIs by using Stata 10 (Stata Corp, College Station, TX).

**Vaccination Status of Hospitalized Children**

The Vaccine Information and Vaccine Administration System (VIVAS) is the vaccination register and management system that records all vaccines that are administered in Queensland. VIVAS records only vaccines that are administered; it is not a population-based register and does not have records for individuals who receive no vaccines. VIVAS vaccination data are provided to the national, population-based Australian Childhood Immunization Register (ACIR).

RV5 vaccination records for hospitalized children were extracted from VIVAS for the period of July 1, 2007, to December 31, 2008. Rotavirus vaccinations were considered valid when administered ≥14 days before rotavirus hospitalization. For this project, children with RV5 vaccination records marked outside standard practice (receipt of rotavirus vaccine at ≤4...
weeks or \( \geq 52 \) weeks of age or interval between doses of \( \leq 7 \) days) were validated by telephone contact with the vaccine service provider.

**Population Vaccine Coverage**

ACIR captures immunization data from children who are younger than 7 years and enrolled in the Australian universal health insurance scheme, Medicare. This is essentially a complete population register with 99% of the annual national birth cohort registered with Medicare by 1 year of age. Children who are not enrolled in Medicare can be added to the ACIR via a supplementary number.\(^1\) The National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases provided population rotavirus vaccine coverage proportions, including children who had received no vaccine doses, from the ACIR for children who were born between May 1, 2007, and April 30, 2008. ACIR coverage figures for 3-dose, primary-course vaccines are typically calculated by using the “third-dose assumption”: if a child has a record of receiving dose 3 in a series, then they are assumed to have received doses 1 and 2 and therefore to be fully vaccinated for the primary course of that vaccine, even if there is no record for dose 1 or 2 having been administered.\(^2\)\(^,\)\(^3\) For this analysis, coverage data used were as reported and were not modified by using the third-dose assumption.

**Data Linkage and VE**

Data linkage was performed in Microsoft Excel (Microsoft Corp, Redmond, WA). Data from multiple instances of the same individual within VIVAS and QHAPDC were collapsed to a single record, and records in both data sets were linked by using a created key that consists of surname and date of birth. Linkage was validated by using the given name. Minor spelling and other variations in the given name field (including 1-letter differences, addition of the second given name to the first given name field, or addition of a hyphen in first given names with 2 words) were manually reviewed and accepted as valid linkages when surname and date of birth matched.

VE was calculated by using the screening method, comparing the proportion of cases vaccinated and the proportion of the population vaccinated (PPV),\(^2\)\(^0\) with exact 95% CIs for proportions:\(^2\)\(^1\)\(^,\)\(^2\)\(^2\):

\[
\text{VE} = \left( \frac{1 - \left( \frac{PCV}{1 - PPV} \times \frac{1 - PPV}{PPV} \right)}{1 - PPV} \right) \times 100
\]

A case was defined as any child who was born between May 1, 2007, and April 30, 2008, and had a QHAPDC record of hospital admission with a rotavirus or nonrotavirus AGE ICD-10-AM code in any field. The minimum age of analysis for eligible children was 35 weeks to allow for 3-dose vaccine administration (latest age for third dose delivery: 33 weeks)\(^2\)\(^3\) and development of a protective immune response (2 weeks).\(^2\) This criterion may have excluded some children for whom 3 doses of RV5 were delivered early, but given the structure and timing of routine primary course vaccinations in Australia, this number is likely to be exceedingly small. For the purposes of VE calculation, the unit of comparison was the child rather than the hospital admission. This means that children who had multiple admissions for AGE during the study period were included in the analysis data set once. The VE for RV5 at preventing hospitalization was calculated for the period from January 1, 2008 (6 months after program commencement), to December 31, 2008, in the first 12-month birth cohort of children eligible for publicly funded vaccination.

**Ethics and Confidential Data Approvals**

Ethical approval for this study was granted by Queensland Children’s Health Services and the Australian National University Human Research Ethics Committees. Approval for access to confidential data held by Queensland Health was granted by the Director General of Queensland Health.

**RESULTS**

**Hospital Admission Data**

We extracted 257 061 hospital records with an AGE ICD-10-AM code (including rotavirus) as the primary or any secondary diagnosis with an admission date between January 1, 2000, and December 31, 2008, from QHAPDC. Records for which the usual residence was outside Queensland (7874) or not specified (130) were removed, leaving 249 257 records for additional analysis.

There was an immediate reduction in rotavirus hospital admissions for individuals who were younger than 20 years after vaccine introduction in July 2007, a finding sustained in 2008 (Table 1, Fig 1). There were also reductions in nonrotavirus AGE for children who were aged 1 to 4 years in 2007 and for all children who were younger than 5 years in 2008 (Table 1, Fig 1). Hospitalization rates increased in older age groups for both rotavirus and nonrotavirus AGE in 2007 and 2008, with significantly higher rate ratios for rotavirus hospitalization in those who were aged \( \geq 45 \) years in 2007 and those who were aged \( \geq 65 \) years in 2008; however, these rate increases represented only minor changes in the absolute number of rotavirus hospitalizations. For the 45- to 64-year-olds, the mean annual count of hospitalizations from 2000 to 2006 was 3, increasing to 13 in 2007 and 4 in 2008. During the same period, the number of rotavirus hospitalizations...
for those who were aged ≥65 years increased from an annual mean number of 8 (2000–2006) to 34 and 23 for 2007 and 2008, respectively.

**Vaccination Data**

ACIR coverage figures for the first 12-month cohort of Queensland children who were eligible for RV5 vaccination and born between May 1, 2007, and April 30, 2008 (61 617) at 12 months of age were 73.1% (45 048) for 3 doses, 12.9% (7902) for 2 doses only, 3.6% (2243) for 1 dose only, and 10.4% (6424) for no doses (B. Hull, MPH, personal written communication, November 23, 2009). For 3-dose VE calculations, partially vaccinated children were removed from PPV coverage estimates.20

**Data Linkage and VE**

There were 35 and 488 hospital admissions for rotavirus and nonrotavirus AGE (any diagnosis) from 34 and 425 children, respectively, between January 1, 2008, and December 31, 2008, from the first birth cohort of children who were eligible for RV5 vaccination (date of birth from May 1, 2007, to April 30, 2008). Of the children who were hospitalized for rotavirus, 16 (46%) had no rotavirus vaccination record ≥14 days before hospitalization, 4 (12%) had received 1 dose of RV5, 2 (6%) had received 2 doses, and 12 (35%) had received 3 doses. Of the children who were hospitalized for nonrotavirus AGE, 98 (23%) had no rotavirus vaccination record ≥14 days before hospitalization, 21 (5%) had received 1 dose of RV5, 54 (13%) had received 2 doses, and 254 (58%) had received 3 doses. For 3-dose VE estimates, hospitalizations for 6 and 75 partially vaccinated children were excluded, leaving 28 rotavirus and 350 nonrotavirus AGE hospitalizations for calculations of proportion of cases vaccinated, respectively (Table 2). The 3-dose VE for preventing any hospitalization was high for both rotavirus and nonrotavirus AGE as primary or any diagnosis (Table 2).

**DISCUSSION**

This study demonstrates the very high VE (89.3%–93.9%) of 3-dose RV5 at preventing rotavirus hospitalization in a high-coverage, developed country setting. Furthermore, 3-dose RV5 was highly effective (62.2%–63.9%) at preventing nonrotavirus AGE hospitalizations in the first annual birth cohort for which vaccine was used in Queensland. Our ecological findings show the substantial indirect effects of this vaccine in nonvaccinated age groups for both rotavirus and nonrotavirus AGE hospitalizations. We found immediate and sustained reductions in rates of rotavirus hospitalization of all patients who were younger than 20 years and nonrotavirus AGE hospitalization of children who were younger than 5 years.

It is interesting that we identified marked increases in rotavirus hospitalization rates in older age groups in 2007 and 2008, with minimal increments in nonrotavirus AGE hospitalizations. These findings are most likely attributable to changes in laboratory testing behavior rather than real changes in severe disease incidence. We previously showed that there have been dramatic increases in rotavirus testing in Queensland public hospitals in older age groups, with a 307% and 184% increase in 2007 and 2008, respectively, for those aged ≥65 years compared with the mean number of annual tests between 2000 and 2006.24 This rise in testing may be attributable to increased awareness of the morbidity and mortality that are associated with gastroenteritis in the institu-

### Table 1

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Mean Annual Rate (100 000/y) 2000 to 2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate (100 000/y) Rate Ratio (95% CI)</td>
<td>Rate (100 000/y) Rate Ratio (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Rotavirus hospitalizations (ICD code A08.0, any field)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>457.9</td>
<td>472.2</td>
<td>486.9</td>
</tr>
<tr>
<td>1</td>
<td>142.8</td>
<td>153.1</td>
<td>160.2</td>
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<td>2</td>
<td>76.4</td>
<td>86.9</td>
<td>94.7</td>
</tr>
<tr>
<td>3</td>
<td>66.4</td>
<td>77.1</td>
<td>86.8</td>
</tr>
<tr>
<td>4</td>
<td>550.9</td>
<td>650.9</td>
<td>765.0</td>
</tr>
<tr>
<td>0–4</td>
<td>149.2</td>
<td>162.5</td>
<td>176.5</td>
</tr>
<tr>
<td>5–19</td>
<td>7.9</td>
<td>9.4</td>
<td>11.1</td>
</tr>
<tr>
<td>20–44</td>
<td>5.8</td>
<td>13.7</td>
<td>16.4</td>
</tr>
<tr>
<td>45–64</td>
<td>3.1</td>
<td>3.1</td>
<td>3.1</td>
</tr>
<tr>
<td>≥65</td>
<td>1.7</td>
<td>1.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Nonrotavirus AGE hospitalizations (ICD codes A00–A09, K32 excludes A02.2, A06.4–A06.8, A08.0, any field)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>1687.7</td>
<td>1945.6</td>
<td>2231.0</td>
</tr>
<tr>
<td>1</td>
<td>1531.1</td>
<td>1824.5</td>
<td>2107.6</td>
</tr>
<tr>
<td>2</td>
<td>1280.9</td>
<td>1579.9</td>
<td>1975.4</td>
</tr>
<tr>
<td>3</td>
<td>785.7</td>
<td>947.9</td>
<td>1232.5</td>
</tr>
<tr>
<td>4</td>
<td>550.9</td>
<td>650.9</td>
<td>775.0</td>
</tr>
<tr>
<td>0–4</td>
<td>1239.4</td>
<td>1472.3</td>
<td>1882.6</td>
</tr>
<tr>
<td>5–19</td>
<td>192.6</td>
<td>213.5</td>
<td>248.9</td>
</tr>
<tr>
<td>20–44</td>
<td>252.0</td>
<td>272.0</td>
<td>308.9</td>
</tr>
<tr>
<td>45–64</td>
<td>302.0</td>
<td>313.7</td>
<td>342.2</td>
</tr>
<tr>
<td>≥65</td>
<td>655.5</td>
<td>837.8</td>
<td>983.4</td>
</tr>
</tbody>
</table>

20 vaccinated children were removed from PPV coverage estimates.
ionalized elderly and modified laboratory testing behavior. Regardless, the increase in testing was associated with a 52% and 23% reduction in proportion of tested specimens that were rotavirus positive in 2007 and 2008, respectively, coinciding with RV5 introduction.

As with all observational methods, bias and other issues need to be considered when interpreting our findings. Because the screening method compares the proportion of 2 groups vaccinated rather than rates in different exposure categories, we presented only 3-dose VE. If a vaccine requires multiple doses and is effective, then the distribution of dose coverage in the population (noncases), compared with cases, will show that more children have complete rather than partial coverage. Because our 3-dose coverage was very high, VE values for at least 1 dose (any dose) or at least 2 doses were dominated by children who had received 3 doses, making VE estimates very similar to the 3-dose only VE (data not shown).

The PPV value used in VE calculations in this study was not the result of a limited sampling exercise, and the key data sets—ACIR and QHAPDC—are routinely collected and population based. Queensland children’s vaccination records are provided to ACIR from VIVAS, and the validity of ACIR data has been assessed previously. The most likely ACIR inaccuracy is for PPV to be underestimated, which would result in an underestimation of VE, meaning that our VE estimates may be conservative. We previously demonstrated that rotavirus coding for public hospital admissions is highly specific for rotavirus disease. Between 2001 and 2006, of 222 children who were younger than 5 years and had rotavirus-coded hospitalizations, 197 (98%) of 201 with rotavirus testing available were laboratory confirmed.

### Table 2: Rotavirus and Nonrotavirus AGE Hospitalizations, Case and Population Vaccination Status, and 3-Dose VE for Preventing Hospitalization

<table>
<thead>
<tr>
<th>Hospitalization Diagnoses</th>
<th>Case Vaccination Status</th>
<th>PCV</th>
<th>Population Vaccination Status</th>
<th>PPV</th>
<th>VE % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fully Vaccinated</td>
<td>Unvaccinated</td>
<td>Fully Vaccinated</td>
<td>Unvaccinated</td>
<td></td>
</tr>
<tr>
<td>Nonrotavirus AGE ICD code in any field</td>
<td>254</td>
<td>96</td>
<td>0.728</td>
<td>45,048</td>
<td>6424</td>
</tr>
<tr>
<td>Nonrotavirus AGE ICD code as primary diagnosis</td>
<td>195</td>
<td>77</td>
<td>0.717</td>
<td>45,048</td>
<td>6424</td>
</tr>
<tr>
<td>Rotavirus ICD code in any field</td>
<td>12</td>
<td>16</td>
<td>0.429</td>
<td>45,048</td>
<td>6424</td>
</tr>
<tr>
<td>Rotavirus ICD code as primary diagnosis</td>
<td>6</td>
<td>14</td>
<td>0.300</td>
<td>45,048</td>
<td>6424</td>
</tr>
</tbody>
</table>

PCV indicates proportion of cases vaccinated.
control for any potential confounding as a result of age.

In other settings, rotavirus-specific ICD coding has been shown repeatedly to be an insensitive means of measuring rotavirus hospitalization burden in children. In Australia, between 1993 and 2002, rotavirus-specific ICD coding identified 4260 hospitalizations per year of children who were younger than 5 years, whereas a method that estimated admissions by using linked hospitalization and laboratory testing data between 1998 and 2003 gave an estimate of 9970 in the same age group. In Queensland, between 2000 and 2006, of 1383 nonrotavirus AGE–coded hospitalizations of children who were younger than 5 years, 113 (26%) of 428 for whom rotavirus testing was performed were laboratory confirmed. This misclassification is confirmed by the solid 3-dose VE for RV5 preventing nonrotavirus AGE hospital admissions of 63.9%, and this impact can be further observed in the sudden blunting of nonrotavirus AGE admissions during rotavirus season (Fig 1).

Our findings around nonrotavirus AGE are similar to the VE values reported for a complete 3-dose course of the now-withdrawn RotaShield vaccine (Wyeth Lederle Vaccines, Philadelphia, PA): 83% for preventing all-cause gastroenteritis hospital admissions and 43% for all-cause gastroenteritis ED visits during a 1-year follow-up period. In effect, our findings also present a population-wide vaccine probe study, suggesting that misclassification of hospitalizations as a result of rotavirus by using incorrect or less specific AGE codes is common.

Indirect vaccine effects are seen in older age groups with reductions in rates of rotavirus and nonrotavirus AGE admissions in unvaccinated children and adolescents. This coincides with immediate reductions in the proportion of laboratory tests that were positive for rotavirus in all age groups after RV5 introduction. In our setting, a prompt decrease in rotavirus transmission is likely to have occurred after the very rapid 1-dose (89.6%) and 3-dose (73.1%) coverage seen in the first 12-month birth cohort. The timing of Queensland's rotavirus season may also have been of benefit, with at least 2 months of publicly funded vaccination occurring in 2007 before the traditional peak rotavirus month of September. Similar to 7-valent protein-polysaccharide conjugate pneumococcal vaccine, these indirect effects were unable to be calculated in infant efficacy studies, and additional documentation of such benefits in other populations is required.

CONCLUSIONS

There is now a small but increasing collection of studies that show postlicensure effectiveness or ecological changes in rotavirus activity after RV5 introduction. Our findings confirm these and provide ecological evidence of reductions in hospitalization rates in older, unvaccinated children and adolescents for rotavirus and nonrotavirus AGE. Additional postimplementation research is required to identify means to improve 3-dose coverage and to understand better the effectiveness variations in the various settings where RV5 is currently used. Our findings should encourage consideration of vaccine use in similar industrialized countries.

ACKNOWLEDGMENTS

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