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A large-scale gastroenteritis outbreak associated with *Norovirus* in nursing homes

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SUMMARY

An increase in gastroenteritis outbreaks due to *Norovirus* has been reported worldwide. We investigated a large-scale outbreak affecting 246 residents and 33 staff members in six nursing homes in the Tel-Aviv district, Israel, during 3 weeks in 2002. Person-to-person spread was noticed in all nursing homes. The spread of disease could not be attributed to social interactions. Among the elderly residents, the hospitalization rate was 10·2% and the case-fatality rate was 2·0%. Bacteriological cultures were negative. Overall, 7 out of 15 stool specimens were positive for *Norovirus* by RT–PCR. All were sequenced and found to be 90% identical. The characteristics of this outbreak and the RT–PCR results suggest that illness was caused by *Norovirus*. Due to the high case-fatality rate of *Norovirus* gastroenteritis, there should be a high index of suspicion when encountering a gastroenteritis outbreak among the elderly. This will enable prompt action to stop the spread of illness.

INTRODUCTION

The burden of infectious gastrointestinal illnesses has been studied extensively. Although acute gastroenteritis incidence rates are lower in adults compared to children, it has been recognized that old age is a risk factor for hospitalization and death attributable to gastroenteritis [1, 2]. In addition, people living in nursing homes are at a higher risk for death from gastroenteritis than those not living in nursing homes [3]. A recent study in nursing homes in Maryland showed that 80% of gastroenteritis outbreaks were due to *Norovirus* (a member of the Caliciviridae family) [4].

The Tel-Aviv district is the second largest district in Israel, and contains 54 nursing homes for the elderly. Between 10 April and 9 May 2002, an outbreak of acute gastroenteritis occurred in six different nursing homes in the district. Of the six affected nursing homes, five were located within a 1·5 km radius.

An epidemiological investigation of each outbreak was initiated.

METHODS

Upon receiving the initial notification from each nursing home, the health services of the Tel-Aviv district conducted an epidemiological investigation. These residential facilities for the elderly have nursing

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departments, departments for cognitive impaired (mainly demented) individuals, and sheltered accommodation for independent individuals. Residents are admitted to nursing departments if they require long-term medical supervision and suffer from disabilities that confine them to bed or wheelchair, or suffer from incontinence. A case was defined as any person residing or working at one of these homes who, according to the nurses' reports, developed either vomiting or diarrhoea, with or without fever, no later than 48 h from the last case. Diarrhoea was defined as at least three loose stools per day. Information was collected on the patients' symptoms, date of onset of symptoms, laboratory tests, hospitalization and complications (including death). For all hospitalized patients, discharge summaries were reviewed.

We also investigated any possible connections between the homes that could explain the occurrence of outbreaks in six places concurrently.

Environmental

The environmental health investigation included inspection of the institution's sanitary conditions and food storage, handling and preparation. We collected 82 samples of foods prepared within 48 h of the onset of the outbreaks, which were served at different meals, and four samples of tap water. These were sent for bacterial analysis to the central public health laboratory.

Laboratory investigation

Norovirus identification

Faecal and vomitus specimens ($n=23$) were obtained and stored at 4 °C until RNA extraction. Specimens were suspended in 800 μl sterile distilled water and RNA was extracted by using EZ-RNA isolation kit (Biological Industries, Beit Haemek, Israel). RNA was denaturated and precipitated in phenol/chloroform solution. The purified RNA was resuspended in H_2O and used in an RT–PCR reaction.

The assay to detect *Norovirus* RNA was a modified form of that used by Ando et al. [5]. Two sets of specific primers were designed (Steve Monroe, Center for Disease Control and prevention – CDC), to give an expected product length of 213 bp (MON431: 5′-tgg acI agR ggI ccY aaY ca-3′; MON432: 5′-tgg acI cgY ggI ccY aaY ca-3′; MON433: 5′-gaa Yct cat cca Yct gaa cat-3′; MON434: 5′-gaa Scg cat cca Rcg gaa cat-3′; I = inosine, R = purimidine, Y = pyrimidine, S = strong). The primers were designed to amplify the 3′-end of region B within ORF1 [6]. One-step RT–PCR assay was preformed with the SuperScript II Reverse Transcriptase (Invitrogen, CA, USA) and AmpliTaq *Taq* polymerase (PerkinElmer, MA, USA). The amplification products were separated on 3% agarose gels and viewed with ChemiImager™ 4000 Low Light Imaging System (Alpha Innotech Corp., San Leandro, CA, USA). The identities of all positive RT–PCR products were confirmed by DNA sequencing.

These, and other specimens, were also tested for routine bacterial pathogens (*Shigella*, *Salmonella*, *Campylobacter*, *E. coli* and in some cases *Rotavirus*).

RESULTS

Epidemiology

A total of 279 people met the case definition criteria, of these 246 were residents and 33 were staff members. The outbreaks were of propagated nature in all six nursing homes, with symptoms recognized first in a resident and subsequently spreading to residents and staff. The outbreaks began in all homes during a 3-week period, with a mean duration of 8 days (range 3–12 days). The outbreaks did not start simultaneously in all six homes, as illustrated in the epidemic curve presented in the Figure. Table 1 summarizes the size of the outbreaks, the attack rates as well as hospitalization and death rates by home. In some nursing homes the attack rate was approximately 50%. The attack rates were higher in nursing wards, compared with independent and cognitive impaired wards (19–73% *vs.* 8–61% respectively, $P=0{\cdot}049$). Table 2 summarizes the prevalence of symptoms according to residential home. Most of the residents suffered from severe vomiting. In uncomplicated patients, the duration of disease was less than 48 h. Twenty-five residents (10·2%) were admitted to hospital, of whom five died of aspiration pneumonia. The crude case-fatality rate was 2·0%, with death occurring in three of the six nursing homes. In these homes the case-fatality rates ranged between 3·6 and 9·3%. All cases of death were among residents of the nursing wards.

Our investigation revealed social interactions between staff members of five of the homes. A nurse and a caregiver worked in home A (where the first outbreak started) and in home B (the second one to be affected). In addition, a worker in home A regularly visited a relative who was a resident in home B. Two

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Table 1. *Numbers of residents affected and attack rates by nursing home and department*

Home	Department	Dates	Residents (*n*)	Affected (*n*)	Attack rate (%)	Hospitalization rate [*n* (%)]	Case fatality [*n* (%)]
A	Total	10–18 Apr.	67	33	49·3	11 (33)	3 (9·1)
	Nursing B		25	9	36·0		
	Nursing C		27	13	48·1		
	Demented		15	11	73·3		
B	Nursing	17–19 Apr.	42	8	19·0	0	0
C	Total	20 Apr.–1 May	405	103	44·9	6 (5·82)	0
	Independent A		94	24	21·3		
	Independent B		119	42	30·3		
	Independent C		99	9	8·1		
	Demented A		28	10	35·7		
	Demented B		28	17	60·7		
	Nursing		37	0	0		
	Unknown			1			
D	Total	22–27 Apr.	59	17	28·8	3 (17·64)	1 (5·88)
	Nursing		29	17	58·6		
	Independent		30	0	0		
E	Total		105	57	54·3	0	0
	Nursing		37	24	64·9		
	Independent		68	33	48·5		
F	Total	1–9 May	88	28	31·8	5 (17·8)	1 (3·6)
	Nursing		17	11	64·7		
	Independent		71	17	23·9		
Total		10 Apr.–9 May	766	246	32·1	25 (10·2)	5 (2·0)

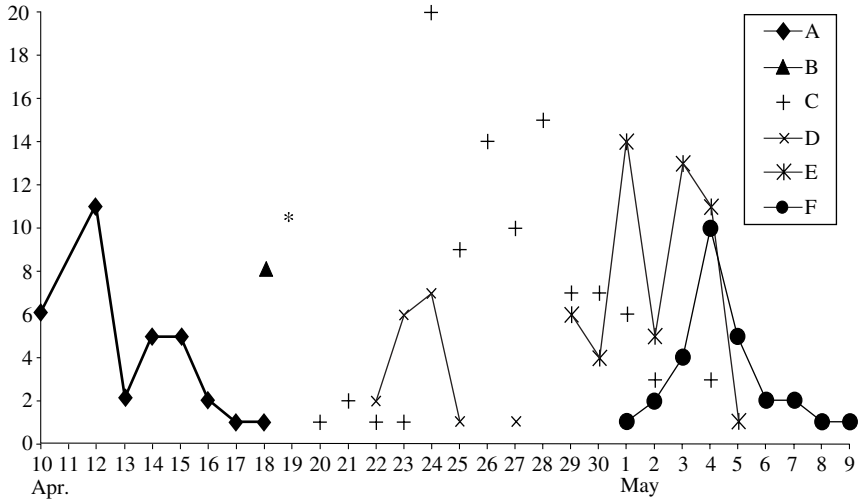

Fig. Cases of gastroenteritis in residents ($n = 246$) by date of onset and nursing home. * The distribution in time of onset of eight cases during the period 17–19 April is not available.

workers from home B also worked in home C. Homes C and E were situated on opposite sides of a park, which was visited by residents of both homes. Staff of homes C and E shared organized transport to and from work. One nurse worked in both home C and home F, and the mother-in-law (who became ill) of a member of the administrative staff in home F was a resident in home C. These workers who had interactions with more than one home did not develop symptoms. We were unable to identify connections

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Table 2. *Distribution of symptoms among 235 nursing-home residents*

Symptom	*n*	%
Nausea and abdominal pain	235	100
Vomiting	190	81·2
Diarrhoea	162	69·2
Fever (>37·5 °C)	26	11·1

between home D and any other home. All homes with the exception of home D were situated within a 1·5 km radius.

Environmental

The sanitary conditions and food-handling routines were found to be satisfactory. All food and water specimens that were tested were negative except for two salad food specimens from nursing home C that were positive for *E. coli*. These positive salads had been prepared approximately 1 week after the first case of gastroenteritis in that particular home.

Laboratory investigation

In total, 23 specimens (8 vomitus and 15 stool) were analysed for *Norovirus*. Only one patient submitted both types of samples. No specimens for analysis were available from nursing home A.

Seven of the 15 (46·7%) stool specimens were positive for *Norovirus*. All specimens of vomitus were negative. The RT–PCR products of the seven positive stool specimens were sequenced. Analysis by rooted dendogram of genetic distances showed very high similarity (90%) between the seven sequences. These products were characterized into a single genetic cluster GII [7, 8]. The closest norovirus, by blast analysis, strain was Hu/NLV/ukB7s2 (accession number AY588030).

All bacteriological cultures and enteropathogen analyses were negative.

DISCUSSION

We have described six gastroenteritis outbreaks in nursing homes in the Tel-Aviv district that affected 276 individuals. These outbreaks occurred within 3 weeks and had similar clinical characteristics, therefore, they could be considered to be one large-scale outbreak. This is the first *Norovirus*-associated outbreak described in Israel, and one of the largest published outbreaks in nursing homes [9, 10]. The clinical presentation was that of prominent vomiting, diarrhoea, fever and short duration of illness. These characteristics, together with the identification of a single strain of *Norovirus* in stool specimens are highly suggestive of a *Norovirus*-associated outbreak.

We were unable to determine how the outbreak spread between homes. Social interactions were found between the affected nursing homes, but the persons suspected of transmitting the disease were asymptomatic. Transmission of the virus by asymptomatic individuals is possible; previous reports have described evidence of *Norovirus* in stool specimens of asymptomatic patients [11–13]. There was no common supplier or caterer for the homes.

The main mode of transmission of *Norovirus* has been described as person-to-person spread, either by the faecal–oral route or by vomiting droplet formation [14]. Other transmission modes include foodborne and waterborne transmission (which cause point-source outbreaks) [15–18], and the suggested airborne transmission [19]. The propagated, rather than point-source, nature of the present outbreak is suggestive of a person-to-person transmission. This is in agreement with Lopman et al., Milazzo et al. and Ward et al. [20–22] who described person-to-person transmission of *Norovirus*-associated outbreaks in institutions and hospitals. Most of the population in this outbreak was bedridden; this suggests that transmission was from staff members to residents, most probably by direct contact. Staff members may have encountered the pathogen either by direct contact with vomitus or faeces or by indirect contact via environmental contamination of surfaces. It is possible that staff members could have remained free of infection due to the protection afforded by gloves and aprons, or they may have had asymptomatic infection.

Interruption of the person-to-person propagation of *Norovirus*-associated illness can be difficult, especially when taking into account the low infective dose (<100 virus particles) and environmental stability of *Norovirus* to chlorination, freezing and heating, thereby enabling environmental contamination. Measures recommended by the CDC to prevent person-to-person spread of disease include frequent and vigorous hand washing with soap and water for more than 10 s, wearing masks while cleaning areas substantially contaminated by faeces or vomitus, cleaning soiled surfaces, handling laundry as little as possible and washing it for the maximum length and temperature cycle

available [23]. The recommendations given to staff members by the district health authorities at the time of the outbreak, in addition to the CDC recommendations, were: discarding gloves and apron after treating each patient, isolating the affected from the unaffected, and using disposable plates and cutlery for the duration of the outbreak. A few days subsequent to our visits there were no new cases. It is not possible to ascertain whether this was due to our intervention or rather the natural course of the outbreak. The mean duration of the outbreak (8 days, range 3–12 days) is similar to that found in another study [20]. There is a need for a controlled trial in order to evaluate measures for preventing the spread of the disease [24].

One of the limitations of our investigation was the small number of stool and vomitus specimens available for RT–PCR analysis of *Norovirus*. The detection rate depends on the quantity of specimens, viral concentration in the specimen, condition of the specimens (inhibitors), and timing of their collection. We further sequenced the positive specimens as suggested previously by Iritany et al. [25]. The very high sequence similarity found between the outbreak samples supports a single source of these outbreaks. It is unclear whether the vomitus samples tested negative for *Norovirus* infection because of technical problems or absence of virus. We recommend a study examining the validity of testing vomitus samples for *Norovirus* by RT–PCR.

In our study, among the residents, the hospitalization rate was 10·2% and case-fatality rate was 2·0%. These rates are higher than the reported *Norovirus*-associated hospitalization rate of 0·33% and case-fatality rate of 0·075% described in England & Wales [20]. In the United States the estimated case-fatality rate attributed to *Norovirus* was less than 0·001% [15]. However, in both studies these were crude rates that described the entire population rather than the elderly population, as in our study. The highest rates of mortality from gastroenteritis in the United States were found among people older than 75 years [26]. Age was found to be the most important risk factor for death subsequent to hospitalization due to gastroenteritis, with an odds ratio of 52·6 (95% CI 37·0–76·9, for age $\geqslant$70 compared with age $<$5 years) [27]. A recent study has identified nursing-home residence as a risk factor for death from gastroenteritis of unknown cause [28]. Therefore, although acute gastroenteritis is generally a self-limiting mild disease, this bedridden population is at increased risk for complications and death.

The surveillance system in Israel is passive, relying on mandatory reporting by physicians and laboratories; therefore, under-reporting of acute gastroenteritis is likely. We do not know whether this outbreak was restricted to nursing homes, or if it was widespread in the community. It is possible that this outbreak was confined to nursing homes; over 50% of the *Norovirus*-associated illnesses in England & Wales were in residential homes for the elderly [20].

The recent reports [29–32] suggesting a rise in *Norovirus* outbreaks might be a reflection of improvements in the diagnosis and increasing awareness of this pathogen. This was the largest reported outbreak in nursing homes in the Tel-Aviv district during the last decade, but also the first in which patients were tested for *Norovirus*. Therefore, we cannot draw any conclusions on trends in *Norovirus*-associated illnesses in Israel.

The high complication and case-fatality rates in the elderly population warrant the development of a sensitive monitoring system for the early detection of a *Norovirus*-associated outbreak. This system should be geared towards preventing the spread of illness among old and debilitated members of the population.

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