Clinical Spectrum and Transmission Characteristics of Infection with Norwalk-Like Virus: Findings from a Large Community Outbreak in Sweden

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A large foodborne outbreak caused by Norwalk-like virus (NLV) among children and staff at 30 day care centers provided an opportunity to study symptomatology and attack rates among patients in different age groups, as well as secondary transmission rates in centers and households. A retrospective cohort study of 775 subjects from 13 randomly chosen centers was performed. Diarrhea was more common in adults than in children (P < .001), whereas the reverse was noted with regard to vomiting (P < .003). The primary attack rate was 27% (142 of 524 subjects): 54% of adults versus 19% of children (P < .001). The mean incubation time for foodborne cases of infection was 34 hours. The secondary attack rate was 17%. Risk factors for spread into households were the primary case being a child (relative risk [RR], 3.8; 95% confidence interval [CI], 1.9–7.6) and vomiting (RR, 2.4; 95% CI, 1.0–5.5). The incubation time for person-to-person transmission was approximated by a mean serial interval of 52 hours. This is the first reported outbreak of NLV infection in which secondary transmission into households by individuals has been studied.

Infections caused by Norwalk-like viruses (NLVs) are usually reported as outbreaks of gastroenteritis; in these reports, clinical characteristics are used to make an empirical diagnosis. These characteristics include a brief illness of 2–3-days’ duration, vomiting as a prominent symptom for >50% of the affected individuals, an incubation period of 24–48 h, a high secondary attack rate, and cultures of stool samples that are negative for bacterial pathogens [1, 2]. Because the infectious dose is very low, the attack rate is often high: it ranges from 30% to 80% in reports of foodborne outbreaks [3–9] and from 30% to 60% in outbreaks that involve person-to-person transmission [10, 11].

During foodborne outbreaks, secondary person-to-person transmission is common. However, because duration of incubation can be very brief [12], it becomes difficult to distinguish cases of primary infection from cases of secondary infection: early onset of illness in secondary cases often overlaps with late onset of primary cases.

In a previously prepared article, we described a large foodborne outbreak of NLV gastroenteritis that occurred in Sweden in 1999 (unpublished data, H.G., J.L., B.d.J., K.O.H., and K.E.; hereafter, “authors’ unpublished data”). That article concentrated on the extent and probable source of the outbreak and included the findings of electron microscopy and molecular typing, which were used to verify diagnosis and to find the source of infection, respectively. The aim of the present...
article was to use the data from that study of the outbreak to answer the following questions: What is the distribution of symptoms in patients with NLV infection, and does this distribution vary by age group? Do primary cases differ from secondary cases with regard to symptoms? Does attack rate vary by age group? What is the secondary transmission rate for symptomatic cases? What is the serial interval for person-to-person–transmitted NLV infection?

**MATERIALS AND METHODS**

The characteristics and basic epidemiological findings regarding the outbreak are described elsewhere (authors’ unpublished data). In brief, a large outbreak of gastroenteritis among children and staff at 30 child centers occurred in northern Stockholm in March 1999. (A “child center” is defined as either a day care facility for preschool children or an after-school center for young children. Both types of center provide meals for the children.) Cultures of stool samples were negative for *Salmonella*, *Shigella*, *Campylobacter*, and *Yersinia* species. NLV was found by means of electron microscopy in 5 of 5 symptomatic children from whom samples were obtained and in 1 of 3 persons who were working in the large kitchen that provided catering for all 30 centers.

Validated reverse-transcriptase PCR and reverse line blot hybridization were performed [13]. NLV genogroup II was detected in all 5 samples obtained from children and in 2 of the 3 samples obtained from kitchen workers, and sequence analysis of a 250-nucleotide stretch of the RNA polymerase region showed that all 7 samples were identical.

A retrospective cohort study was performed that involved approximately half the exposed population: 775 subjects from 13 randomly chosen child centers. The epidemiological analysis strongly suggested that a raw vegetable salad was the source of the outbreak. The mode of transmission could not be conclusively shown, but contamination by one of the food-handlers seemed to be the most likely means of transmission.

**Definition of primary cases and secondary cases.** A “primary case” was defined as a person in the child center who became ill and who had diarrhea, vomiting, or nausea during the first 3 days of the outbreak. A “secondary case” was defined as a person who became ill from day 4 through day 12 of the outbreak. A secondary household case was defined as someone who became ill at >6 h but <10 days after the onset of disease in the corresponding patient who acquired the infection in the child center.

**Data collection.** Age and sex were registered for all responding subjects at the child centers. For the patients, data were collected regarding symptoms, the date and time of onset of symptoms, and the duration of symptoms, as well as the size of household and the age, sex, time of onset, and symptoms of any ill members of the household.

**Statistical analysis.** Calculations were performed by use of Epi Info, version 6.04c (Centers for Disease Control and Prevention). Standard χ² and Fisher’s exact (2-sided) statistical tests were used for analysis of proportion and rates. Frequency of symptoms was analyzed for all patients who acquired infection at the child center early in the course of the outbreak (during the first 3 days) and those who acquired infection late in the course of the outbreak (from day 4 through day 12), as well as secondary cases in the households. Furthermore, cases in adult subjects were compared with cases in children.

For the calculation of the attack rate for secondary cases in the child centers, the primary cases were excluded from the denominator, because they were no longer susceptible. For the calculation of secondary attack rates in the households, all households in which there were cases of gastroenteritis occurring too early to fulfill the aforementioned case definition were excluded, because in these instances it would be impossible to know the source of household cases. For the same reason, families that had >1 attendee of a child center who became ill were also excluded.

To assess risk factors for household transmission and to calculate the period between onset of symptoms in patients who attended a child center and onset in secondary cases in the household (serial intervals) [14], these cases were linked individually using Microsoft Office Access 97 (Microsoft). Relative risks and 95% CIs were calculated for characteristics of the cases in the child center who infected a member of the household, compared with those child center cases who did not bring the infection home.

**RESULTS**

**Description of primary cases and secondary cases.** Five hundred twenty-four (68%) of the 775 subjects (both children and the staff of the child centers) who were given a questionnaire regarding the outbreak returned a questionnaire that could be analyzed. Our original analysis identified 195 cases among the responders, of which 142 were primary and 53 were secondary (although there is bound to be some misclassification here, our previous analysis showed very clear differences in risk factors for disease between these 2 groups of patients). The 79 adult patients were 20–61 years old (mean age, 41 years), and the 114 children were 1–10 years old (mean age, 5 years). Age was unknown for 2 of the patients.

The 195 patients in the child centers were members of households that had a total of 459 other members. There were 79 secondary cases in the household: 58 adults, who were 19–73 years old (mean age, 36 years), and 21 children, who were 1–13 years old (mean age, 7 years).
Symptoms. Types of symptoms were reported by 142 primary cases and 131 secondary cases from child centers and households. When comparing distribution of symptoms by acquisition, we found just 2 notable differences between these 2 groups: (1) The frequency of vomiting was higher among primary cases than it was among secondary cases (110 of 139 patients vs. 80 of 123 patients, respectively; \( P = .01 \)). After stratification by age group, however, this difference between primary cases and secondary cases was no longer statistically significant. (2) Although there was no statistically significantly difference between primary cases and secondary cases with regard to the frequency of diarrhea, among children, secondary cases reported diarrhea more frequently than did primary cases (37 of 59 patients vs. 29 of 68 patients, respectively; \( P = .02 \)). Therefore, because the mode of infection seemed to matter little for symptoms, the 2 groups were merged into just 1 group that included 137 adults and 136 children, and our analysis concentrated on the relationship between age and symptoms.

As shown in table 1, nausea and stomach pain were the most common symptoms for both adults and children. Diarrhea was more common among adults than it was among children (\( P = .001 \), whereas the reverse was noted with regard to vomiting (\( P = .003 \)). Twenty-seven adults and 56 children reported vomiting without diarrhea, and diarrhea without vomiting was reported by 33 adults and 20 children.

Duration and frequency of symptoms could be assessed only among the subjects at the child centers. A total of 108 of these patients reported vomiting that lasted 1–72 h (median duration, 6 h) and 65 patients reported diarrhea (≥1 loose stools per day, as reported by a caretaker) that lasted 1–99 hours (median duration, 15 h). Of 51 adults, 31 (61%) had diarrhea >3 times and 20 (39%) vomited >3 times. Of 49 children, 26 (53%) had diarrhea >3 times, and 43 (51%) of 84 children vomited >3 times.

Attack rate. There was no difference between male and female patients with regard to the primary or secondary attack rate. As is shown in table 2, the overall primary attack rate was 27%, and it was much higher among adults than it was among children (54% vs. 19%, respectively; \( P < .001 \)). The secondary attack rate in the child centers was significantly higher (\( P = .02 \)) in the youngest children.

In 19 of the households that included a patient from the child center, the existence (or lack thereof) of secondary transmission was unclear. In most of these households, another case of gastroenteritis occurred outside of the time period specified in the case definition for secondary household cases. These 19 households were excluded from the denominator, which left 403 household members as the denominator for the 79 secondary household cases.

With this adjustment, the overall secondary attack rate was 17% (132 of 785 patients); it was slightly higher in the households (79 [20%] of 403 patients) than it was in the child centers (53 [14%] of 382 patients). Because we did not know the total age distribution in the households, the association between age and attack rate could be calculated only for the patients who acquired infection at the child centers.

For the children in the child centers, the attack rate (primary and secondary combined) did not vary according to age in any clear pattern, as is shown in figure 1. In addition, the secondary attack rate did not differ for adults and children. However, the secondary attack rate in the child centers was higher among children aged 1–5 years than it was among children aged 6–10 years (17% vs. 8%, respectively; \( P = .02 \); table 2).

Risk factors for household transmission. After the 19 households with unclear status regarding secondary transmission had been omitted, 176 households that had been exposed to NLV remained. However, 23 of these households included only members of the child center staff who each lived alone.

### Table 1. Symptoms of all patients (from child centers and households) who acquired Norwalk-like virus (NLV) infection during an outbreak of NLV infection in child centers in Sweden, March 1999.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Adults (n = 137)</th>
<th>Children (n = 136)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>93/130 (71.5)</td>
<td>66/127 (52.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Vomiting</td>
<td>82/128 (64.1)</td>
<td>108/134 (80.6)</td>
<td>.003</td>
</tr>
<tr>
<td>Nausea</td>
<td>122/126 (96.8)</td>
<td>94/101 (93.1)</td>
<td>.22</td>
</tr>
<tr>
<td>Stomach pain</td>
<td>100/114 (87.7)</td>
<td>94/106 (88.7)</td>
<td>.82</td>
</tr>
<tr>
<td>Headache</td>
<td>56/88 (63.6)</td>
<td>30/69 (43.5)</td>
<td>.01</td>
</tr>
<tr>
<td>Chills</td>
<td>39/88 (44.3)</td>
<td>16/77 (20.8)</td>
<td>.001</td>
</tr>
<tr>
<td>Fever</td>
<td>38/85 (44.7)</td>
<td>31/88 (35.2)</td>
<td>.2</td>
</tr>
<tr>
<td>Myalgia</td>
<td>40/83 (48.2)</td>
<td>11/63 (17.5)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*a Age, >16 years.

*b Age, <16 years.

### Table 2. Attack rates in 13 child centers during an outbreak of Norwalk-like virus infection in child centers in Sweden, March 1999.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Primary cases</th>
<th>Secondary cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (n)</td>
<td>Attack rate, no. (%) of patients</td>
</tr>
<tr>
<td>All</td>
<td>130</td>
<td>44 (34)</td>
</tr>
<tr>
<td>Adults</td>
<td>68 (54)</td>
<td>.23</td>
</tr>
<tr>
<td>Children</td>
<td>31 (19)</td>
<td>.23</td>
</tr>
<tr>
<td>0–5 years old</td>
<td>30 (22)</td>
<td>.23</td>
</tr>
<tr>
<td>6–10 years old</td>
<td>30 (22)</td>
<td>.23</td>
</tr>
</tbody>
</table>

*a Age of >16 years.

*b Age of 1–15 years.
Figure 1. Attack rates (ARs) among patients who acquired Norwalk-like virus infection at a child center, by 1-year age group. Numbers in columns denote numbers of persons; black bars, cases; white bars, noncases.

Thus precluding household transmission. Of the remaining 153 households, transmission occurred in 49 (32%). In 29 of these households, there was 1 case secondary to the case from the child center; in 12 households, there were 2; in 7 households, there were 3; and in 1 household, there were 5.

Among the patients who acquired infection at a child center and who transmitted the infection to a person in the household, there were 20 children and 2 adults who had vomiting but not diarrhea. Two adults and 2 children who reported diarrhea without vomiting and 1 child who reported only nausea transmitted infection to secondary cases. To assess risk factors for transmission among household members, the 49 patients who acquired infection at a child center and who transmitted that infection to secondary cases were compared with the 104 patients who did not transmit infection to members of their households. Children were more likely to have transmitted infection to secondary cases in the households than were adults (RR, 3.8; 95% CI, 1.9–7.6). Vomiting was a risk factor for causing secondary cases as well (RR, 2.4; 95% CI, 1.0–5.5). Exposure to a patient from a child center who had diarrhea was not associated with a higher risk of acquiring secondary infection (RR, 0.8; 95% CI, 0.5–1.3). Of the 61 patients who had only vomiting, 22 (36%) transmitted infection to members of their households, whereas 4 (15%) of the 27 patients who had only diarrhea transmitted infection to members of their households.

Risk of transmission of infection to the household also increased in relation to the frequency of vomiting: such information was available for 125 patients who transmitted infection to members of their households. These patients were categorized into 3 groups according to the frequency of vomiting (patients who vomited only once, 2–3 times, or ≥4 times), and a χ² test for linear trend was performed. There was a dose-response relationship between frequency of vomiting and causing secondary cases in the households (χ², 6.9; P = .008).

Size of household was not a risk factor for acquisition of secondary infection (χ² for linear trend, 2.085; P = .14). To find out whether infectivity is highest immediately after onset of disease, we divided the patients who acquired infection at a child center into 2 groups: patients who had onset of disease at the child center (between 8:00 AM and 5:00 PM) and those who had onset of disease at home (between 5:00 PM and 8:00 AM). However, patients who experienced the onset of disease at the child center were not less likely to transmit infection to a member of the household than were patients who became ill at home (RR, 0.9; 95% CI, 0.6–1.6). The epidemic curves for the outbreak in the child centers, for first household cases, and for later household cases are shown in figure 2.

Incubation period of NLV infection and serial intervals.
In our previous analysis of this outbreak, we found a strong association between primary cases and consumption of the vegetable salad that was served at 11:00 AM on day 1 (authors’ unpublished data). On the basis of our case definition, which truncates all primary cases that occurred after day 3, the median incubation period for primary cases involved in the foodborne outbreak would be 34 h (range, 2–61 h). The distribution of incubation times is shown in figure 3.

The serial intervals could be calculated for 65 household cases, of which 39 were first household cases. The median serial interval between a case in a child center and its linked household case was 73 h (4–198 h). If only the first case in each household is counted, the median serial interval was 59 h (range, 4–198) for 39 first household cases (figure 4). This figure also quite nicely illustrates the existence of 2 waves of household cases, with one peak that occurred ~3 days after the onset of disease in the primary cases and another peak that

Figure 2. Date of onset of disease in patients who acquired Norwalk-like virus [NLV] infection at a child center (black bars) and first and later household cases (white bars and striped bars, respectively) during the outbreak of NLV infection.
occurred ∼3–4 days later, which may well indicate tertiary transmission. Truncating at 96 h, the median serial interval for the 31 first household cases was 52 h (range, 4–96 h).

The period between cessation of vomiting among patients who acquired infection at a child center and onset of symptoms in the first household case varied in duration from 21 h to 180 h (it could be calculated for 16 instances of such transmission). The serial interval for each of the cases in the households is shown in figure 5.

DISCUSSION

Previously, there have been few studies of secondary transmission during foodborne outbreaks of NLV infection. This foodborne outbreak of NLV infection in child centers, with secondary transmission that occurred in the child centers as well as in the households of patients, enabled us to study in detail the age-related differences in clinical pictures and the transmission dynamics of NLV infection, including individual secondary person-to-person transmission.

Patients mainly reported symptoms of abdominal pain and nausea, sometimes accompanied by myalgia, fever, and headache, as described in the literature [2, 15]. Both vomiting and diarrhea occurred, and either could have been the sole clinical symptom. Vomiting has always been regarded as a major feature of NLV infection, and >50% of our patients also experienced vomiting. It should be noted, however, that although vomiting was reported by the children to be more common than diarrhea, the opposite was true for the adults. This discrepancy has been noted elsewhere [15, 16].

Previously, a history of vomiting in >50% of patients has been used as a rudimentary clinical indication that an outbreak was caused by NLV. However, Hedberg et al. [15] suggested that use of the increased frequency of vomiting in relation to the frequency of fever might be a better clinical criterion for differentiating outbreaks of infection caused by NLV from outbreaks caused by bacteria. The ratio of frequency of vomiting to fever was 1.42 in children versus 2.29 in adults; therefore, this criterion holds for both children and adults in our outbreak. After adjusting for age differences, we found that primary cases did not differ from secondary cases with regard to symptoms, which indicates that the route of transmission does not influence the clinical picture. The fact that there were secondary cases in the households associated with patients in the centers who reported only vomiting proves that the virus can be transmitted via vomitus.

The duration of incubation is generally reported to be 24–48 h [12], but longer durations of incubation have been described. These findings might have been the result of misclassification of secondary cases of infection. In our study, we found that exposure to the vegetable salad was associated clearly only with the patients who had an onset of symptoms on days 1–3; this association disappeared for patients who had onset of symptoms on day 4 or later (authors’ unpublished data). Therefore, we estimate the median foodborne incubation time to be 34 h, with the lower quartile at 30 h and the higher quartile at 43 h.

The incubation time for secondary household cases could not be calculated, because neither the onset of infectiousness in the primary cases nor the exact moment of infection is known. Therefore, serial intervals were computed, and we found a median serial interval of 52 h between onset of illness in cases at child centers and the first respective household cases in the first wave of secondary infection. One cannot make any conclusions regarding the incubation time of person-to-person transmission on the basis of our data, but it is likely that the mean incubation time could be approximated by use of the serial interval. Figures 3 and 4 provide evidence to support this assumption.

One effect of a possibly higher dose in primary foodborne cases could be that the duration of incubation is shorter for these cases than it is for cases of person-to-person transmission. Because we included durations of incubation of up to 216 h in the definition of household secondary cases, we would not have missed even those persons with NLV infections who had long durations of incubation.

We were able to represent serial intervals of individual families. Almost two-thirds of the first patients with household

Figure 3. Duration of incubation for 126 primary cases who acquired foodborne Norwalk-like virus infection (n = 126).

Figure 4. Serial intervals between cases at a child center and secondary cases in households. White bars, first case in each household; black bars, later cases. The interval could be calculated for 65 of the household cases.
Transmission Characteristics of NLV Infection

Figure 5. Serial intervals for 49 patients who acquired Norwalk-like virus (NLV) infection at a child center and infected members of their respective households. Intervals were filled in at 12-h increments. On the Y-axis, 0 marks the onset of symptoms for patients who acquired NLV infection at a child center. ○, female child; ●, female adult; ▼, male child; ▼, male adult.

cases of infection had a serial interval of <4 days. Later cases of infection in the households appeared after 1–3 days, which is in accordance with expected durations of incubation. It is striking that the last 10 households shown in figure 5 had serial intervals of >96 hours. In all but the last household presented, there could have been asymptomatic members of the household who passed the infection on to the first clinical secondary case, which would indicate that the artificially long serial interval was in actuality 2 serial intervals. In 2 of these households, the primary case reported diarrhea of long duration; the period from the disappearance of symptoms in the patient who acquired infection at the child center to the appearance of the symptoms in the infected members of the household would then be 3–4 days. In the last household shown in figure 5, the serial interval was 198 h; the third and the last family member became ill 2 days after the first member of the household became ill. It seems unlikely that those 2 cases were secondary cases associated with the outbreak.

Secondary attack rates in households are described as having a range of 19%–33% [1, 10]; one study described an attack rate of 44% per household [6]. Our overall household secondary attack rate of 20% is relatively low, possibly because hygienic measures were promptly taken.

A shortcoming of our study is that we could not compare the rate of secondary household transmission for symptomatic versus asymptomatic center cases, because we only interviewed the families of the clinical center cases. However, awareness about this outbreak among all parents of children in the centers was high, and it did not come to our attention that many cases would have occurred in families of children without symptoms who were possibly infected.

We could show that the main risk factors for secondary transmission in the household were the age of the primary cases (childhood) and vomiting. These are plausible risk factors for transmission when one considers the hygienic behaviors of children and the fact that the main symptom was vomiting. We did not find any difference with regard to household transmission for patients who became ill in the child center versus those who became ill at home. This is not surprising, because even if most patients had vomiting as their first symptom, the majority of the patients reported that they vomited more than once and, therefore, they may have vomited at both places. The relation between vomiting and transmission is clearly indicated by the dose-response relationship we found.

Several seroepidemiological studies in industrialized countries have shown that, in contrast to rotavirus, human (classic) calicivirus, and astrovirus infections, which all occur in young children, NLV infection occurs in older children and adults [16–19]. In contrast, other studies [20, 21] report that NLV infection is more common in infants and young children than has commonly been believed—the incidence of NLV infection even appeared to decrease in association with increasing age in one study [20]. Patients with NLV infection can be asymptomatic, and a study from Brazil [22] showed that seroconversion rates were not associated with symptoms in the first year of age. Our study included only 5 children from the child centers who were <1 year of age, but the attack rates were high for those children who were ≥1 of age. O’Ryan et al. [23] found child center attendance to be a risk factor for acquisition of NLV, and the outbreak that we describe exemplifies this.

Heun et al. [6] described secondary attack rates in households that occurred during a foodborne outbreak at a school; the authors suggested that this mode of secondary transmission favored the preschool-aged population over adults, whereas no different attack rates were found in foodborne cases between adults and preschool-aged children.

We found that the attack rate for the child center was higher among adults than it was among children, which could be explained by consideration of the food that was consumed: the
source was a vegetable salad, and as any parent would know, young children often try to eat as little of this as possible (authors’ unpublished data.) We could show that all age groups of children were affected. In contrast to the foodborne cases that occurred in children, a significant difference was found between children who were 1–5 years old and those who were 6–10 years old among the secondary cases. The higher attack rate in the younger group might have been a result of low immunity and possible hygienic factors.

One of the limitations of our study was that we did not ask the age of the household members. If we assume that each child has 2 parents, then the attack rates in the households would have been 24% for adults and 13% for children. In reality, however, there are households with only 1 caretaker, which would increase the attack rate for adults. The higher attack rate for adults could have been due in part to low immunity in adults, but it is probable that exposure to vomiting children played a major role.

Our investigation describes one of the largest groups of NLV infections among adults and children, and it illustrates individual secondary person-to-person transmission. The demonstration that vomiting constituted the main risk factor for transmission substantiates the need of isolation of vomiting patients.

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References