Hospital Admissions for Rotavirus Infection in the Netherlands

M. A. S. de Wit,1 M. P. G. Koopmans,2 J. F. van der Blij,3 and Y. T. H. P. van Duynhoven1

The development of a vaccine against rotavirus (RV) infection has necessitated the estimation of the number of hospitalizations for RV infection in the Netherlands. During 1998, pediatricians have reported all hospitalizations with RV infection and supplied information on the duration of admission, clinical picture, indication for admission, and treatment. Also, data from the National Disease Registry on hospitalizations for gastroenteritis (International Classification of Disease codes 006.6, 006.8, 009, and 558.9) and laboratory surveillance data for 1996–1998 were combined in a linear regression model to indirectly estimate the incidence and proportion of hospitalizations attributable to RV infection. The direct estimate of admissions for RV infection in children aged <5 years was 0.9 per 1000, and the indirect estimate was 2.7 per 1000 in 1998 (1996, 3.4; 1997, 1.6). The proportion of hospitalizations for gastroenteritis attributable to RV ranged from 32% in 1997 to 58% in 1996.

Rotavirus (RV) is a major cause of severe gastroenteritis, mainly in young children. One third of all hospitalizations for diarrhea worldwide are estimated to be attributable to RV infection and an estimated 870,000 deaths per year [1]. Although in industrialized countries the mortality due to RV infection has decreased in the past decades, the disease burden remains high because of high morbidity and high numbers of patients requiring hospitalization. Some deaths from diarrhea still occur, especially in children aged <1 year [2].

To control RV illness, several RV vaccines have been developed in the past years, and one tetravalent rhesus RV vaccine was approved by the US Food and Drug Administration. However, this was withdrawn from the market in the summer of 1999 because of the possible adverse event of intussusception [3]. In the Netherlands and other European countries, the implementation of RV vaccination is still under debate. For this discussion, data on disease burden are crucial. For a well-founded cost-benefit analyses, we reviewed available data concerning incidence and disease burden of RV infection in the Netherlands and concluded that information on hospitalization rates was lacking [4]. To fill this gap, a 1-year surveillance program on hospital admissions for RV infection was started in 1998 in cooperation with the Dutch Pediatric Surveillance Unit (NSCK). In addition, hospital discharge data were obtained from the National Disease Registry, and data on RV diagnostics were collected from a passive laboratory-based reporting system. Combined data from these 3 surveillance systems were analyzed in order to estimate the disease burden of hospital admissions for RV infection in the Netherlands and to provide information for cost-benefit analyses of RV vaccination.

Methods

The NSCK. The NSCK has a surveillance system for a variable set of diseases in hospitalized children. Hospital admissions for RV infection were included in this system from 1 January 1998 through 31 December 1998. All pediatricians receive monthly notification cards from the NSCK to report all children aged <15 years that meet the various case definitions; recorded data include the patients’ initials and date of birth. For our study, the National Institute of Public Health and the Environment (RIVM) received a copy of all reports of admission for RV infection and sent a questionnaire to the notifying pediatrician. The questionnaire asked for information on the duration of admission, the duration of illness, the indications for admission, the clinical picture, treatment, and other microbiological tests that were performed. Questionnaires were completed after the patient was discharged. If the pediatrician was not prepared to complete the questionnaire, a letter of discharge with the name of the patient removed was sent to our institute as an alternative. The case definition used was as follows: children aged <15 years hospitalized with a microbiologically confirmed RV infection; this included children admitted for RV infection as well as children with nosocomial RV infection. All different methods of testing for RV that were used by the hospitals were accepted. No change in the diagnostic practices of pediatricians was requested. In both 1997 and 1998, 91% of all weekly cards, addressing the reportable diseases of that year, were returned to the NSCK by the pediatricians [5].

Hospitalization data. The National Disease Registry collects data on all hospital discharge diagnoses from all hospitals in the Netherlands. Hospitalizations with a primary or any of the secondary diagnosis coded with International Classification of Disease...
Laboratory surveillance data. In the Netherlands, 17 virological laboratories reported the number of samples that tested positive for RV on a weekly basis. These laboratories provide the majority of virological testing in the Netherlands, and the laboratories primarily focus on hospitalized patients. An estimated 92% of samples positive for RV were taken from children aged <5 years [4]. A separate surveillance system of bacterial pathogens, including Salmonella and Campylobacter, provided weekly data on positive results from regional public health laboratories, covering ~55% of the Dutch population [7].

Statistical analyses. Data from notification cards and questionnaires submitted by pediatricians were entered in Epi-Info version 6.01B (USD, Stone Mountain, GA) and analyzed in SAS version 6.11 (SAS, Cary, NC). First, a description was given of children notified by the pediatricians in the NSCK surveillance system. Data on clinical picture and treatment were presented only for children for whom a completed questionnaire was available. By use of census data on age distribution from the Central Bureau of Statistics, a direct incidence of hospitalizations for RV infection was calculated for children aged 0-4 years, as reported by the pediatricians [8, 9].

We compared weekly laboratory surveillance reports of RV and the weekly number of hospitalizations for gastroenteritis as registered by the National Disease Registry by linear regression to estimate the proportion of hospitalizations for gastroenteritis attributable to RV. We constructed a linear regression model ($Y = a + bX$) that best estimated the number of admissions for gastroenteritis ($Y$) assuming a constant number of admissions attributable to other factors than RV infection ($a$) and a constant scaling factor ($b$) for the number of RV-positive laboratory samples ($X$). The constant $a$ and scaling factor $b$ were estimated by fitting the model [10-12]. The number of admissions attributable to RV infection was the scaling factor ($b$) times the number of positive laboratory results ($X$) per week. Dividing this by the total number of hospitalizations ($Y$) gives the percentage attributable to RV infection. The analyses were restricted to admissions of children aged <5 years because older children are barely covered by the laboratory surveillance data. The analyses were done separately for admissions with primary diagnoses gastroenteritis and for primary or secondary diagnoses gastroenteritis; and for admissions with ICD codes related to an infectious viral or unknown agent (ICD codes 008.6-009.3), ICD codes related to identified nonviral agents (ICD codes 001-008.5 and 558.1-558.2), and ICD codes for an unknown noninfectious origin (ICD code 558.9).

If the correlation coefficient of admissions for a group of ICD codes and the laboratory surveillance data was lower than 0.4, this group of ICD codes was not included in the final regression model. The weekly number of laboratory results positive for Salmonella and Campylobacter were included in the analyses to account for the most important bacterial causes. Unfortunately, no distinction could be made by age group in these data. For calculation of the indirect incidence by use of the estimate from the model, the same census data on age distribution were used [8, 9].

Because in general the biases are likely to outweigh the random error, conventional confidence intervals would not provide a reliable indicator of uncertainty, and therefore are not presented.

Results

The NSCK surveillance in 1998. In 1998, 1103 hospitalizations with RV infection were recorded by the pediatricians participating in the study. Additional information was received at the RIVM for 82.6% (911 of 1103) of children with RV infection, 56.6% ($n = 624$) by questionnaire and 26.0% ($n = 287$) by letter of discharge. Of all hospitalizations for which additional information was available, 86.6% were admissions for RV infection and 13.4% were nosocomial RV infections.

A clear seasonal distribution was observed, with a maximum number of cases in February. Most hospitalizations were reported in the first quarter of 1998. In the first quarter, a higher percentage of admissions for RV was reported (88%) than of nosocomial RV (74%; $\chi^2, P = .01$).

A smaller percentage of children admitted for RV infection (29%) was aged <1 year than of children with nosocomial RV infection (66%; table 1). There were more boys than girls admitted for RV infection. This was more pronounced for nosocomial RV infection than for admissions for RV infection.

Almost all children admitted for RV infection suffered from diarrhea (95%), vomiting (88%), and dehydration (85%). Weight loss was less common (46%). Most children for whom we have questionnaire information were rehydrated orally through a stomach tube (58%), or they received a combination of oral and iv rehydration therapy (24%). In total, 37.0% of all children admitted for RV infection received iv rehydration therapy. Plasma volume expanders were administered to 1.7% of patients. The median duration these therapies was as follows:

Table 1. Age distribution in children with rotavirus infection in different admission groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Admission for RV infection ($n = 789$)</th>
<th>Nosocomial RV infection ($n = 122$)</th>
<th>Admission with no additional information ($n = 185$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n$</td>
<td>%</td>
<td>$n$</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2 mo</td>
<td>26</td>
<td>3.3</td>
<td>27</td>
</tr>
<tr>
<td>3-5 mo</td>
<td>42</td>
<td>5.3</td>
<td>19</td>
</tr>
<tr>
<td>6-11 mo</td>
<td>159</td>
<td>20.2</td>
<td>35</td>
</tr>
<tr>
<td>Sbtl, &lt;1 y</td>
<td>227</td>
<td>28.8</td>
<td>81</td>
</tr>
<tr>
<td>1 y</td>
<td>293</td>
<td>37.1</td>
<td>23</td>
</tr>
<tr>
<td>2 y</td>
<td>127</td>
<td>16.1</td>
<td>12</td>
</tr>
<tr>
<td>3 y</td>
<td>69</td>
<td>8.8</td>
<td>1</td>
</tr>
<tr>
<td>4 y</td>
<td>35</td>
<td>4.4</td>
<td>2</td>
</tr>
<tr>
<td>Sbtl, 0-4 y</td>
<td>751</td>
<td>95.2</td>
<td>119</td>
</tr>
<tr>
<td>&gt;5 y</td>
<td>38</td>
<td>4.8</td>
<td>3</td>
</tr>
</tbody>
</table>

Sex

Male       | 398 | 54.5 | 66  | 60.6 | —   | —     |
Female     | 352 | 45.5 | 43  | 39.4 | —   | —     |

NOTE. RV, rotavirus; sbtl, subtotal. The sex of 14 children was not recorded, and the ages of 72 children were not recorded.
oral rehydration, 2 days; iv rehydration, 3 days; and treatment with plasma volume expanders, 2 days.

The median duration of hospital stay for children admitted for RV infection was 3 days (mean, 4.0 days; range, 1–41 days). One 10-month-old boy admitted for RV infection (with the indications of diarrhea, vomiting, and suspicion of sepsis) was admitted to the intensive care unit for 3 days of his 7-day stay. Ninety-two percent of children admitted for RV infection were released within a week. The median duration of illness before admission for children admitted for RV infection was 3 days (mean, 3.7 days; range, 0–37 days). Ninety-one percent of admissions took place in the first week of illness. At discharge, 95% of the children were recovered and 5% had residual symptoms, mainly diarrhea. No deaths were reported.

Direct incidence, based on NSCK surveillance data. The number of children aged 0–4 years in the Netherlands on 1 January 1998 was 969,367 [9]. Under the assumption that the distribution of admissions for RV infection and nosocomial RV infection was the same for hospitalizations with and without additional data, the estimated number of admissions for RV infection of children aged <5 years was 907 (incidence, 0.9 per 1000 person-years), of nosocomial RV infection 140 (incidence of 0.1 per 1000 person-years), and of all notified hospitalizations with RV infection 1047 (incidence of 1.1 per 1000; incidence per 100 for children aged <1 year, 1.7; for children aged 1 year, 1.6; for children aged 2–4 years, 0.9).

Hospital discharge diagnoses and laboratory surveillance. The majority of registered hospitalizations for gastroenteritis in children aged <5 years were coded as gastroenteritis caused by an unknown infectious or viral agent (40–42%) and gastroenteritis caused by an unknown noninfectious agent (52%; table 2). The distribution of the different codes remained almost constant over the years, but the number of hospitalizations decreased.

The ICD codes for noninfectious gastroenteritis (558.9) and gastroenteritis caused by an infectious viral or unknown agent (codes 008.6, 008.8, and 009) followed the seasonal distribution of RV infection (figure 1). The ICD codes for gastroenteritis caused by an identified nonviral agent (codes 001–007, 008.0–008.5, 558.1, and 558.2) showed no seasonal distribution, and the correlation coefficient of this group with the laboratory surveillance data was only 0.03, although that value is significant (P = .04). Therefore, this group of ICD codes was not included in the estimation of the number of hospitalizations for RV infection. Inclusion of the laboratory surveillance data for Salmonella and Campylobacter had no effect on the correlation coefficients, nor did the regression coefficients differ significantly from zero. Therefore, these bacterial data were excluded as well.

The following linear regression models were calculated. First, we calculated a model including admissions with primary diagnoses for viral or unknown origins for children aged <5 years:

$$\Sigma Y_i = \Sigma (61.1 + 2.85X_i), \quad r^2 = .85 \ .$$

Second, we calculated a model including secondary diagnoses:

$$\Sigma Y_i = \Sigma (44.8 + 2.38X_i), \quad r^2 = .88 \ .$$

In these models, Y is the number of admissions, X is the number of RV-positive laboratory results, and i is the week number.

On the basis of these regressions models, a predicted number of hospitalizations for RV infection was calculated per week (figure 2). By this approach, in 1998, the winter peak in hospitalizations for gastroenteritis was almost entirely attributable to RV. Outside the winter peaks, there were hardly any hospitalizations attributable to RV. The seasonal pattern was similar when including secondary diagnoses.

Indirect incidence and percentage of hospitalizations attributable to RV, based on linear regression models. In 1996 and 1997, the number of children aged 0–4 years in the Netherlands was 980,906 and 971,065, respectively [8, 9]. The incidence of admissions for RV infection was the highest for children aged 1 year (table 3). The percentage of hospital admissions for gastroenteritis attributable to RV was 58% in 1996, 32% in 1997, and 53% in 1998 (average, 48%). The incidence of all hospitalization with RV infection (primary and secondary diagnoses) was 4.1 per 1000 in 1996, 1.9 per 1000 in 1997, and 3.2 per 1000 in 1998. The percentage accounted for by children aged <1 year was higher for all hospitalizations of children aged <5

<table>
<thead>
<tr>
<th>Year</th>
<th>Positive laboratory results</th>
<th>Infectious unknown or viral agents (ICD 008.6–009.3)</th>
<th>Unknown noninfectious agents (ICD 558.9)</th>
<th>Identified nonviral agents (ICD 001–008.5, 558.1–558.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>1395</td>
<td>2318</td>
<td>640</td>
<td>3023</td>
</tr>
<tr>
<td>1997</td>
<td>663</td>
<td>2024</td>
<td>600</td>
<td>2547</td>
</tr>
<tr>
<td>1998</td>
<td>1088</td>
<td>2094</td>
<td>455</td>
<td>2480</td>
</tr>
</tbody>
</table>

Table 2. Number of positive laboratory results and registered hospitalizations for gastroenteritis according to International Classification of Disease (ICD) codes and by diagnosis.
years with RV infection (30.5%) than for admissions for RV infection alone (26.9%). Children in the other age groups accounted for the following percentages of all hospitalizations with RV infection: aged 1 year, 33.3%; aged 2 years, 20.7%; aged 3 years, 9.5%; and aged 4 years, 6.0%.

Discussion

The direct incidence based on the reports of pediatricians was 0.9 per 1000 person-years for admissions for RV infection and 1.1 per 1000 for all hospitalizations with RV infection for children aged <5 years in 1998. In 1998, the indirect incidence based on the linear regression model was 2.7 per 1000 person-years for admissions for RV infection and 3.2 per 1000 for all hospitalizations with RV infection. Both estimates of the incidence are lower than the incidences found in most other countries. In England and Wales, the incidence of primary diagnoses was estimated at 5.2 per 1000 from May 1993 to March 1994 [10], in Australia 7.5 per 1000 in 1993–1996 [11], in Hungary 8.4 per 1000 in 1993–1996 [13], and 8.7 per 1000 in New South Wales, Australia, from 1991 to 1993 [12]. The incidences reported for Sweden (3.7 per 1000) [14], the United States (2.8 per 1000) [2, 15], and Spain (2.5 per 1000) [16] were similar to our estimate. These differences are likely partly due to differences in the admission policy for children with acute gastroenteritis. For instance, in England, the number of consultations at general practitioners for gastroenteritis is higher than in the Netherlands, which may imply that the health care system is more easily accessible than in the Netherlands [17, 18]. Another factor is the differences in the intensity of RV activity in the different years of study by different countries. In the Netherlands, the estimated incidence in 1996 was twice as low as in 1997.

Although several groups have used the linear regression approach combining laboratory data and hospital registration data to obtain estimates for the incidence of hospitalizations for RV infection, there are some limitations of this approach that should be addressed [10–12, 16]. First, the linear regression method is based on a number of assumptions. If RV is not the main pathogen responsible for the winter peak in hospitalizations in young children, this method will overestimate the percentage of hospitalizations attributable to RV infection. Several studies have shown, however, that among the pathogens for which routine testing is available, RV is the main pathogen responsible for the winter peak in hospitalizations of children aged <5 years [19, 20]. The proportion of children admitted for gastroenteritis that is attributable to RV ranges between one-third and two-thirds in different developed countries and in different years [10, 11, 13, 21–23]. The range in this percentage based on the regression analyses for the Netherlands (32%–58%) is similar to the percentages reported for other countries. The fact that these percentages are also similar to percentages based on epidemiological studies among hospitalized patients supports the validity of the regression method.
[24–28]. Furthermore, it is assumed that the number of admissions for RV infection is a constant multiple of the number of positive laboratory samples in the surveillance system. It is possible that less microbiological testing is performed in winter because the clinical picture, the age of the child, and the season are sufficient indication for the diagnosis of RV infection. On the other hand, testing for RV infection might be requested less often in summer because of the low likelihood of RV infections in summer. These 2 effects might counterbalance each other.

Because the coverage of the laboratory data is not known exactly, we could not differentiate between hospitalized patients and outpatients. Nevertheless, there is no indication that the proportion of samples originating from hospitalized patients changes over the years, so no bias is suspected as a result of the assumption of a constant multiplication factor.

The directly estimated incidence in children aged <5 years of admissions for RV infection (0.9 per 1000) was only 34% of the indirectly estimated incidence for 1998 (2.7 per 1000). This could be due to the underreporting of the pediatricians in the NSCK surveillance system. The 9% nonresponse, as reported by the NSCK, covers only part of the total nonresponse, because the receipt of a reporting card does not mean it was properly completed. An analysis of reports of whooping cough found that the NSCK response rate was 43% [29]. The relatively high incidence of hospitalizations with RV infection could have led to a lower response rate, especially because the NSCK usually restricts surveillance to rare diseases. Several pediatricians have actively indicated that they are not prepared to notify the NSCK of their patients’ hospitalizations with RV infection because of the heavy workload related to the RV infection surveillance. Further, the restriction of the case definition to microbiologically confirmed RV infections has also limited the number of notified hospitalizations. The fact that the estimate of the NSCK data (1103 hospitalizations in 1998) is close to the number of positive samples in the laboratory surveillance (1088 positive results in 1998) supports a high coverage of hospitalized patients in the laboratory data. This assumption is supported by the fact that the laboratories included in the laboratory surveillance are hospital-based, and only virological data from laboratories that have no virological department but only some standardized virological tests are missed. This could imply that only one third of patients hospitalized for RV infection is confirmed by a microbiological test.

According to the data of the NSCK, 13.4% of the hospital-

### Table 3. Number of estimated admissions with primary diagnosis for rotavirus by age group.

<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Incidence</td>
<td>n</td>
<td>Incidence</td>
</tr>
<tr>
<td>0–11</td>
<td>893</td>
<td>4.7</td>
<td>424</td>
<td>2.2</td>
</tr>
<tr>
<td>12–23</td>
<td>1158</td>
<td>5.9</td>
<td>550</td>
<td>2.9</td>
</tr>
<tr>
<td>24–35</td>
<td>725</td>
<td>3.7</td>
<td>345</td>
<td>1.8</td>
</tr>
<tr>
<td>36–47</td>
<td>335</td>
<td>1.7</td>
<td>159</td>
<td>0.8</td>
</tr>
<tr>
<td>48–59</td>
<td>209</td>
<td>1.0</td>
<td>99</td>
<td>0.5</td>
</tr>
<tr>
<td>Total</td>
<td>3320</td>
<td>3.4</td>
<td>1577</td>
<td>1.6</td>
</tr>
</tbody>
</table>

* Incidence per 1000 person-years. The population in the denominator was derived from census data [9, 10].

![Figure 2](https://academic.oup.com/cid/article-abstract/31/3/698/296914)
izations with RV infection was nosocomial. The linear regression method estimated 16.5%. This is lower than the percentages reported for Sweden (28%), Spain (49%), and Germany (51%) [24, 30, 31]. However, these studies only report on data from 1 or a few hospitals, and the variation between the hospitals is expected to be high. On the other hand, it might reflect real differences between countries.

The NSCK surveillance network and the linear regression estimation show similar age distributions for children admitted for RV infection. The overall distribution—two-thirds of infected children are aged <2 years—is similar to that of other countries. The sex distribution of children admitted for RV infection was similar to other countries, with slightly more boys affected than girls. Children with nosocomial RV infection were more often boys and were younger than children admitted for RV infection. This can be explained by the fact that in hospitals, there are relatively more children aged <1 year (9%) than in the general population (1%) and that the rate of hospitalization among children aged 0–14 years is higher for boys (5.9 per 100) than for girls (4.2 per 100) [8, 9].

The median duration of stay was 3 d for children admitted for RV infection. Other countries have reported a median length of stay ranging 2–4 d [10, 11, 31]. Only in Poland has a rather long mean duration of 9.5 d been reported [32]. This could be related to differences in treatment in the hospital, but it could also be related to differences in the primary care system that takes over the care of patient after discharge. The treatment of most children consisted of oral rehydration treatment, as advised by the World Health Organization and the European Society of Pediatricians on Gastroenteritis, Hepatology, and Nephrology [33]. However, 37% received iv treatment.

Although the data from the NSCK surveillance system were not complete, the data concerning the duration of hospitalization and disease, clinical picture, and treatment are not likely to differ between reported and unreported hospitalizations, and therefore, these data give a valid description of all children hospitalized with RV infection in the Netherlands.

Conclusion

In the Netherlands, the incidence of admissions for RV infection in 1998 was estimated at 0.9 (on the basis of hospital surveillance) and 2.7 (on the basis of combined laboratory and registry data) per 1000 children aged <5 years. The incidence varied for the 2 other years of study (1996, 3.4 per 1000; 1997, 1.6 per 1000). The highest incidence was found for children aged <2 years. To these totals, 13%–17% nosocomial infections should be added. The incidence is relatively low compared with other countries. The percentage of hospitalizations for gastroenteritis attributable to RV ranged from 32% to 58%, which is similar to the results for other industrialized countries.

However, a cost-benefit analysis will have to show whether implementation of vaccination is cost-effective in the Netherlands. Apart from the financial aspect, other factors play a role in the decision on implementation of vaccination, such as acceptance of the vaccine by the target population and logistic factors in administering the vaccine. Recent experiences in the United States show that intussusception might be a side effect related to vaccination with the current vaccine [34]. Therefore, this vaccine has been withdrawn from the market and the Centers for Disease Control and Prevention is currently investigating the issue by implementing a reporting system of vaccine adverse events, an active surveillance of 20,000 vaccinated infants, and active case finding in 15 states [3]. If intussusception is proven to be a side effect, the development of other vaccines, such as nonliving vaccines or bovine reassortant vaccines, will revive, but it is likely to be several years before different vaccines will become available. In developing countries, where RV infection is still a major cause of death, different judgments will be made about implementation of this vaccine on the basis of relative mortality rates. Finally, the consequences of introduction of vaccination should be monitored. A surveillance system is necessary to monitor the incidence of RV infection and the distribution of circulating RV strains. Such a surveillance system is currently not present in the Netherlands.

Acknowledgments

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