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Original Article

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Norovirus acute gastroenteritis amongst US and European travellers to areas of moderate to high risk of travellers' diarrhoea: a prospective cohort study

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Abstract

Background: Acute gastroenteritis (AGE) is a major medical condition for travellers worldwide, particularly travellers to low- and middle-income countries. Norovirus (NoV) is the most common cause of viral AGE in older children and adults, but data on prevalence and impact amongst travellers is limited.

Methods: Prospective, multi-site, observational cohort study conducted 2015–2017, amongst adult international travellers from the US and Europe to areas of moderate to high risk of travel-acquired AGE. Participants provided self-collected pre-travel stool samples and self-reported AGE symptoms whilst travelling. Post-travel stool samples were requested from symptomatic subjects and a sample of asymptomatic travellers within 14 days of return. Samples were tested for NoV by RT-qPCR, genotyped if positive and tested for other common enteric pathogens by Luminex xTAG GPP.

Results: Of the 1109 participants included, 437 (39.4%) developed AGE symptoms resulting in an overall AGE incidence of 24.7 per 100 person-weeks [95% confidence interval (CI): 22.4; 27.1]. In total, 20 NoV-positive AGE cases (5.2% of those tested) were identified at an incidence of 1.1 per 100 person-weeks (95% CI: 0.7; 1.7). NoV-positive samples belonged mostly to genogroup GII (18, 85.7%); None of the 13 samples sequenced belonged to genotype GII.4. Clinical severity of AGE was higher for NoV-positive than for NoV-negative cases (mean modified Vesikari Score 6.8 vs 4.9) with more cases classified as severe or moderate (25% vs 6.8%). In total, 80% of NoV-positive participants (vs 38.9% in NoV-negative) reported at least moderate impact on travel plans.

Conclusions: AGE is a prevalent disease amongst travellers with a small proportion associated with NoV. Post-travel stool sample collection timing might have influenced the low number of NoV cases detected; however, NoV infections resulted in high clinical severity and impact on travel plans. These results may contribute to targeted vaccine development and the design of future studies on NoV epidemiology.

Key words Epidemiology, viral gastroenteritis, incidence, genotype, symptoms, impact, travel plans, vomiting

Background

Travellers' Diarrhoea (TD) remains the most common health problem amongst international travellers to low- and middle-income countries despite the decreased risk brought by improved hygiene conditions.[1,2] Moderate to high-risk regions are mainly found in Africa, Asia, Mexico and parts of South America.[2–4] Studies conducted in the past 20 years estimate that TD affects between 8 and 50% of all international travellers. The wide range can be explained by differences concerning the geographic region, the characteristics of the study population (type of travel, age groups, etc.), the duration of exposure and the study methods.[1,2,5–8] TD is usually characterized by loose/watery stools with or without other symptoms like abdominal cramps, nausea or vomiting whilst travelling or upon return. Affected individuals may present vomiting in the absence of diarrhoea; thus, TD may also be designated as 'travel-acquired acute gastroenteritis (AGE)'. Episodes are usually self-limiting, and post-acute complications are rare and rather associated with specific risk groups.[9,10] However, affected travellers may experience an impact on their trip including changes to planned activities (≈21%), confinement to their accommodation whilst travelling (≈13%) and inpatient hospital stays (≈1%),[8] which may result in substantial health and economic burden for the traveller.[11]

Travel-acquired AGE is caused by a range of different pathogens, including bacteria, parasites and viruses.[4,12–15] Bacteria such as Enterotoxigenic *Escherichia coli* (ETEC) and Enteroaggregative *E. coli* are the most frequently identified pathogens in Latin America, Africa and Southeast Asia (≈30–70% of cases), although *Campylobacter* plays an important role in travellers to Southeast Asia (≈15–30% of cases).[4]

Noroviruses (NoV) are a leading cause of overall AGE worldwide[4,16–18] and the main viral cause of AGE.[12,19] NoV AGE frequently presents as isolated vomiting without diarrhoea.[20] Although incidence rates (IR) amongst travellers are rarely reported, NoV has been estimated to cause 8–27% of all travel-acquired AGE cases, with up to 39% of cases showing co-infection with bacterial pathogens.[5,7,12,15,19,21,22] The frequency of NoV-positive AGE cases varies with travel region and study methods, but studies have reported higher frequencies in Latin America,[22] closer to the return date[5] and in cruise ship outbreaks.[23] NoV AGE contracted during travel has been reported to seed new outbreaks upon return.[23,24]

NoV phylogeny and nomenclature has been evolving rapidly with ten genogroups and 49 capsid genotypes currently recognized.[25] Genogroups I (GI) and II (GII) are the main cause of human illness. Genotype GII.4 is the most frequently identified cause of NoV AGE[26,27] and can be associated with severe outcomes.[28] Viral genotype, combined with host factors like histo-blood group antigens, has been shown to play a role in susceptibility and duration of immunity to NoV.[29–31]

Though travel-acquired AGE (or TD) has repeatedly been described, information on NoV-specific incidence, clinical presentation, healthcare utilization and post-acute sequelae is still scarce. Several studies suffer from ascertainment bias, either because they are based on self-reporting, because they fail to capture isolated vomiting without diarrhoea or because they focus only on cases that seek healthcare upon return, thus missing those with or without medical care during travel.[3,8,15,32] Furthermore, many previous studies did not distinguish travel-acquired from non-travel-acquired infection nor did they provide information on NoV genotype or co-infections.[13,33]

A detailed description of the travel-acquired NoV AGE will help inform prophylactic and therapeutic agents and prevent and manage this infection. This prospective study aimed to identify the overall burden of AGE, particularly that caused by NoV, amongst travellers leaving from North America and Europe to areas with moderate to high risk of travel-acquired AGE. The primary objective was to estimate the incidence of AGE due to travel-acquired NoV. As secondary objectives, we aimed to: (i) assess the incidence according to host risk factors, travel behaviours and region of travel; (ii) examine NoV genotype distribution and estimate the proportion of co-infections and (iii) describe the clinical course of illness and the impact on travel plans.

Methods

A detailed protocol describing the rationale, objectives and full methodology has been published.[34] The present study followed this protocol unless otherwise specified. All participants provided signed informed consent, and the study was approved by the respective ethical review board at each study site.

Study design, setting and participants

This was a prospective, multi-site, observational cohort study amongst adult (≥18 years) travellers from the US and Europe to areas of moderate to high risk of travel-acquired AGE. Five study sites were established: three in Europe (one in Germany and two in Switzerland) and two in the US. Participants travelling for a period between 3 and 15 days were recruited between March 2015 and July 2017 amongst residents from the US, Switzerland and Germany planning foreign travel to international destinations other than the US, Canada, Europe, Australia, New Zealand and Japan. Individuals were also included if travelling by cruise ship including an international port stop in a country other than the country of origin. Participants were excluded if travelling to areas of high Ebola transmission.

Baseline and follow-up procedures

Data collection included a baseline survey and a travel diary to be filled daily whilst travelling and on days 2, 7 and 14 post-travel to capture behavioural and self-reported health data. Self-collected pre-travel stool samples were requested from all participants in

the week prior to travel onset. Post-travel stool samples were requested from all participants who experienced AGE symptoms during travel and from a subset of asymptomatic travellers within 14 days of return. AGE was defined as the self-reported onset of: (i) any vomiting; OR (ii) three or more loose or watery stools OR (iii) two or more loose or watery stools plus symptoms (fever, abdominal cramps, urgency or nausea); within 24 h.

Laboratory methods

Laboratory methods are detailed in the published protocol.[34] NoV genogroup testing (GI and GII) was performed for all post-travel stool samples and for paired pre-travel samples of the positive subjects. Briefly, viral ribonucleic acid (RNA) was extracted using QIAGEN QIAamp Viral RNA Mini Kit and subjected to the NoV Duplex Real-time Reverse Transcription Polymerase Chain Reaction (RT-PCR) Assay (TaqMan), using the Applied Biosystems 7500 Fast DX Real-time PCR system (Thermo Fisher Scientific, USA). Tests with a cycle threshold ≤40 were considered positive for NoV. NoV-positive samples were sequenced centrally at the Naval Health Research Centre, San Diego, California, USA, to determine the genotype. Sequencing was performed using a 'dual-typing' method based on the partial open reading frame (ORF) 1 polymerase gene sequence (region B) and ORF2 partial capsid gene sequence (region C), in separate RT-PCR reactions for GI and GII NoV. This method combines previously published region B[35] and region C[36] RT-PCR assays. The size of the PCR products was 579 bp for GI and 570 bp for GII. Cases were classified as travel-acquired NoV AGE when the post-travel sample was NoV-positive and the pre-travel sample was negative, or when both were positive but with different NoV genotypes. A random sample (≈50%) of all post-travel samples obtained from travellers who experienced travel-acquired AGE was tested via Luminex xTAG GPP (luminexcorp.com) for multiple enteric pathogens at designated study sites (Emory University, Atlanta, GA, USA for samples collected from participants originating from the US or the LMU Munich, Germany for samples collected from participants originating from Germany or Switzerland).

Sample size and data analysis

Sample size calculations, analysis and definitions are described in detail in the protocol.[34] A target sample size of 2152 participants was deemed necessary across the two regions (the US and Europe), assuming that 70% would be followed-up successfully.

Statistical analyses included the computation of descriptive statistics and IR using the total time at risk of that population (in weeks) as denominator. Clinical severity of symptoms was described using a modified Vesikari Score (MVS)[37] and categorized as mild (≤8), moderate (9–10), or severe (≥11).

Results

Participant characteristics

From March 2015 through July 2017, 1368 participants were enrolled across all sites, corresponding to 64% of the target sample size. Of the total enrolled, 1109 (80.0%) were finally included in the analysis, with 513 participants travelling from Europe and 596 from the US. Of the total participants enrolled, exclusions were mostly due to missing diary entries (200/1368, 14.4%) and/or stool samples (130/1368, 9.4%) and/or travel duration outside of that defined in the inclusion criteria (79/1368, 5.7%). Data by site and reasons for exclusion detailed in Supplementary Table 1.

The participants' baseline characteristics are summarized in Table 1. Most subjects recruited were female (60.1%) and in the 25–34-year age group (33.9%). In total, >60% of the study population was under 45 years. Only 27.5% participants reported any pre-existing health conditions, with lactose intolerance and irritable bowel syndrome (IBS) being reported most frequently. The most frequent blood types were O (19.7%) and A (16.8%) across all groups. Travel duration was ≥7 days for 78.4% of participants. Most participants travelled to Latin America and the Caribbean (44.7%) and 17% of all participants travelled by cruise ship. The characteristics of participants who experienced AGE during travel was similar at baseline to those who did not experience AGE.

AGE and laboratory results

Of all 1109 study participants, 437 (39.4%) developed AGE symptoms during travel (Table 2). Of all participants, 646 (58.3%), provided a post-travel sample, including 388 AGE cases. Of the 646 participants providing a post-travel sample, 21 (3.3%) had a NoV-positive result. This corresponds to 20 (5.2%) AGE cases and one asymptomatic case. All NoV-positive cases had a valid, NoV-negative pre-travel result. Thus, all the detected NoV infections were travel acquired. Almost all of the NoV-positive travellers (20/21, 95%) detected were symptomatic. Most NoV-positive samples belonged to genogroup GII (18, 85.7%); 13 samples had valid sequencing results and 12 different genotypes were detected (Table 2). The only genotype identified in two samples was GII.P17-GII.17B. Notably, none of the samples sequenced belonged to genotype GII.4. Although only half of the total samples of AGE cases (49%) had their sample collected within 8 days of symptom onset, we identified no relationship between the RT-qPCR Ct values and the time of sample collection (Supplementary Table 2).

Valid Luminex results were obtained for 228 (35.6%) stool samples (Table 2; note that, according to the protocol, only a subset of all samples was tested) and positive results were identified in 36 samples (Supplementary Table 3). The pathogen most frequently identified was ETEC (18 AGE cases and two non-AGE cases). Amongst NoV-positive travellers, there was only one co-infection identified via the Luminex panel test which occurred in a symptomatic traveller who also tested positive for ETEC.

Incidence of AGE and NoV AGE amongst travellers

For a total observation period of 1769 person-weeks, the overall incidence of travel-acquired AGE was estimated at 24.7 per 100 person-weeks [95% confidence interval (CI): 22.4; 27.1] and the incidence of travel-acquired AGE due to NoV was estimated at 1.1 per 100 person-weeks (95% CI: 0.7; 1.7)

Table 1. Participant characteristics at baseline, overall and by AGE/NoV status

	All subjects	AGE cases			No AGE
		All AGE	NoV+	NoV–	
N	1109	437	20	324	672
Demographics					
Age at travel start, median (range)	35 (18–87)	32 (18–87)	27 (20–66)	32 (19–77)	37 (18–86)
Age group distribution, *n* (%)					
18–24	176 (15.9)	79 (18.1)	7 (35.0)	59 (18.2)	97 (14.4)
25–34	376 (33.9)	170 (38.9)	8 (40.0)	127 (39.2)	206 (30.7)
35–44	203 (18.3)	79 (18.1)	3 (15.0)	57 (17.6)	124 (18.5)
45–54	146 (13.2)	63 (14.4)	0 (0.0)	50 (15.4)	83 (12.4)
55–64	156 (14.1)	33 (7.6)	1 (5.0)	22 (6.8)	123 (18.3)
≥65	52 (4.7)	13 (3.0)	1 (5.0)	9 (2.8)	39 (5.8)
Sex, *n* (%)					
Female	667 (60.1)	266 (60.9)	9 (45.0)	202 (62.3)	401 (59.7)
Male	442 (39.9)	171 (39.1)	11 (55.0)	122 (37.7)	271 (40.3)
Region of origin, n (%)					
US	596 (53.7)	213 (48.7)	7 (35.0)	156 (48.1)	383 (57.0)
Europe	513 (46.3)	224 (51.3)	13 (65.0)	168 (51.9)	289 (43.0)
Germany	336 (30.3)	154 (35.2)	9 (45.0)	113 (34.9)	182 (27.1)
Switzerland	177 (16.0)	70 (16.0)	4 (20.0)	55 (17.0)	107 (15.9)
Medical history					
Underlying health conditions, *n* (%)					
None	804 (72.5)	318 (72.8)	17 (85.0)	235 (72.5)	486 (72.3)
Any underlying health condition	305 (27.5)	119 (27.2)	3 (15.0)	89 (27.5)	186 (27.7)
Solicited underlying health conditions or immunosuppressed defined by subjects[a]	125 (11.3)	48 (11.0)	1 (5.0)	37 (11.4)	77 (11.5)
Lactose intolerance	82 (7.4)	30 (6.9)	1 (5.0)	24 (7.4)	52 (7.7)
IBS	30 (2.7)	14 (3.2)	0 (0.0)	11 (3.4)	16 (2.4)
Cancer of the bowel	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Crohn's disease	3 (0.3)	1 (0.2)	0 (0.0)	1 (0.3)	2 (0.3)
Ulcerative colitis	2 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
Cystic fibrosis	1 (0.1)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Coeliac disease	5 (0.5)	3 (0.7)	0 (0.0)	3 (0.9)	2 (0.3)
Surgical bowel obstruction	3 (0.3)	1 (0.2)	0 (0.0)	1 (0.3)	2 (0.3)
Current pregnancy	3 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.3)
Human immunodeficiency virus (HIV), acquired immunodeficiency syndrome or cancer	3 (0.3)	1 (0.2)	0 (0.0)	1 (0.3)	2 (0.3)
Blood type, *n* (%)					
A	186 (16.8)	64 (14.6)	2 (10.0)	48 (14.8)	122 (18.2)
B	84 (7.6)	28 (6.4)	2 (10.0)	21 (6.5)	56 (8.3)
AB	27 (2.4)	7 (1.6)	0 (0.0)	6 (1.9)	20 (3.0)
O	219 (19.7)	89 (20.4)	6 (30.0)	61 (18.8)	130 (19.3)
Not known	593 (53.5)	249 (57.0)	10 (50.0)	188 (58.0)	344 (51.2)
Travel					
Travel mode, *n* (%)					
Cruise	189 (17.0)	60 (13.7)	1 (5.0)	42 (13.0)	129 (19.2)
Non-cruise	920 (83.0)	377 (86.3)	19 (95.0)	282 (87.0)	543 (80.8)
Broad region of travel with a stay ≥3 days, *n* (%)[a]					
Latin America and the Caribbean	496 (44.7)	189 (43.2)	5 (25.0)	138 (42.6)	307 (45.7)
Asia	269 (24.3)	116 (26.5)	8 (40.0)	86 (26.5)	153 (22.8)
Africa	248 (22.4)	105 (24.0)	7 (35.0)	77 (23.8)	143 (21.3)
North America/Europe/Australia/New Zealand/Japan	52 (4.7)	23 (5.3)	0 (0.0)	15 (4.6)	29 (4.3)
Other	5 (0.5)	2 (0.5)	0 (0.0)	2 (0.6)	3 (0.4)
Multiple regions	25 (2.3)	14 (3.2)	0 (0.0)	8 (2.5)	11 (1.6)
Traveller type, *n* (%)[a]					
Tourism	807 (72.8)	320 (73.2)	13 (65.0)	233 (71.9)	487 (72.5)

(*Continued*)

Table 1. Continued

	All subjects	AGE cases			No AGE
		All AGE	NoV+	NoV–	
N	1109	437	20	324	672
Humanitarian	101 (9.1)	43 (9.8)	5 (25.0)	28 (8.6)	58 (8.6)
Educational	64 (5.8)	28 (6.4)	3 (15.0)	24 (7.4)	36 (5.4)
Visit family/friends	112 (10.1)	39 (8.9)	3 (15.0)	29 (9.0)	73 (10.9)
Business	99 (8.9)	38 (8.7)	2 (10.0)	25 (7.7)	61 (9.1)
Other	30 (2.7)	14 (3.2)	1 (5.0)	11 (3.4)	16 (2.4)
Travel duration (as per baseline form), *n* (%)					
3–7 days	240 (21.6)	65 (14.9)	0 (0.0)	51 (15.7)	175 (26.0)
8–15 days	869 (78.4)	372 (85.1)	20 (100.0)	273 (84.3)	497 (74.0)
Travel in prior 3 months, *n* (%)					
Yes	157 (14.2)	61 (14.0)	4 (20.0)	42 (13.0)	96 (14.3)
No	952 (85.8)	376 (86.0)	16 (80.0)	282 (87.0)	576 (85.7)
Month of travel start, *n* (%)					
January	50 (4.5)	15 (3.4)	1 (5.0)	12 (3.7)	35 (5.2)
February	78 (7.0)	29 (6.6)	1 (5.0)	22 (6.8)	49 (7.3)
March	162 (14.6)	79 (18.1)	2 (10.0)	60 (18.5)	83 (12.4)
April	102 (9.2)	37 (8.5)	2 (10.0)	30 (9.3)	65 (9.7)
May	122 (11.0)	42 (9.6)	1 (5.0)	30 (9.3)	80 (11.9)
June	99 (8.9)	43 (9.8)	5 (25.0)	29 (9.0)	56 (8.3)
July	93 (8.4)	40 (9.2)	2 (10.0)	30 (9.3)	53 (7.9)
August	99 (8.9)	33 (7.6)	1 (5.0)	20 (6.2)	66 (9.8)
September	73 (6.6)	33 (7.6)	1 (5.0)	21 (6.5)	40 (6.0)
October	82 (7.4)	30 (6.9)	0 (0.0)	25 (7.7)	52 (7.7)
November	87 (7.8)	35 (8.0)	4 (20.0)	26 (8.0)	52 (7.7)
December	62 (5.6)	21 (4.8)	0 (0.0)	19 (5.9)	41 (6.1)

[a]Subjects may be in more than one group. Percentages are based on the number of subjects (N in each column).

(Table 3). An exploratory analysis identified no significant associations between subgroups and incidence at a significance level of $P = 0.05$ (Supplementary Table 4).

Only one asymptomatic NoV infection was detected in the study, yielding an overall incidence of 0.1 per 100 person-weeks. This case was a 56-year-old male from the US with no underlying disease who acquired the infection during travel to Latin America and the Caribbean region.

Clinical severity and impact on travel plans

AGE symptoms were similar in NoV-positive and NoV-negative participants although generally NoV-positive participants reported symptoms more frequently (Table 4). The most common symptoms amongst travellers with AGE were loose or watery stools (94.1%), abdominal gurgling and/or bloating (87.4%) and a sense of urgency for bowel movement (80.5%). All 20 NoV-positive AGE cases reported a general feeling of being unwell, and 65% of NoV-positive AGE cases reported vomiting compared to 21.6% of NoV-negative AGE cases. The median duration of protocol-defined AGE was also higher in NoV-positive than in NoV-negative AGE episodes (3 vs 2 days). The mean MVS for AGE severity was 6.8 for NoV-positive cases compared to 4.9 for NoV-negative cases and more cases were classified as severe (15%) or moderate (10%) in the NoV-positive group than in the NoV-negative group (2.8 and 4.0%, respectively). However, none of the NoV-positive AGE cases sought medical care. Of note, several participants reported gastrointestinal symptoms but did not meet our definition of an AGE case (321 reported non-specific gastrointestinal symptoms, 179 reported any loose or watery stools and five reported vomiting) and/or sought medical care (19 outpatient visits and one hospitalization).

The impact of AGE illness on travel plans was higher for NoV-positive than for NoV-negative cases across all the indicators analysed (Table 4). Of the 20 NoV-positive AGE cases, 16 (80.0%, vs 38.9% in NoV-negative) reported at least moderate impact and 11 (55%, vs 18.5% in NoV-negative) reported severe impact including being bed-ridden or missing activities.

Discussion

This study prospectively followed more than one thousand travellers from the US and Europe to areas of moderate to high risk of contracting travel-acquired AGE. Over one-third of the participants reported AGE, but amongst them, only 20 NoV cases were detected. Our IR of 1.1 NoV AGE cases per 100 person-weeks is nearly ten times higher than values estimated for NoV disease in the community amongst adults in the UK and the US (reported values are on the order of ≈0.1 cases per 100 person-weeks depending on the age group[18,38,39]) corroborating the evidence that travel plays a role in NoV infection. This difference may be even more significant if we consider that this study of travellers includes a different age distribution of individuals than studies

Table 2. NoV results in post- and pre-travel samples and interpretation regarding timing of NoV infection

	All subjects	AGE cases	No AGE
Number of subjects (*N*)	1109	437	672
Subjects providing a post-travel sample, *n* (%[a])	646 (58.3)	388 (88.8)	258 (38.4)
NoV result			
Positive post-travel sample, *n* (%[b])	21 (3.3)	20 (5.2)	1 (0.4)
Genogroup sequencing (%[c])			
GII	18 (85.7)	17 (85.0)	1 (100.0)
GI	3 (14.3)	3 (15.0)	0 (0.0)
Genotype sequencing (%[c])			
GI.1	1 (4.8)	1 (5.0)	0 (0.0)
GI.7B	1 (4.8)	1 (5.0)	0 (0.0)
GI.9	1 (4.8)	1 (5.0)	0 (0.0)
GII.13	1 (4.8)	1 (5.0)	0 (0.0)
GII.17B	1 (4.8)	1 (5.0)	0 (0.0)
GII.3B	1 (4.8)	1 (5.0)	0 (0.0)
GII.6A	1 (4.8)	1 (5.0)	0 (0.0)
GII.6B	1 (4.8)	1 (5.0)	0 (0.0)
GII.P12-GII.2	1 (4.8)	1 (5.0)	0 (0.0)
GII.P17-GII.17A	1 (4.8)	1 (5.0)	0 (0.0)
GII.P17-GII.17B	2 (9.5)	2 (10.0)	0 (0.0)
GII.Pc-GII.1	1 (4.8)	1 (5.0)	0 (0.0)
Fail	8 (38.1)	7 (35.0)	1 (100.0)
Positive pre-travel sample, *n* (%[b])	0 (0.0)	0 (0.0)	0 (0.0)
Negative pre-travel sample (travel-acquired NoV), *n* (%[b])	21 (3.3)	20 (5.2)	1 (0.4)
Negative post-travel sample (no NoV infection), *n* (%[b])	546 (84.5)	324 (83.5)	222 (86.0)
Missing post-travel sample (unknown NoV infection status), *n* (%[b])	79 (12.2)	44 (11.3)	35 (13.6)
Valid Luminex results, *n* (%[b])	228 (35.63)	205 (52.8)	23 (8.9)
Positive samples, *n* (%[d])			
NoV GI/GII	4 (1.8)	4 (2.0)	0 (0.0)
Any pathogen other than NoV	32 (14.0)	30 (14.6)	2 (8.7)
ETEC	20 (8.8)	18 (8.8)	2 (8.7)
Adenovirus 40/41	3 (1.3)	3 (1.5)	0 (0.0)
Campylobacter jejuni	3 (1.3)	3 (1.5)	0 (0.0)
Clostridium difficile, toxin A/B	2 (0.9)	2 (1.0)	0 (0.0)
Salmonella spp.	2 (0.9)	2 (1.0)	0 (0.0)
Shigella spp.	2 (0.9)	2 (1.0)	0 (0.0)
STEC	2 (0.9)	2 (1.0)	0 (0.0)
E. coli 0157	1 (0.4)	1 (0.5)	0 (0.0)
Other pathogens tested (*Vibrio cholerae*, *Yersinia enterocolitica*, Rotavirus A, *Giardia lamblia*, *Cryptosporidium* spp. and *Entamoeba histolytica*)	0 (0.0)	0 (0.0)	0 (0.0)

Percentages are based on:
[a]total number of subjects (N). [b]subjects providing post-travel sample. [c]NoV-positive subjects. [d]Samples with valid Luminex results; STEC: Shiga-toxin-producing *E. coli.*

in the community, with fewer elderly individuals and children. In fact, though the burden of NoV disease is known to be higher in children and elderly individuals,[40] NoV cases in this study were not particularly high in the elderly population. Whilst NoV infection resulted in travel disruption, the absence of episodes seeking medical care is likely reflective of the relatively small number of infections amongst a predominately healthy adult study population aged under 65.

Although NoV prevalence tends to be higher in community than in hospital settings,[18,41] the lack of NoV-positive individuals seeking medical care suggests that hospital- or outpatient-based studies may underestimate NoV incidence. However, the proportion of travel-acquired NoV AGE in this study was 5.2% and, therefore, on the lower range of proportions reported in the literature (depending on the region of travel, reported values ranged from ≈3 to 30% but more frequently between 10 and 20%[5,12,15,19,21,32,42,43]). This wide range in the reported prevalence may be partly explained by the lack of standardized NoV case definitions and clinical severity measures, which also hinders adequate comparisons. Although we did not observe an association between RT-qPCR Ct values and the time between symptom onset and sample collection ($R^2 = 0.1667$), we cannot exclude that our detection rate might have been higher if the stool samples had been collected closer to symptom onset. NoV was mostly detected as a single pathogen (only one case had a co-infection with ETEC). This adds to the evidence supporting the role of NoV as a causative pathogen in travel-acquired AGE.[4]

Travel-acquired AGE had relevant severity and impact on travel plans. Clinical severity and impact for NoV-positive participants were higher than for NoV-negative AGE participants

Table 3. IR of AGE illness acquired during international travel

IR, cases per 100 person-weeks (95% CI)	AGE	NoV+ AGE
All subjects	24.7 (22.4; 27.1)	1.1 (0.7; 1.7)
Age group		
18–64 years	25.2 (22.8; 27.7)	1.1 (0.7; 1.8)
≥65 years	14.7 (7.8; 25.1)	1.1 (0; 6.3)
Gender		
Female	25.6 (22.6; 28.9)	0.9 (0.4; 1.6)
Male	23.3 (19.9; 27.0)	1.5 (0.7; 2.7)
Region of origin		
US	26.6 (23.1; 30.4)	0.9 (0.4; 1.8)
Europe	23.1 (20.1; 26.3)	1.3 (0.7; 2.3)
Underlying health conditions		
None	24.9 (22.3; 27.8)	1.3 (0.8; 2.1)
Any	23.9 (19.8; 28.6)	0.6 (0.1; 1.8)
Solicited underlying health conditions or immunosuppressed (cancer, HIV+)	24.9 (18.4; 33.0)	0.5 (0; 2.9)
Travel mode		
Cruise	23.6 (18.0; 30.4)	0.4 (0; 2.2)
Non-cruise	24.8 (22.4; 27.5)	1.3 (0.8; 2.0)
Region of travel with a stay ≥3 days[a]		
Asia	23.0 (19.0; 27.6)	1.6 (0.7; 3.1)
Latin America and the Caribbean	27.2 (23.5; 31.4)	0.7 (0.2; 1.7)
Africa	23.3 (19.1; 28.2)	1.5 (0.6; 3.2)
North America/Europe/Australia/New Zealand/Japan	27.8 (17.6; 41.7)	0 (0; 4.5)
Other	20.0 (2.4; 72.2)	0 (0; 36.9)
Multiple regions	34.1 (18.7; 57.3)	0 (0; 9.0)
Traveller type		
Tourism	24.5 (21.9; 27.3)	1.0 (0.5; 1.7)
Visit family/friends	20.8 (14.8; 28.5)	1.6 (0.3; 4.7)
Business	25.2 (17.8; 34.5)	1.3 (0.2; 4.8)
Humanitarian/educational/other	27.2 (21.5; 34.0)	2.5 (1.0; 5.1)
Travel duration (as per baseline form)		
3–7 days	28.1 (21.7; 35.9)	0 (0; 1.6)
8–15 days	24.1 (21.8; 26.7)	1.3 (0.8; 2.0)
Blood type		
A	20.3 (15.7; 26.0)	0.6 (0.1; 2.3)
B	22.2 (14.7; 32.1)	1.6 (0.2; 5.7)
AB	16.7 (6.7; 34.5)	0 (0; 8.8)
O	25.7 (20.6; 31.6)	1.7 (0.6; 3.8)
Not known	26.4 (23.2; 29.9)	1.1 (0.5; 1.9)
Travel in prior 3 months		
Yes	23.8 (18.2; 30.5)	1.6 (0.4; 4.0)
No	24.8 (22.4; 27.4)	1.1 (0.6; 1.7)

[a]Subjects may be in more than one group.

in all parameters analysed. These findings are consistent with a recent study on military travellers.[43] The small number of NoV-positive participants in our study did not allow statistical comparisons, and it may also explain the absence of hospitalizations or outpatient medical visits in this group.

The NoV genotypes identified in 13 samples were diverse, which may be explained by the different locations of origin of the infection. However, the genotype most frequently found in community-based surveillance worldwide, GII.4,[26,27,44] was not identified in this study. This suggests that travellers can pick up endemic strains in the local population from both symptomatic as well as asymptomatic individuals—the latter group are unlikely to contribute information about circulating genotypes in the population. This might also result from the small number of NoV-positive samples tested. We expect that the total number of cases and the impact of NoV AGE on travel plans could have been even higher if this genotype was detected, given that infections with this genotype are frequently symptomatic and associated with severe outcomes.[28] The heterogeneity of genotypes found in the present study and reported by others,[45–47] as well as changes in dominance of circulating genotypes through time (recent data point to a decline in dominance of GII.4 genotypes[48]), will complicate the selection of vaccine candidates in NoV immunoprophylaxis trials designed to prevent AGE.

Thanks to the prospective design, this study allowed us to estimate the incidence of overall AGE and NoV AGE during travel and upon return, both in general and according to participant characteristics, travel destination and other variables. By obtaining pre-travel and post-travel stool samples, we were able to distinguish travel-acquired infections from potential pre-existing infections. Furthermore, we captured AGE episodes presenting with vomiting without diarrhoea, an approach that

Table 4. Clinical severity and impact on travel plans

	AGE	NoV+ AGE	NoV- AGE
N	437	20	324
Clinical symptoms, *n* (%)			
Protocol-defined AGE	437 (100.0)	20 (100.0)	324 (100.0)
Any non-specific (feeling unwell)/gastrointestinal/stomach-related symptoms	437 (100.0)	20 (100.0)	324 (100.0)
Any loose or watery stools	411 (94.1)	19 (95.0)	305 (94.1)
Abdominal gurgling and/or bloating	382 (87.4)	17 (85.0)	285 (88.0)
Sense of urgency for bowel movement	352 (80.5)	16 (80.0)	266 (82.1)
General feeling of being unwell	346 (79.2)	20 (100.0)	256 (79.0)
Abdominal cramps, pain and/or discomfort	294 (67.3)	16 (80.0)	221 (68.2)
Three or more loose stools within 24 h	265 (60.6)	14 (70.0)	205 (63.3)
Loss of appetite	249 (57.0)	17 (85.0)	187 (57.7)
Nausea	247 (56.5)	14 (70.0)	181 (55.9)
Two loose stools within 24 h plus additional symptoms	243 (55.6)	10 (50.0)	180 (55.6)
Dehydration	150 (34.3)	9 (45.0)	117 (36.1)
Muscle aches/myalgia	117 (26.8)	8 (40.0)	85 (26.2)
Any vomiting	97 (22.2)	13 (65.0)	70 (21.6)
Fever/feverish (hotter than normal)	92 (21.1)	11 (55.0)	68 (21.0)
Chills	91 (20.8)	9 (45.0)	67 (20.7)
High fever (≥103°F or ≥ 39.4°C; if taken axillary ≥102°F or ≥ 38.84°C)	1 (0.2)	0 (0.0)	1 (0.3)
Any other symptom	79 (18.1)	0 (0.0)	62 (19.1)
Number of days with protocol-defined AGE, median (range)	2 (1/11)	3 (1/8)	2 (1/11)
Medical care from travel day 2 to post-travel day 14, *n* (%)			
Outpatient visits	26/432 (6.0)	0 (0.0)	19/321 (5.9)
Hospitalizations	3/433 (0.7)	0 (0.0)	3/322 (0.9)
MVS			
Mean (±SD)	4.8 (±2.3)	6.8 (±2.9)	4.9 (±2.2)
Median (range)	4 (2/14)	6 (3/12)	4 (2/14)
Categories, *n* (%)			
Mild	406 (92.9)	15 (75.0)	302 (93.2)
Moderate	16 (3.7)	2 (10.0)	13 (4.0)
Severe	15 (3.4)	3 (15.0)	9 (2.8)
Impact on travel plans, *n* (%)			
At least moderate AGE based on impact on travel plans and incapacitation (change in any activities or any level of incapacitation)	170 (38.9)	16 (80.0)	126 (38.9)
Severe AGE based on impact on travel plans and incapacitation (bed-ridden or missing any activities)	86 (19.7)	11 (55.0)	60 (18.5)
Change of planned activities			
Symptom(s) caused change in planned activities	146 (33.4)	14 (70.0)	108 (33.3)
Symptom(s) caused missing planned activities	82 (18.8)	11 (55.0)	56 (17.3)
Incapacitation			
Bed-ridden part of the day	69/436 (15.8)	9 (45.0)	49/323 (15.2)
Restricted to lodging but mobile throughout day	63/436 (14.4)	3 (15.0)	47/323 (14.6)
Bed-ridden all day (except medical care)	20/436 (4.6)	6 (30.0)	13/323 (4.0)

[a]Subjects may be in more than one group. Percentages are based on the number of subjects (N in each column).

we could only identify in a recent study by Ashbaugh *et al.*[19] Nevertheless, this study also had limitations; the number of participants enrolled did not reach the target sample size even if we consider that this assumed 30% of loss-to-follow-up, and not all enrolled were finally included in the analyses. This is likely due to a lack of interest or reminder of actively filling diaries during a period of leisure and without the support or reminder of study staff; furthermore, participants might have been unwilling to provide stool samples (post-travel samples were missing for 49 out of 437 AGE cases). Though we have not compared included and excluded participants at baseline, a drop-out for these reasons is not expected to bias the results. The number of NoV-positive samples was also very small, which limited the explanatory power of analyses. Additionally, IR and proportions should be interpreted with caution, particularly in the groups with fewer observations, and information on outbreaks in cruise ships was not collected. Thus, the burden of travel-acquired NoV AGE in underrepresented populations (elderly and children), and the impact of outbreaks may be underestimated. AGE status was based on self-reported symptoms which may be biassed by

different self-assessments of the participants, and NoV infections occurring and resolving during travel could have been missed. Time at risk (for incidence calculations) might be slightly overestimated since subjects experiencing AGE on the first day of travel and person-time after AGE onset were not excluded. Only in a subset of stool samples, a limited number of predefined other pathogens was assessed. Whilst NoVs are an important cause of AGE in travellers and non-travellers, bacterial pathogens like ETEC can cause vomiting as well as watery diarrhoea[49] and resemble NoV infection as seen in our study group. Finally, the study was conducted amongst travellers to moderate- and high-risk areas of TD, and the conclusions may not be generalizable to all travellers.

The incidence data obtained here are relevant to guide future studies and the development of drugs to prevent or treat travel-acquired AGE, including potential vaccines against NoV infection and other enteric pathogens.[27,50,51] Future studies should aim for larger sample sizes to validate the observations regarding NoV-AGE severity and need for medical care, and to determine the most relevant NoV genotypes in travel-acquired AGE, whilst considering protocol modifications based on lessons learned from this study. Furthermore, changes in travel habits caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) epidemic might have a relevant impact on the extent and genotype of circulating NoV[52] since early 2020, which highlights the need for additional studies.

Conferences where this paper has been presented

Study protocol was published in: Estimating the incidence of NoV AGE amongst US and European international travellers to areas of moderate to high risk of traveller's diarrhoea: a prospective cohort study protocol. Lindsay L, DuPont HL, Moe CL, Alberer M, Hatz C, Kirby AE, Wu HM, Verstraeten T, Steffen R. BMC Infectious Diseases 2018, 18:605. https://doi.org/10.1186/s12879–018–3461-6.

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Project background/rationale: Acute NoV Gastroenteritis amongst International Travellers: A Collaborative Epidemiologic Project. Nothdurft HD, DuPont HL, Hatz C, Kirby AE, Lindsay L, Moe CL, Steffen R, Wu HM. Northern European Conference on Travel Medicine 2014.

Preliminary results: Acute NoV Gastroenteritis Amongst International Travellers: Results From a Prospective Cohort Study. Moe CL, M Alberer, C Hatz, AE Kirby, L Lindsay, HD Nothdurft, R Steffen, T Verstraeten, HM Wu, HL DuPont. 69th Annual Meeting American Society for Tropical Medicine and Hygiene. 15–19 November 2020.

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