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## A school outbreak of Norwalk-like virus: evidence for airborne transmission

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(Accepted 20 March 2003)

### SUMMARY

An outbreak of gastroenteritis affected a school attended by children aged 4–11 years. Epidemiological features suggested this was due to Norwalk-like virus (NLV) and this was confirmed by polymerase chain reaction (PCR). Nucleotide sequence analysis of the PCR amplicons revealed identical strains in all five positive stool samples. Pupils were significantly more likely to become ill following an episode of vomiting within their classroom (adjusted odds ratio 4·1, 95% CI 1·8–9·3). The times from exposure to illness were consistent with direct infection from aerosolized viral particles where exposure to vomiting was high.

Cleaning with quaternary ammonium preparations made no impact on the course of the outbreak. However, the outbreak stopped after the school closed for 4 days and was cleaned using chlorine-based agents. This study confirms the importance of vomiting in the transmission of NLV and provides evidence that direct infection with aerosolized viral particles occurs.

### INTRODUCTION

Norwalk-like viruses (NLVs) are a genetically diverse group of highly infectious RNA viruses of the family Caliciviridae [1] which were first reported following an outbreak of gastroenteritis in Norwalk, Ohio in 1972 [2]. NLVs have the ability to cause outbreaks of gastrointestinal infection characterized by vomiting, which is often of sudden onset and projectile, and diarrhoea [3, 4]. NLV infection is the most important cause of non-bacterial gastroenteritis worldwide [5]. The Infectious Intestinal Disease Study in England [6] reported an incidence rate of 12·5 per 1000 patient

years in the community. However, that study did not use polymerase chain reaction (PCR) techniques to detect NLV and will therefore have significantly underestimated the true incidence.

Outbreaks due to contaminated food [7], particularly oysters [8–10], and water [11–13] have been described. Faecal-oral spread of NLV infection is important, but vomitus also represents a major source of infection [14]. The production of viral aerosols and airborne transmission following vomiting have been suggested [15–17]. Widespread environmental contamination may occur [18] and widespread cleaning has been advocated [14]. However, the importance of environmental cleaning in controlling the transmission of NLV has not been proven.

In this report we describe an outbreak of NLV gastroenteritis in a primary school during which

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vomiting occurred in some, but not all classrooms. This resulted in a 'natural experiment' which enabled us to investigate the importance of vomiting as a mode of transmission of NLV, and the likelihood that environmental contamination played a role in the spread of the outbreak.

## THE OUTBREAK

The outbreak occurred in a primary school and nursery attended by children aged 4–11 years. The 15 classrooms were situated in two buildings: one for younger children aged 4–6 years and the other for 7–11 year olds. Children did not move between classrooms for different lessons. Children in the nursery attended for either the morning or afternoon. Morning and afternoon groups were taught in the same room. All children, whether eating school meals or lunches prepared at home ate in the same dining room. The school roll at the onset of the outbreak was 492.

The initial case was first absent from school on 25 June 2001 (day 1) and the local Environmental Health Department was notified on day 11 that a number of pupils had vomiting and diarrhoea. In total 186 pupils had some absence from school with gastrointestinal symptoms. Five members of staff were also ill. The onset of vomiting was often sudden with a number of children vomiting within classrooms. Vomiting also occurred in corridors and lavatories, but not in the dining room. The areas visibly contaminated by vomitus were cleaned immediately.

Extensive environmental cleaning of the school took place on days 13 and 14. Despite advice about their potential lack of efficacy, concerns about the health and safety implications of using chlorine-releasing agents meant that a quaternary ammonium compound was used for this cleaning. Cleaning took place again on days 19 and 20, this time using chlorine-based products. The school closed from days 18–21 inclusive. After the second cleaning operation and closure no further school absences occurred, although three pupils reported symptoms on day 22.

## METHODS

### Epidemiological investigation

Lists of pupils attending each class and sickness absence records were supplied by the school. The number of pupils absent because of gastrointestinal symptoms compatible with NLV infection (diarrhoea, vomiting

or abdominal pain) was recorded. A questionnaire was designed asking about the pupil's date of birth, whether they had vomiting or diarrhoea, the date of onset and cessation of symptoms, the number of adults and children residing in the household, how many of them had been ill and the dates of their illnesses. The parents or guardians of each pupil were asked to complete this on day 22 of the outbreak, and return them to the pupil's class teacher. Stool samples were requested from 15 pupils who had symptoms.

Cases were defined as follows:

- for those pupils who returned a questionnaire: those who reported either diarrhoea or vomiting or both from 25 June to 16 July 2001 inclusive,
- for those pupils who did not return a questionnaire: those who were absent from school with symptoms compatible with NLV infection from 25 June to 16 July 2001 inclusive.

Secondary cases were defined as other household members reporting diarrhoea or vomiting on the questionnaire after a pupil had been ill.

Data from the questionnaire and school absence records were analysed using Microsoft Excel 97 and SPSS for Windows, version 9. Attack rates were calculated by sex, class and age group. Classes were grouped according to the number of vomiting episodes which occurred within the classroom and attack rates calculated for each group. Chi square test for trend was undertaken on these data. Logistic regression was used to calculate odds ratios (OR) with exact 95% confidence intervals (CI) and two-sided *P* values. Odds ratios were adjusted for the child's age and sex, and the school building in which the child's classroom was located.

Comparisons were also made between those classrooms where a pupil vomited less than 24 h after the first case becoming ill in that class and those classes where nobody vomited in the classroom. Logistic regression was used to calculate odds ratios with exact 95% CI and two-sided *P* values. Odds ratios were again adjusted as outlined above.

The date of onset of illness was taken to be the first recorded day on which a pupil was absent from school. For those pupils who were not absent the onset date given in the questionnaire was used. Mean and median times from exposure to illness were calculated for those classes where episodes of vomiting within the classroom occurred on one day only. Medians were compared using the Mann–Whitney *U* test.

Table 1. Summary of school absences and reports of illness on questionnaires

	No diarrhoea or vomiting reported on questionnaire	Diarrhoea or vomiting or both reported on questionnaire	No response to questionnaire	Total
Absent from school with diarrhoea, vomiting or abdominal pain	48	60	78	186
Not absent from school with diarrhoea, vomiting or abdominal pain	166	15	125	306
Total	214	75	203	492

Cells shaded grey indicate those pupils classified as 'ill' by the case definition used.

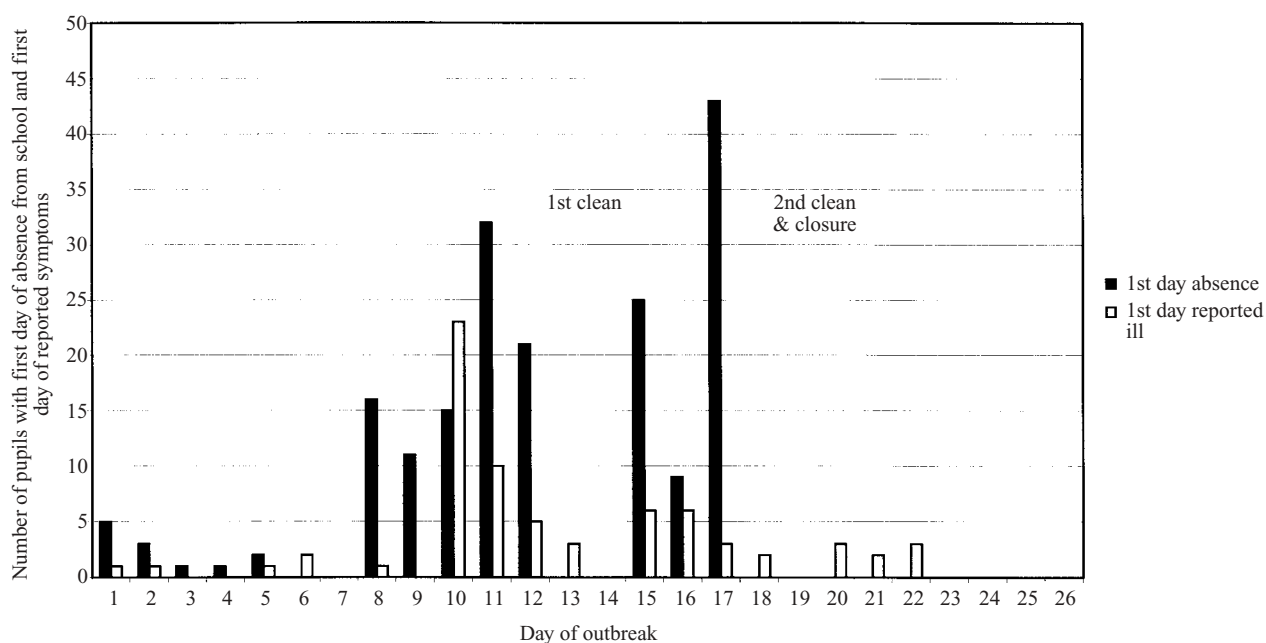


Fig. 1. Epidemic curve for whole school.

Secondary household attack rates were calculated from the questionnaire data.

### Laboratory investigation

Faecal specimens were sent to Bristol Public Health Laboratory and analysed by solid phase immune electron microscopy (SPIEM), an in-house antigen capture enzyme immuno assay (EIA) [19] specific for Lordsdale strain, and reverse transcription-polymerase chain reaction (RT-PCR) using broadly reactive inosine containing primers targeting a region of the polymerase gene [15]. Further PCR

investigations used alternative combinations of broadly reactive PCR primers (YGDD [20] and Ni [21]).

Nucleotide sequencing of purified amplicons was carried out using the Beckman Dye Termination Cycle Sequencing Kit and analysed on a CEQ2000XL DNA Analysis System running software version 4.3.9. PCR products were sequenced in both directions using the same primers used to amplify the DNA.

Sequences were edited using the BioEdit [22] software package and alignments and phylogenetic trees were generated using the ClustalX [23] and TreeView [24] software packages.

Table 2. Attack rates by sex, age and class

	Attack rate (%)	95% CI (%)
Sex		
Male	79/260 (30.4)	25.1–36.2
Female	72/230 (31.3)	25.7–37.6
Age group		
3 to <4 yr	6/30 (20.0)	9.5–37.3
4 to <5 yr	15/58 (25.9)	16.3–38.4
5 to <6 yr	26/58 (44.8)	32.7–57.5
6 to <7 yr	23/44 (52.3)	37.9–66.2
7 to <8 yr	23/59 (39.0)	27.6–51.7
8 to <9 yr	17/60 (28.3)	18.5–40.8
9 to <10 yr	20/74 (27.0)	18.2–38.1
10 to <11 yr	14/63 (22.2)	13.7–33.9
11 to <12 yr	7/42 (16.7)	8.3–30.6
Class		
1	19/86 (22.1)	14.6–31.9
2	15/36 (41.7)	27.1–57.8
3	6/25 (24.0)	11.5–43.4
4	14/29 (48.3)	31.4–65.6
5	5/32 (15.6)	6.9–31.8
6	3/27 (11.1)	3.9–28.1
7	8/28 (28.6)	15.3–47.1
8	6/33 (18.2)	8.6–34.4
9	13/36 (36.1)	22.5–52.4
10	17/24 (70.8)	50.8–85.1
11	12/28 (42.9)	26.5–60.9
12	10/29 (34.5)	19.9–52.7
13	3/30 (10.0)	3.5–25.6
14	10/29 (34.5)	19.9–52.7
15	12/20 (60.0)	38.7–78.1

## RESULTS

Completed questionnaires were returned for 289 pupils (response rate 59%). In total 153 pupils met our case definition (Table 1), giving an attack rate of 31%. The epidemic curve for the outbreak is shown in Figure 1. The mean duration of illness was 2.3 days and the median 2 days (range <1 to 13 days).

The attack rates by age (Table 2) show an inverted 'U' shaped pattern, with the highest rate in children aged between 6 and 7 years old.

### Exposure to vomiting in classroom

Fifteen children vomited within ten classrooms. Table 3 shows attack rates for classes grouped by the number of episodes of vomiting occurring within the relevant classrooms. There was a significant trend, with attack rates increasing with the number of vomiting episodes to which pupils were exposed ( $\chi^2$  for linear trend = 37.8,  $P < 0.00001$ ). The results of

logistic regression analyses are also shown in Table 3. These demonstrate increased odds ratios when vomiting occurred within the classroom, with an adjusted odds ratio of 14.6 for those classrooms where three episodes of vomiting occurred.

In four classrooms (classrooms 2, 7, 9 and 10 – Figs 2–5) the vomiting occurred in the classroom less than 24 h after the first case in that class. In one of these classes (class 9 – Fig. 4) a second episode of vomiting occurred 9 days later. These four classrooms were taken as those in which the children in the class were exposed to another child vomiting. The unadjusted odds ratio for having been exposed to another child vomiting in the classroom was 3.9 (Table 4). When adjusted for the child's age and sex, and the building in which the classroom was situated these odds ratios remained similar at 4.1.

In three classrooms vomiting episodes occurred on one day only. In two of these (classrooms 2 and 7 – Figs 2, 3) only one child vomited. In the third (classroom 10 – Fig. 5) three episodes of vomiting occurred on the same day. In classroom 10 the median time from exposure to onset of illness was 1.0 day and the mean 1.5 days (standard deviation (s.d.) 1.1 days). In classroom 2 the median time was 14.0 days (mean 11.1, s.d. 5.4 days) and in classroom 7 it was 15.0 days (mean 12.6, s.d. 3.3 days). The median time from exposure to onset of illness was significantly shorter in the class where three pupils vomited on the same day than in the other two classrooms where vomiting occurred only once (1.0 vs. 14.0 days; Mann–Whitney  $U$  test = 17.0,  $P < 0.001$ ).

### Household secondary attack rates

Two hundred and fifty-six people (143 adults and 113 other children) were reported to be living in the households of the 75 children who reported diarrhoea and/or vomiting on the questionnaire. Of these, 24 adults (attack rate 17%) and 52 children (attack rate 46%) became ill after the initial case in the household, giving an overall attack rate of 30%. Each ill school child produced, on average, 1.01 household secondary cases.

### Laboratory investigations

Seven faecal specimens were analysed in the laboratory for viral agents of gastroenteritis. One specimen was reactive in the EIA. The initial RT–PCR using inosine containing primers targeting the region of the

Table 3. *Attack rates and odds ratios by number of vomiting episodes within classrooms*

Number of vomiting episodes within classroom	Attack rate (%)	Unadjusted OR (95% CI)	<i>P</i>	Adjusted OR (95% CI)†	<i>P</i>
0*	23/147 (15.6)	1.0	<0.001	1.0	<0.001
1	78/236 (33.1)	2.7 (1.6–4.5)	<0.001	5.1 (2.2–11.6)	<0.001
2	23/65 (35.4)	3.0 (1.5–5.8)	0.002	3.9 (1.8–8.6)	0.001
3	29/44 (65.9)	10.4 (4.8–22.4)	<0.001	14.6 (5.9–36.5)	<0.001

\* Baseline variable.

† Adjusted for sex, age and building in which classroom was situated.

Table 4. *Attack rates and odds ratios for exposure to another child vomiting in classroom*

	Attack rate (%)	Unadjusted OR (95% CI)	<i>P</i>	Adjusted OR (95% CI)*	<i>P</i>
Exposed	53/125 (42.4)	3.9 (2.2–7.0)	<0.001	4.1 (1.8–9.3)	0.001
Not exposed	23/146 (15.8)				

\* Adjusted for sex, age and building in which classroom was situated.

polymerase gene were all negative. The use of alternative combinations of broadly reactive PCR primers (YGDD and Ni) led to detection of viral RNA in five of the clinical samples (including the EIA positive specimen). Nucleotide sequence analysis revealed a single strain of NLV with identical nucleotide sequence amongst the cases within the outbreak.

Phylogenetic analysis revealed that this strain was closely related to viruses in the Melksham virus cluster (Fig. 6).

## DISCUSSION

This study provides convincing evidence that vomiting is important in the transmission of NLV infection. However, there are certain limitations. Two sources of case ascertainment were used: school sickness absence records and a questionnaire to parents. Both sources have shortcomings. The questionnaire responses may be affected by recall bias, particularly with regard to dates of illness, and non-responders who have been symptomatic will not be recorded. School sickness absences will fail to record those children who were ill at weekends and those who were symptomatic but did not take time off school. It would appear that some children were absent from school with reported symptoms compatible with NLV

infection, but reported no vomiting or diarrhoea when completing the questionnaires. Thus, there were some discrepancies between the two sources of information. This would suggest that either some parents kept their children off school at the height of the outbreak as a precaution, or that they failed to recall the illness correctly on the questionnaire.

The clinical features of the illness suggested NLV infection and the outbreak met three of the four epidemiological criteria proposed by Kaplan et al. [25], namely that all stools submitted were negative for bacterial pathogens, the mean or median duration of illness was 12–60 h and that vomiting occurred in at least 50% of cases. Data to meet the fourth criterion, that the mean or median incubation period was 24–48 h could not be obtained.

The clinical and epidemiological features of this outbreak were supported by the identification of NLV by PCR in 5 of 7 stool samples analysed. The presence of a single strain of virus confirmed a common source of infection. The failure to detect the virus with a standard set of PCR primers indicated that the viral genome had mutated at the primer binding site such that the primer could no longer bind. The Lordsdale specific EIA detected a virus in a single specimen, showing that the outbreak strain is antigenically related to Lordsdale virus. However, phylogenetic

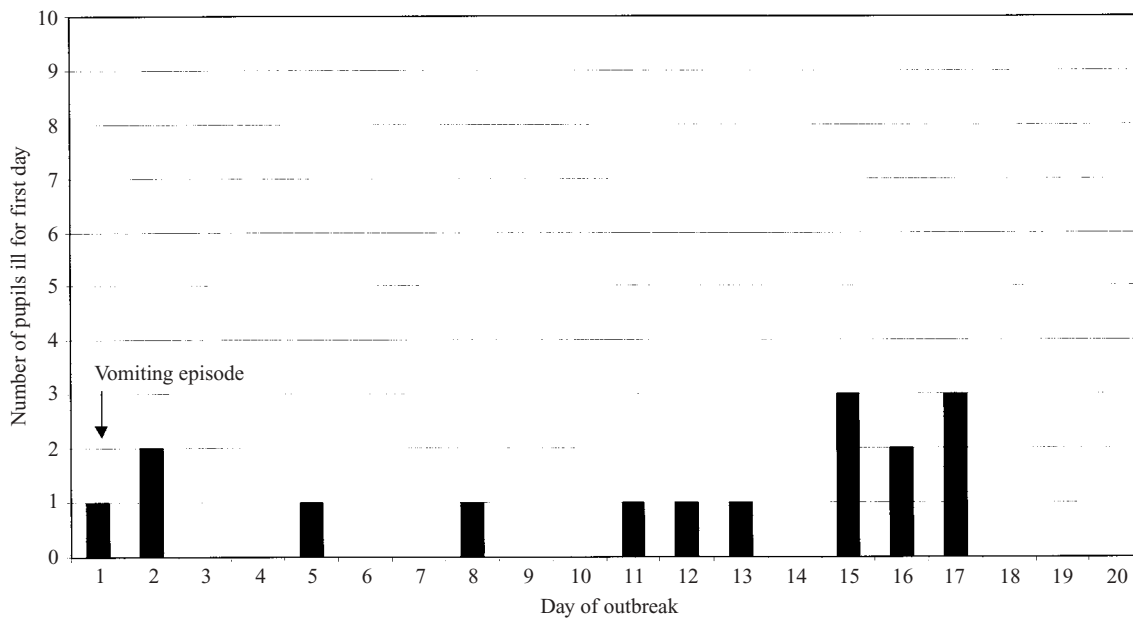


Fig. 2. Epidemic curve for class 2.

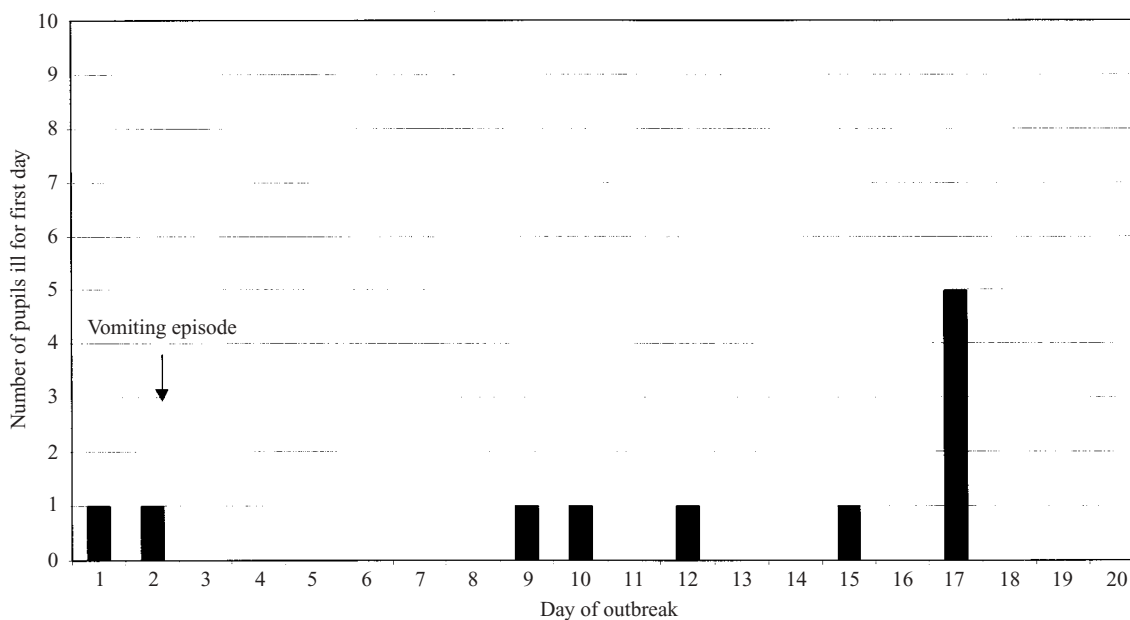


Fig. 3. Epidemic curve for class 7.

analysis revealed that the outbreak strain was more closely related to viruses in the Melksham virus cluster, rather than Lordsdale-like strains (Fig. 6). Unfortunately, the primers used in this PCR generate a smaller amplicon than the standard PCR, and so contain less sequence information. The phylogenetic trees based upon this smaller region were less reliable in accurately describing genetic relationships of known strains from the genetic database. Consequently, interpretation of the phylogenetic tree should be treated with caution.

Attack rates in males and females were similar, but varied by age with a peak in children aged 6–7 years. Younger and older children had lower attack rates. It may be that the attack rates were lower in younger children because they were more intensively supervised when hand washing, and in older children because they have developed better standards of hygiene.

In the classrooms where vomiting occurred, pupils were significantly more likely to be ill than pupils in classrooms where no vomiting occurred. There was

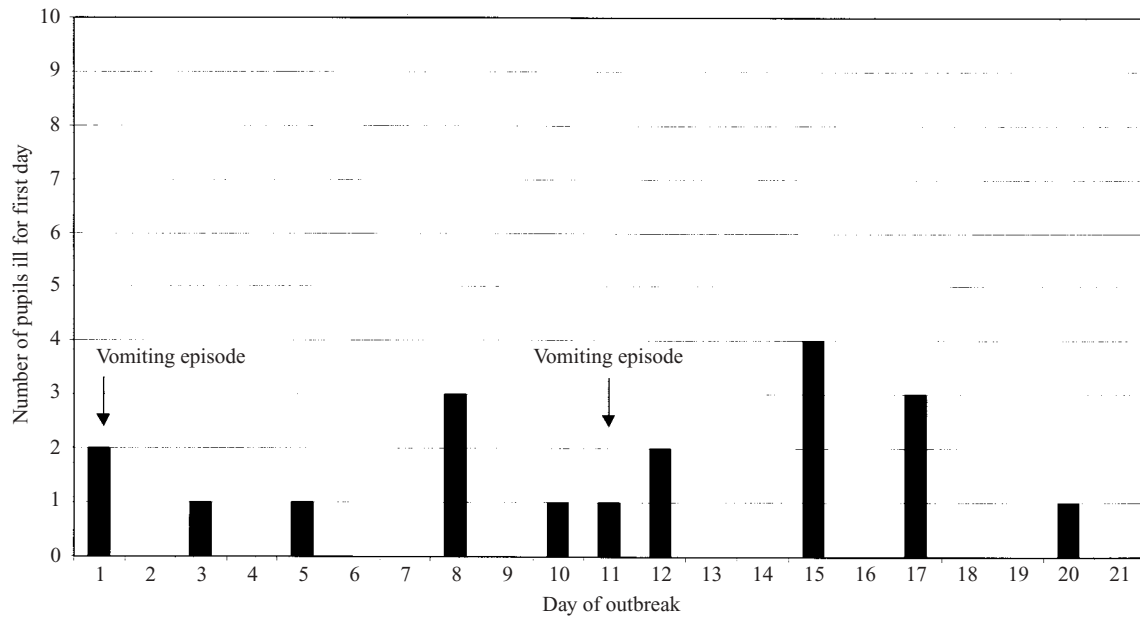


Fig. 4. Epidemic curve for class 9.

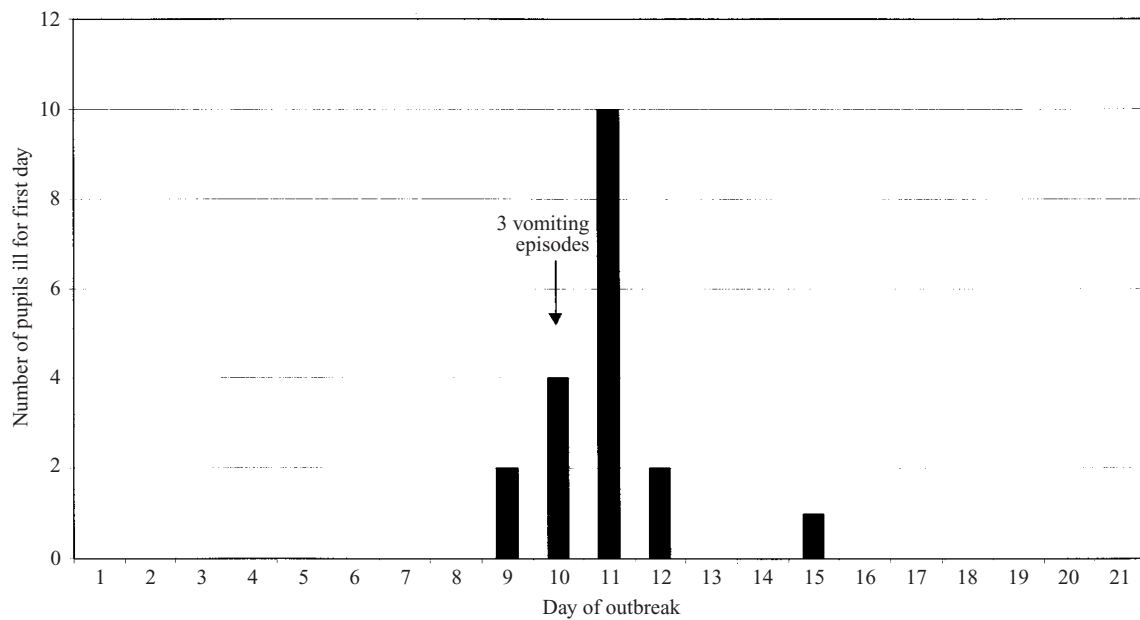
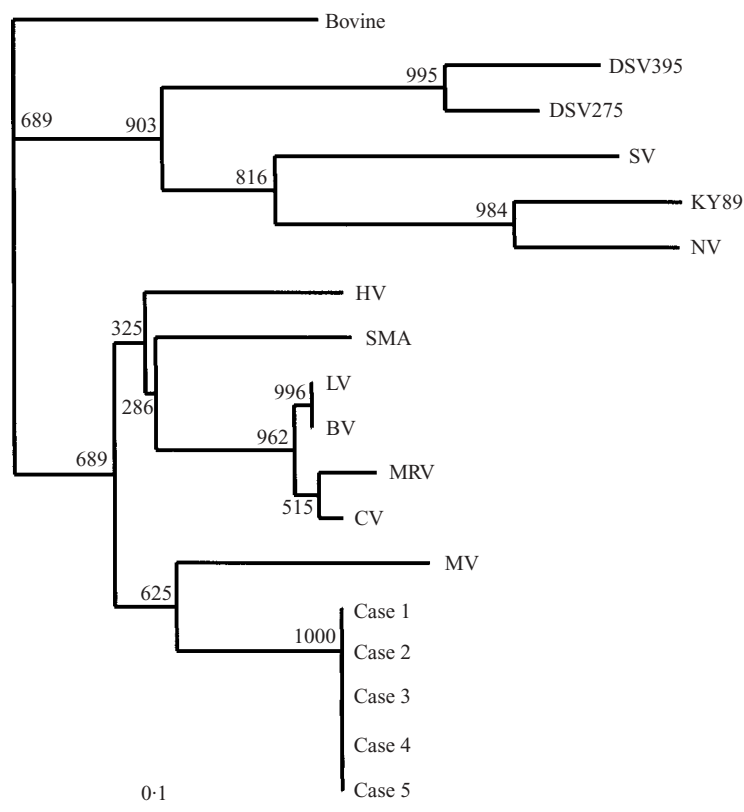


Fig. 5. Epidemic curve for class 10.

a highly significant trend. Significantly high odds ratios persisted after adjustment for possible confounding factors. However, these analyses take no account of temporal relationships. It may be argued that increased numbers of ill children in a class make it more likely that someone will vomit within the classroom, rather than exposure to vomiting causing the high attack rates.

In an attempt to overcome the issue of the time sequence, comparisons were made between those classrooms where vomiting occurred within 24 h of

the first case in that class and those where no vomiting at all occurred during class. The significantly high odds ratios obtained make it clear that the illnesses followed the exposure. Taken together these analyses support the hypothesis that exposure to vomiting is a significant risk factor for development of infection with NLV. As each area where a child vomited was cleaned immediately after vomiting had occurred, spread must have been by airborne transmission directly to susceptible individuals, or via contamination of the wider environment.



**Fig. 6.** Dendrogram showing the genetic relationships of the polymerase region amplicons of NLV strains identified among pupils and staff in this outbreak, with the equivalent region of known strains from the GenBank database. Accession numbers for strains include: SV: Southampton (L07418); KY89: KY-89/89/JPN (L23828); NV: Norwalk (M87661); DSV395: Desert Shield 395 (U04469); DSV275: Desert Shield 275 (U04538); TV24: Toronto (U02030); MV: Melksham (X81879); SMA: Snow Mountain (L23831); HV: Hawaii (U07611); CV: Camberwell (U46500); MRV: Maryland (U07612); LV: Lordsdale (X86557); BV: Bristol (X76716). The tree was rooted using the equivalent region of the bovine strain of NLV 'Jena' (AJ011099). The length of the abscissa to the connecting node is proportional to genetic distance between sequences. The scale bar represents nucleotide substitutions per site. Numbers at the nodes of the tree indicate bootstrap values from 1000 replicates.

In one classroom where three episodes of vomiting occurred on the same day, the median time from exposure to illness was consistent with a point source of infection and suggests that aerosolized viral particles were inhaled and subsequently swallowed. This is a similar pattern to that previously described when an episode of vomiting occurred during a meal [15]. However, in the current outbreak, contamination of food cannot be implicated. In addition, any increased risk of eating food in the presence of aerosolized virus can be excluded.

The incubation period for NLV is widely accepted as being 24–48 h from exposure [4]. Therefore cases in the two classrooms with extended times from exposure to onset could not be due to direct infection. Transmission must have occurred by person-to-person spread or through exposure to a contaminated environment. Given that opportunities for

person-to-person spread are likely to be similar in children within the same age group and that the differences in attack rates at different levels of exposure persist after adjustment for age, sex and the building in which the child's classroom was situated, it is possible that environmental contamination could have accounted for the increased attack rates in classrooms where vomiting had occurred. As NLV cannot be cultured, the length of time that it can survive in the environment is difficult to assess. However, a closely related cultivable virus, feline calicivirus, has been shown to survive for between 21 and 28 days in a dried state at room temperature [26]. If the survival of NLV is similar, this could account for the extended time between a vomiting incident and onset of illness in some classrooms.

During the outbreak widespread environmental cleaning was undertaken on two occasions. Because of



concerns about the potential adverse effects of chlorine-releasing agents, the first of these used quaternary ammonium products and anionic surface cleaners. This cleaning intervention clearly made no impact on the course of the outbreak. Although it has been reported that a combination of quaternary ammonium compounds and sodium carbonate at twice the recommended concentration was effective in removing feline calicivirus from surfaces [27], other researchers have found that quaternary ammonium compounds at twice the manufacturer's recommended concentration failed to inactivate feline calicivirus [26]. The experience during this outbreak supports the view that cleaning with quaternary ammonium compounds is unlikely to be effective at inactivating NLV.

Following the second round of cleaning which involved the use of chlorine-based products three pupils reported an onset of illness on the first day the school reopened but none of these stayed away from school. These cases almost certainly occurred from person-to-person transmission in the community whilst the school was closed. This second cleaning was undertaken when the school was closed for 4 days and it is not possible to ascertain whether the dramatic decrease in cases when the school reopened was due to the closure reducing opportunities for person-to-person spread or the removal of environmental contamination by cleaning.

It could be argued that the outbreak would have burnt itself out at this stage without cleaning or closure. Against this possibility is the fact that reported attack rates in other outbreaks have been greater (42–62% [28–31]) and a study of human volunteers using sensitive diagnostic techniques suggested that around 70% of young adults are susceptible to NLV infection [32]. This implies that there would have been a pool of susceptible individuals in the school to allow the outbreak to continue.

The level of secondary household cases in this study (30%) is similar to that reported by Taylor et al. (32%) [33]. The basic reproductive number greater than one demonstrates the ability of NLV infection to spread in the community, even when awareness of the problem is high. Simple counts of those affected within an institution where an outbreak occurs will significantly underestimate the burden of the disease. When outbreaks occur in institutions it is important to reinforce advice about hygiene not only in the institution at the centre of the outbreak, but also with other people who come into contact with it.

Outbreaks of NLV infection within institutions cause considerable disruption and have significant economic implications [5]. This study has produced firm evidence that vomiting is important in the transmission of the disease. It also produced further evidence to suggest that aerosolization of virus particles can lead to direct infection. Transmission via environmental contamination may also account for some of the increased risk following exposure to vomiting episodes. Further research is needed to elucidate the optimal control measures for institutional outbreaks of NLV, but this study supports laboratory evidence that cleaning with quaternary ammonium products is unlikely to alter the course of an outbreak.

## ACKNOWLEDGEMENTS

The authors would like to thank the staff of the school involved in this outbreak for their help with collection of data for this study. We would also like to thank Drs David Bullock and Selina Hoque and the staff of the microbiology laboratories of the Southern Derbyshire Acute Hospitals Trust for undertaking bacteriological examination of the stool samples. We also thank Dr Keith Neal for comments on previous drafts of this paper.

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