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Rotavirus in infant-toddler day care centers: Epidemiology relevant to disease control strategies

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A 15-month prospective longitudinal study of diarrhea and rotavirus (RV) infection was conducted concurrently in infants and toddlers in day care centers (DCCs) and in a large pediatric clinic in Houston. The mean number of children in the DCCs was 223; the diarrhea rate during the first 12 months was 2.62 episodes per child-year. Rotavirus accounted for approximately 10% of the total episodes of diarrhea in the pediatric clinic and DCC populations, but 50% during the winter months. The occurrence of RV in the DCCs paralleled that seen in the pediatric clinic. The annual rate of RV infection in DCCs was 0.55 episodes per child-year, with diarrhea occurring in only 40% of the episodes (0.22 episodes per child-year). There were 45 diarrhea outbreaks in DCCs, for a mean of 3.8 per center per year; nine of these outbreaks were associated with RV. Polyacrylamide gel electrophoresis of RNA genome patterns of RV strains from eight of these outbreaks showed that in seven outbreaks a single strain was identified in children in that DCC, whereas multiple strains were identified simultaneously in the community. The age distributions of symptomatic and asymptomatic RV infections in DCC study children were not significantly different. In symptomatic RV-infected children in DCCs, 42% had RV identified in stool specimens within 2 days before diarrhea occurred. Thirty-eight DCC children had more than one episode of RV infection, but only five had two symptomatic RV infections. Diarrhea caused by RV is common in children in DCCs, often occurs in outbreaks due to the same strain, and parallels disease in the community; asymptomatic RV infection is also common in children in DCCs.

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Infants and toddlers in day care centers tend to have high rates of diarrheal illness.14 Moreover, clusters of diarrheal disease, including diarrhea caused by rotavirus, are common in infant-toddler day care centers.2,3 The identification of such clusters, along with limited molecular epidemiologic studies, supports the assumption of child-to-child transmission of enteric agents in DCCs.6,8 Prevalence studies in Houston DCCs have also suggested frequent asymptomatic shedding of RV among young DCC children; such shedding could play an important role in transmission within child groups.5 However, the existing data regarding RV in this setting are incomplete and are not adequate to support a reliable study design for expensive preventive undertakings such as vaccine trials.

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We performed a prospective longitudinal study in Houston infant-toddler DCCs of the incidence of RV infection and diarrhea, the temporal pattern of RV in these DCCs compared with RV illness in the community, patterns of entry and transmission in the DCC child groups, and the role of asymptomatic RV infection in these groups. We also conducted a concurrent clinic-based study of diarrhea and RV in a large pediatric clinic representing a broad cross-section of Houston children comparable to those attending study DCCs.

**METHODS**

**DCC-based active surveillance.** Twelve DCCs licensed to care for infants and toddlers and having at least 10 children 0 to 24 months of age enrolled at the time of recruitment were randomly selected from licensing lists of all such DCCs located within 5 miles of the University of Texas Medical School at Houston (UTMSH). Enrollment of the DCC required consent of the owner or director and permission of parents of study age children. The protocol was approved by the Committee for the Protection of Human Subjects of the UTMSH.

On enrollment, children 0 to 24 months of age in each DCC were placed under continuous active surveillance for diarrhea and RV infection. Children were divided by age group and were cared for in different rooms according to the policy of the individual DCC; a total of 26 classroom groups participated in the study. These children and new entry children in each age group were observed for the duration of the study or until they left the study child group or the DCC. To determine annual rates of RV infection and outbreaks, this surveillance was conducted from January 13, 1986, to January 16, 1987. Surveillance was extended through March 31, 1987, to compare patterns of RV infection in DCCs and in the reference pediatric clinic, and of symptomatic and asymptomatic RV infection, during a second epidemic season.

Surveillance included collection of demographic information for each child 0 to 24 months of age by standardized questionnaire at time of entry into the study. Each DCC was visited at least twice weekly by a study nurse, and was contacted daily to identify cases of diarrhea among study children. If a child was absent, information on whether diarrhea occurred during absence was obtained from the parent or the caregiver.

Stool specimens for RV identification were obtained routinely each week from study children, and whenever a study child had diarrhea. If RV was identified in any specimen, stool specimens were collected twice weekly from all children in the child care room until RV was no longer identified for 2 consecutive weeks in that room.

**Pediatric clinic reference population.** A concurrent study of acute diarrhea in Houston children was conducted from September 1985 through March 1987. RV testing was performed on stool specimens from children 0 to 30 months old identified at a pediatric clinic of a large health maintenance organization. Because participation in this HMO is frequently a fringe benefit of employment, the population consisted largely of young families socioeconomically comparable to the DCC study population. Of ill HMO children tested, 25% attended a DCC, but none attended the DCCs under study.

**Specimen collection and identification of RV.** Stool specimens were collected by DCC workers or study nurses at the time of diaper changing. Specimens were then transported to the laboratory within 3 hours in temperature-stabilized containers. Aliquots of specimens were placed into phosphate-buffered saline suspension for enzyme-linked immunosorbent assay testing and held at 4°C until assayed (within 24 hours). Stool specimens were also tested for other enteropathogens as outlined below. Remaining bulk stool was stored at -70°C for additional testing.

Rotavirus testing was performed using a monoclonal antibody ELISA assay (Kallestad Laboratories, Inc., Austin, Texas). This test has demonstrated sensitivity and specificity of better than 95% in controlled studies. However, because large numbers of stools from well children were tested under this study protocol, a substantial number of false positive results were expected (giving a low predictive value of a positive result). Therefore, each specimen that was positive by initial ELISA was assayed a second time in the same assay. Those specimens that were again positive were then tested in a blocking ELISA using polyclonal goat anti-SV-40 antibody. In this report, "positive" specimens include only those that were doubly ELISA positive and successfully blocked. This combination of procedures is expected to yield a false positive rate of <1 per 1000 specimens.

Confirmation of these ELISA results was performed independently on subsets of symptomatic and asymptomatic positive and negative specimens in a different ELISA system by Dr. Robert Yolken, The Johns Hopkins University School of Medicine, Baltimore. This testing yielded a 98.5% concordance with our ELISA results.

In addition to RV, all stool specimens were evaluated for form and consistency, fecal leukocytes, and blood. Stools were cultured on MacConkey, Shigella-Salmonella, Terrigol 7, and Campy-BAP agars for isolation of *Shigella, Salmonella, Escherichia coli, Aeromonas, and Campylobacter*. The first 100 stool specimens from children with diarrhea had *E. coli* tested for heat-stable and heat-labile enterotoxin production by gene probe analysis. *Giardia lamblia* antigen was tested for by ELISA, and attempts to visualize cryptosporidium were made on stool specimens after modified acid-fast staining.
Purification of rotavirus and preparation of genomic RNA. A modification of the method of Herring et al. was used. Approximately 0.5 gm stool was added to 5 ml phosphate-buffered saline solution (pH 7.4) and vortexed. Five milliliters of Genetron (Aldrich Chemical Co., Milwaukee) was added and the mixture vortexed again. Crude materials were removed by low-speed centrifugation at 3000 \( \times g \) for 30 minutes at 8° C. The supernatant fluid was layered on top of a 40% (wt/vol) sucrose-Tris Cl solution (pH 8.0) and centrifuged at 150,000 \( \times g \) for 2 hours. The resultant pellet was resuspended in a 200 \( \mu L \) solution of sodium acetate (pH 5.0) containing 1% sodium dodecyl sulfate and incubated at 37° C for 1 hour. After this disruption procedure, a phenol-chloroform 3:2 (vol/vol) mix was added in equal volume for deproteinization. This mixture was centrifuged at 8000 \( \times g \) for 5 minutes and the supernatant removed for use.

Polyacrylamide gel electrophoresis of RNA. Mini gels of 7.5% (wt/vol) acrylamide were prepared by the method of Laemmli. RNA preparations from stool specimens were mixed with 2-mercaptoethanol (5:1 ratio). Ten to 20 \( \mu L \) was added to each well, and electrophoresis was carried out at 11 mA for 4 hours at room temperature. The gel was stained with silver stain (Bio-Rad Laboratories, Richmond, Calif.). Final identification of viruses with similar electrophoretic migration patterns was determined by coelectrophoresis.

Definitions. Diarrhea was defined as stools unusually loose or frequent compared with the norm for each child, as ascertained by the caregiver. A diarrhea episode was the occurrence of diarrhea, separated from previous diarrhea in that child by more than 1 week of being well. An RV episode was identification of RV in a child's stool specimen, separated from previous RV positivity in that child by more than 2 weeks of RV-negative stool. A child-week was any week in which a regularly enrolled child attended the DCC for 1 or more days (1 child-month was 4.33 child-weeks). A diarrhea outbreak was three or more cases per classroom group per week, or 5 or more cases per classroom group per 4 weeks.

Statistical methods. Rates of RV identification were calculated based on actual child-weeks of observation for each DCC. Nonparametric methods were used for statistical testing of comparisons of symptomatic and asymptomatic RV infections where indicated, using the chi-square test for univariate comparisons of categorical variables and the Wilcoxon two-sample test for comparisons of distributions.

RESULTS

Rates of diarrhea and RV infection in DCCs. The mean number of study age children in surveillance DCCs was 223 (18.6 per DCC). During the study there were 761 cases of diarrhea, 584 of which occurred during the first 12 months. The rate of diarrhea for the first 12 months of study was 2.62 episodes per child-year. RV was identified in 49 (8.4%) of these episodes, yielding an annual rate of RV diarrhea of 0.22 cases per child-year. These RV diarrhea episodes represented only 40% of all RV infections identified; an additional 74 episodes of asymptomatic RV infection were identified in DCC children during the same period. Thus the annual rate of RV infection was 0.55 cases per child-year.

Temporal pattern of RV diarrhea in DCCs and pediatric clinic patients. Fig. 1 shows the temporal pattern of RV identification among study children with diarrhea in the HMO pediatric clinic and in the study DCCs. Surveillance was conducted for a total of 14.5 months in the DCC to encompass a second epidemic season. The proportion of diarrhea cases in which RV was identified was highest in the winter months in both settings. RV diarrhea was identified in all but 3 months in the DCCs and all but 3 months in the HMO clinic. In the DCCs the pattern of RV diarrhea was not the same as the overall pattern of diarrhea, which generally was more frequent in summer months despite lower average attendance in the DCCs. In December all DCCs closed for 1 to 2 weeks.

Outbreaks and patterns of RV infection within individual DCCs. Forty-five diarrhea outbreaks were identified in DCCs during the study period. RV was identified among ill children in nine (20%) of these outbreaks. In six of the nine RV-positive outbreaks the largest number of RV illnesses occurred in the first week of the outbreak. Consistent with previous studies, in outbreaks in which RV was identified not all ill children had RV-positive stools (28 of 63, or 44%). Seven of the nine RV-positive outbreaks occurred in DCCs with more than one infant-toddler classroom group. Of these seven outbreaks four were accompanied by identification of RV within 1 week in one or more other classroom groups. An etiologic role of RV in these outbreaks is suggested by the identification of RV in 17 of 55 (31%) asymptomatic children tested in outbreaks with RV-positive diarrhea but in none of 214 asymptomatic children in outbreaks with only RV-negative diarrhea. Eight children involved in the RV outbreaks had G. lamblia identified in stool specimens; four had diarrhea and four were well. No other enteropathogens were identified in these children.

Rotavirus genomic RNA. Fifty-three children involved in eight of the nine separate outbreaks with RV-positive diarrhea had electrophoretic patterns of RV RNA determined in stool specimens obtained during the outbreaks. Although differences existed among the different outbreaks, the electrophoretic migration patterns of the genomic RNA of RV in individual outbreaks was the same in seven of these eight outbreaks (Table). In outbreak 3, two
different electropherotypic patterns were seen. Stool specimens obtained from the HMO clinic children with diarrhea during the same month as the outbreaks were also tested for RNA patterns if RV was detected by ELISA. These specimens showed that during each of the outbreaks several strains were present in the community.

**Evaluation of symptomatic and asymptomatic RV infections.** Fig. 2 shows the distribution by month of RV infection in children with and without diarrhea in the DCC. In the DCC population, except for 2 months in which a small number of cases were identified, symptomatic and asymptomatic infection always occurred together. The number of asymptomatic cases of rotavirus infection was greater in the DCC population than in the clinic population because asymptomatic children were not tested more than once in the clinic, compared with at least weekly in the DCC. Although our sampling protocol did not permit exact determination of RV shedding in the DCC, it
did permit an estimation of that duration based on interval from first to last RV-positive specimen in each episode. The mean estimated duration of RV shedding was 6 days (range 1 to 21 days) in symptomatic infections and 4 days (range 1 to 32 days) in asymptomatic infection. Nineteen of 49 (39%) symptomatic infections and 31 of 74 (42%) asymptomatic infections were the index infection. Of these, 68% of symptomatic infections and 42% of asymptomatic infections were associated with additional infections in the same group; this difference was not statistically significant. In 33 symptomatic RV episodes in which specimens were collected within 2 days before illness began, 42% had RV identified before symptoms occurred.14

The age distributions of symptomatic and asymptomatic RV episodes among DCC study children were not significantly different. However, in symptomatic RV infections the mean duration of illness was shorter in children aged 12 to 24 months than in younger children (2.5 vs 4.5 days).

During the 14.5 months of DCC surveillance, we identified 38 children who had more than one episode of RV infection separated by at least 1 month of RV-negative stool examinations. Of these, 19 had two or more asymptomatic episodes, with no symptomatic infection identified during their participation in surveillance. Ten of the remaining 19 children had a single symptomatic episode followed by one or more asymptomatic episodes. Five children had two symptomatic RV infections. Mean age of these five children was 5 months (range 2 to 7 months) at the time of the first episode and 10 months (range 7 to 13 months) at the time of the second; the mean duration of illness in first episodes (15 days) was significantly longer than in second episodes (1.5 days; p <0.05). Four children had asymptomatic infection followed by symptomatic infection. Three of these were in the same DCC and classroom group, and their asymptomatic infections occurred in the first epidemic season of surveillance and their symptomatic infections in the same week of the next year's epidemic season. This pattern suggests entry into their group of a new RV strain to which they lacked resistance. None of these children had other enteropathogens identified in their stools during the RV infections.

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**Figure 2.** Temporal pattern of rotavirus identification among study children with diarrhea ■ and without diarrhea □ in day care centers.

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**Table.** Results of RNA electropherotyping of rotavirus strains from stool specimens from children in day care centers and from children attending HMO clinic

| Outbreak | No. of children with RV infection tested by electropherotyping | No. of electropherotypes |
|----------|---------------------------------------------------------------|--------------------------|
| DCC      | Community                                                     |                          |
| 1        | 5                                                             | 1                        |
| 2        | 4                                                             | 1                        |
| 3        | 7                                                             | 2                        |
| 4        | 9                                                             | 1                        |
| 5        | 7                                                             | 1                        |
| 6        | 13                                                            | 1                        |
| 7        | 4                                                             | 1                        |
| 8        | 5                                                             | 1                        |

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Table entries: "No. of children with RV infection tested by electropherotyping" and "No. of electropherotypes" columns.
DISCUSSION

In the United States, rotavirus is the cause of approximately 50% of pediatric admissions to hospitals because of diarrhea and 20% to 25% of pediatric diarrhea in outpatient clinics. However, in prospective community and DCC studies RV has been identified in 6% to 12.5% of infant-toddler diarrhea episodes. Prospective DCC-based studies in Houston and Phoenix found infant-toddler diarrhea rates of 1.02 to 1.24 episodes per child-year. These data yield an expected incidence of RV diarrhea of 0.06 to 0.16 episodes per infant-toddler child-year. Our observed overall rate of diarrhea was higher than that in previous studies, possibly because we did not enroll children 25 to 36 months old, in whom diarrhea is less frequent and more difficult to ascertain after toilet training. Our observed rate of 0.22 episodes of RV diarrhea per infant-toddler child-year was also higher than predicted.

Design of RV control strategies must consider that diarrheal illness frequently occurs in clusters in DCC child groups. Using somewhat different definitions of "outbreak," the Houston and Phoenix longitudinal studies found the probability of a cluster of diarrhea cases in an infant-toddler DCC to be 0.41 to 0.83 annually. In these studies RV was identified in 25% to 40% of outbreaks, with an attack rate of 40% to 70%. Using a less stringent definition of outbreak, we identified nine outbreaks associated with RV infection, a risk of 0.75 per DCC per year. The mean annual diarrhea rate was 0.43 cases per class-room group per week (95% confidence interval 0.40 to 0.46), so our outbreak definition represented rates above the expected.

In Phoenix, concurrent study in DCCs, day care homes, and households not using day care showed that RV diarrhea appeared within 2 weeks in all three types of care settings in different geographic sections of the large metropolitan area. This would suggest community-based surveillance to be a potential mechanism to determine timing of RV control strategies. However, Rodger et al. found the epidemiology of RV within a neonatal nursery (another closed group setting with high turnover) to be distinct from that in the surrounding community. Which of these patterns pertains to RV in DCCs bears on the potential for timing implementation of a control strategy, and even affects interventions not requiring continuous application (such as vaccine administration), because of the high turnover rates in DCC child groups. Our simultaneous DCC and HMO pediatric clinic surveillance found the temporal patterns of RV diarrhea to be similar in the two settings. Thus identification of increasing rates of RV in the community can be expected to be paralleled by increased RV illness in DCCs.

Other important considerations in design of an intervention strategy are the rapidity with which RV spreads in a child group, and the patterns of introduction and transmission. Studies in adult human volunteers and child household contacts have indicated the incubation period of RV to be between <1 to 2 days. Our observations of frequent clustering of RV in outbreaks, with the largest number of infections occurring in the first week of such outbreaks, is consistent with such an incubation period. This tendency of RV to rapidly involve many children in a DCC group indicates the need for intervention strategies or disease control practices to be in place before RV illness is identified.

Asymptomatic infection accounted for 60% of all identified RV-positive episodes in our DCC study children. This finding is consistent with earlier prevalence studies in Houston DCCs, in which 12% of children 0 to 24 months old were found to be asymptotically shedding RV in their stools. High rates of asymptomatic RV infection have also been reported among young children in Paris, Western Australia, and Costa Rica.

The overall observed rate of RV infection (symptomatic and asymptomatic) was 0.55 per child-year, consistent with serosurveys in which virtually all children are found to be RV seropositive by the end of the second year of life. Almost half of children with RV diarrhea tested within 2 days before illness were already shedding the virus. This presymptomatic excretion of RV may be analogous to that of commonly encountered viral agents of upper respiratory tract infections. Presymptomatic RV shedding and the high rate of asymptomatic RV infections are important potential factors in introduction and transmission of RV in DCCs and in the community at large.

Our basic rate of stool testing for RV was once weekly for each child in the absence of diarrhea. Given the estimated 4-day mean shedding duration of asymptomatic RV infections, we may have failed to detect 43% of such infections. Thus the rate of asymptomatic RV could actually be almost twice that identified, and some detected infections might have been secondary to unidentified asymptomatic infections. On the other hand, our increasing the testing frequency after identifying RV in a group could identify infections more effectively and result in an apparently higher rate of secondary infections. However, our electrophoresis findings are more consistent with intergroup transmission of RV than with simply increased detection of RV present in the DCCs and the community.

We were surprised to find no difference in the age distributions of asymptomatic and symptomatic RV infections, as would be expected if asymptomatic infection followed earlier symptomatic infection. However, we have no information on the RV infection history of these children before they entered surveillance. We did find a shorter duration of symptoms in older children, and in five
RV diarrhea episodes following previous RV diarrhea episodes in the same children. In addition, 10 of 38 sequentially infected children had asymptomatic infection after earlier symptomatic episodes. These findings are consistent with the hypothesis that older children have increased resistance to illness during RV infection; immunization by naturally occurring RV infection may be one mediator of this increased resistance.

Our findings indicate that young DCC children are an appropriate group in which to evaluate RV control strategies and that these children may benefit from application of such strategies once developed. It may be particularly cost effective to control RV disease in this group, because diarrheal illness in DCC children results in high rates of physician visits, lost time from work, and secondary illness in household contacts. However, RV accounts for only about 10% of diarrhea in DCCs, so the overall impact of RV-specific control strategies will be limited. Additional impact on diarrheal disease in child care settings will require improved hygiene, specific strategies to control other pathogens, and small group size.

References

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