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Incidence of Norovirus-Associated Acute Gastroenteritis across Age Groups in a Peruvian Andean Community

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Abstract

Norovirus is the leading cause of acute gastroenteritis (AGE) globally. Few longitudinal studies have assessed norovirus-associated AGE incidence across age groups in community settings in Latin America. During April 2015–April 2019, active surveillance for AGE among community members of all ages was conducted through household visits two to three times per week in San Jeronimo, Cusco, Peru. An asymptomatic control household was selected for every fifth AGE case. Stool specimens were collected from AGE cases, asymptomatic household members, and control household members, and they were tested for norovirus using real-time reverse

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transcriptase polymerase chain reaction. Data on illness characteristics were collected from AGE cases during a 15-day follow-up period. Annual means of 247 households and 1,555 participants were enrolled during each April–March surveillance year, accounting for 4,176 person-years (PY) of observation. Of 1,099 AGE events reported, 1,014 stool specimens were tested, and 186 (18%) were norovirus positive. Norovirus AGE incidence was 4.4/100 PY (95% CI: 3.9–5.1); incidence was highest among those younger than 2 years old (60.9/100 PY; 95% CI: 46.8–79.4). Among 672 stool specimens from asymptomatic controls, 56 (8%) tested positive for norovirus. Odds of norovirus detection were significantly higher among cases compared with controls (odds ratio: 2.2; 95% CI: 1.6–3.1). Age-stratified norovirus incidence in this periurban community aligns with previously published estimates and was highest among those younger than 2 years old. Establishing baseline norovirus incidence in specific communities is crucial to identify target populations and assess effectiveness of future interventions, such as vaccines.

INTRODUCTION

Improvements in sanitation and access to safe water and health care have reduced morbidity and mortality because of enteric disease in recent decades; however, diarrhea remains a leading cause of death globally, with approximately 1.53 million deaths attributed to diarrheal disease in 2019.¹ Norovirus is the leading cause of acute gastroenteritis (AGE), and it causes approximately 18% of AGE cases among all ages worldwide.² Noroviruses are classified into 10 genogroups and 49 genotypes, with genogroup I (GI) and genogroup II (GII) responsible for most human illness.³

In some South American countries, after the introduction of the rotavirus vaccine in the 2000s and subsequent high rates of vaccine uptake, norovirus surpassed rotavirus to become the leading cause of viral AGE among children.^{4,5} In Peru, epidemiological studies on norovirus in the past decade have primarily focused on young children, and they have demonstrated high rates of norovirus, accounting for 23–35% of AGE cases among children younger than 24 months of age.^{6,7} However, there have been few longitudinal community-based surveillance studies of AGE that describe the epidemiology and circulation of norovirus disease across the population.⁵ Previous estimates of norovirus incidence among all ages have been described in the tropical rainforest region of Puerto Maldonado, with a rate of seven norovirus AGE events per 100 person-years (PY).⁸

Candidate norovirus vaccines are currently in clinical trials.⁹ There is a need to understand the baseline incidence and epidemiology of norovirus in various community settings to inform vaccine implementation policies and assess future vaccine impacts. Here, we present estimates of AGE and norovirus-associated AGE incidence as well as the norovirus genotypes identified from a longitudinal community-based cohort across all ages in the San Jeronimo district of Cusco, which is located in the southern highlands of Peru.

MATERIALS AND METHODS

Study population and design.

Active household surveillance for AGE was conducted as a longitudinal cohort study with a nested case-control design from April 2015 to April 2019. Study methods have been described in detail previously.^{8,10} Households were randomly selected for participation from a publicly available census in a geographic area of approximately 8 km² in San Jeronimo, Cusco Province, Peru. San Jeronimo is a periurban district with an average population of 47,635 during 2015–2019, and it has an arid climate at an elevation of 3,400 m.¹¹ Household enrollment into the cohort was conducted annually, during which households were reconsented and replaced if necessary. During the yearly enrollment process, sociodemographic characteristics were collected, and field staff provided training on recognition of AGE symptoms and stool collection to at least one designated adult household representative. Households could be enrolled if at least 60% of household members (i.e., individuals who had lived in the household for ≥ 2 weeks at the time of enrollment with no plans to change residence in the next 2 months) agreed to participate. Consent to participate in the study was obtained from persons 18 years of age or older. Parents and/or legal guardians provided consent for persons younger than 18 years of age; additionally, assent was obtained from children ages 10–17 years. Household members could join or leave the cohort at any time after initial enrollment and only contributed person-time to surveillance when enrolled. Although the surveillance period was intended to encompass 4 years (April 2015–March 2019), surveillance could not be conducted during October 2016 because of administrative issues; surveillance was thus extended for an additional month through April 2019.

Data collection.

An AGE event was defined as any of the following in a 24-hour period: 1) three or more loose or liquid stools, 2) two or more vomiting episodes, or 3) one or more vomiting episodes and one or more loose or liquid stools. Field staff visited households two to three times weekly to inquire whether any household members were currently experiencing AGE or had experienced symptoms since the previous visit. When an AGE event was reported by a household representative, data on illness onset, symptoms, and risk factors were collected from the case. Materials were provided to collect one stool specimen from the case within 10 days of symptom onset. Cases (i.e., individuals with an AGE event) were then followed up twice a week for 15 days after illness onset, and a follow-up questionnaire was administered at each visit to assess the clinical course of illness, including symptoms, duration, and health care-seeking behaviors.

Household transmission of norovirus.

Index cases were defined as the first household member to experience AGE within a 15-day period. All household members were asked to provide a stool specimen during days 7–17 from the index case's symptom onset and were tested for norovirus. Those who developed AGE symptoms during the index case's follow-up period were treated as AGE cases and asked to provide a stool specimen within the 10 days after their own symptom onset. To assess household transmission, we limited to norovirus-positive index cases. Secondary

cases were defined as household members with norovirus-positive AGE events with onset during the index case's follow-up period. Only household members who provided a stool specimen were included in analysis.

Asymptomatic controls.

Upon identification of every fifth AGE case, a control household that was matched on household size and the number of children younger than 5 years old was randomly selected from the cohort. For selection as a control household, all household members were required to be free of AGE symptoms for 14 days before and 7 days after the matched household's index case symptom onset. One stool specimen was collected from each member of the control household during the period from 7 to 17 days after the matched index case's symptom onset. If any control household members became symptomatic during this period, they became an AGE case, and another control household was matched to the index AGE case if still within the follow-up period. Households could be included as matched controls multiple times throughout the study period.

Stool specimen collection and testing.

Stool specimens were self-collected by participants and refrigerated or stored in a cool, dark place until collected by field staff the same day; then, they were stored at -80°C . Frozen specimens were shipped on dry ice to the U.S. Naval Medical Research Unit SOUTH in Lima, Peru and tested for GI and GII noroviruses by real-time reverse transcription polymerase chain reaction using a 7500 Fast real-time platform.⁸ Norovirus-positive specimens were genotyped at the Centers for Disease Control and Prevention in Atlanta, GA using methods described previously.¹² Specimens with a cycle threshold (Ct) value of <40 were considered to be norovirus positive.

STATISTICAL ANALYSES

Incidences of AGE and norovirus-associated AGE were estimated among cases as a function of person-time in years contributed by the annual at-risk study population. CIs were based on quadratic approximation of the Poisson function. All analyses were performed using Stata v. 14.0 (StataCorp, College Station, TX).

RESULTS

Cohort characteristics.

During April 2015–April 2019, study staff enrolled an annual mean of 247 households (range: 235–273), which included an annual mean of 1,555 participants (range: 1,242–1,667), resulting in 4,176 PY of participation (Table 1). The median duration of household participation was 36 months (interquartile range [IQR]: 22–43 months). Among those enrolled, between 9% and 17% of participants each year were lost to follow-up because of voluntary withdrawal or non-AGE death. The median household size was six household members (range: 4–9). The median age of participants was 29 years (range: younger than 1 month to 99 years).

Incidence of AGE and norovirus AGE.

In total, 1,099 AGE events were reported from 235 households and 566 participants. Specimens were collected from 1,014 AGE events (92%), of which norovirus was detected in 186 specimens (18%). These 186 norovirus-positive AGE events occurred among 149 participants from 98 households. Children younger than 2 years of age experienced 181 AGE events with 55 norovirus-positive specimens (30%). The mean durations of AGE and norovirus AGE symptoms were 3.3 days (SD: 2.3 days) and 3.2 days (SD: 2.2 days), respectively. Among all AGE cases, 202 (18%) sought medical attention (physician/nurse visit or emergency room), and 9 (0.8%) were hospitalized; no AGE-associated deaths were reported. Among norovirus-positive AGE cases, 40 (22%) sought medical attention, and 3 (2%) were hospitalized.

Overall AGE incidence was 26.3 events/100 PY (95% CI: 24.8–27.9). AGE incidence across the four surveillance years (April 2015–April 2019) ranged from 24.6 events/100 PY during April 2016–March 2017 to 27.3 events/100 PY during April 2015–March 2016 (Table 2). AGE incidence was highest among participants younger than 2 years of age at 200.6 events/100 PY (95% CI: 173.4–232.0) and lowest among adults ages 18–64 years at 17.1/100 PY (95% CI: 15.5–18.8).

Norovirus-associated AGE incidence was 4.4 events/100 PY (95% CI: 3.9–5.1). Children younger than 2 years of age had the highest norovirus AGE incidence at 60.9 events/100 PY (95% CI: 46.8–79.4); adults ages 18–64 years had the lowest norovirus AGE incidence at 2.6 events/100 PY (95% CI: 2.0–3.3), despite having the highest absolute number of events ($n = 432$ AGE events). By surveillance year, norovirus AGE incidence ranged from 3.5 events/100 PY during April 2015–March 2016 to 5.3 events/100 PY during April 2017–March 2018 (Table 2). No distinct seasonal pattern was observed for norovirus detections (Figure 1).

Infection by genogroup and genotype.

Among the 186 norovirus-positive AGE specimens, 155 specimens (83%) tested positive for norovirus GII, 27 specimens (15%) tested positive for norovirus GI, and 4 specimens (2%) tested positive for both norovirus GI and GII. We did not detect a significant difference in the distribution of GI and GII viruses by age group. Of 127 norovirus-positive AGE specimens available for typing, 96 (76%) could be dual typed successfully, resulting in 19 different genotypes. Four genotypes (GII.27[PNA9], GII.1[P16], GII.6[P7], and GII.4 Sydney[P31]) were detected in 55 (57%) of the typed AGE specimens (Figure 2).

Of 56 norovirus-positive asymptomatic control specimens, 11 (20%) tested positive for norovirus GI, and 45 (80%) tested positive for GII. Among 24 typed control specimens, 13 different dual types were identified, with GII.6[P7], GII.27[PNA9], GII.1[P16], GII.4 Sydney[P31], and G1.3[P3] totaling to 67% of typed specimens (Figure 2). Norovirus GII.4 viruses accounted for 20% (19/96) of norovirus AGE events and 21% (5/24) of norovirus detections among controls. GII.27 viruses were found in 20% ($n = 19$) of specimens from norovirus AGE events and in 13% (3/24) of norovirus-positive control specimens.

Multiple (two to four) norovirus AGE events were experienced by 29 cohort participants, accounting for 66 total events. The median time to recurrence was 7.7 months (IQR: 5.0–16.2 months). Eleven individuals (38%) had both GI and GII norovirus events, whereas the remainder had only GII norovirus detected. Children younger than 5 years of age experienced the most recurring events, with 42 norovirus AGE events among 18 individuals in this age group. Specimens were typed from nine participants who experienced two or more norovirus AGE events. Six of these nine experienced repeat norovirus GII infections with differing genotypes. Only one individual tested positive for the same genotype (GII.27[PNA9]) from more than one AGE event. This individual had two detections with symptom onset dates occurring 31 days apart; however, *Giardia lamblia* was also detected during the second event.

Household transmission.

Among the 186 norovirus events, 166 met the index case definition. In total, 473 household contacts provided symptom data and a stool specimen during the index case's follow-up period. The majority (68%; $n = 323$) of household contacts were negative for norovirus, including 12 AGE cases. Around one third (32%; $n = 152$) of household contacts tested positive for norovirus, including 20 (13%) with AGE symptoms (i.e., secondary cases) and 132 (87%) who were asymptomatic. The secondary attack rate for symptomatic norovirus AGE was 4%. Among norovirus AGE events, the median time from index case illness onset to secondary case onset was 2 days (IQR: 1–7 days; $n = 20$).

There were 67 household contacts with genotyping data for whom the index case also had available genotyping data, including six symptomatic secondary cases. Of these, 51 (76%) were infected with the same genotype as the index case, including all six secondary cases. The four genotypes most commonly identified among cases accounted for 42 of these 51 secondary infections (82%): GII.1[P16] ($n = 12$), GII.6[P7] ($n = 11$), GII.4 Sydney[P31] ($n = 10$), and GII.27[PNA9] ($n = 9$). Symptomatic secondary cases were caused by GII.27[PNA9] ($n = 3$), GII.6[P7] ($n = 2$), and GII.12[P33] ($n = 1$). We did not observe statistically significant differences in household transmission of norovirus by the age of the index cases or the age of the household contacts.

Control specimens.

Stool specimens were provided by 516 AGE-free participants in 128 matched control households. Control households had a median of four (range: three to six) household members. The age distribution among controls was similar to that of the cohort overall. The shortest duration between AGE onset as prior norovirus case and specimen collection as a control was 144 days. Among 672 stool specimens provided by control participants, 8% (56 specimens) were norovirus positive. Norovirus positivity among controls was highest among children younger than 2 years old (5/18; 28%). Across all age groups, the odds of norovirus detection were 2.2 (95% CI: 1.6–3.1) times higher among AGE cases than among healthy controls. As a sensitivity analysis, we reclassified norovirus positives based on stricter Ct cutoffs ($Ct \leq 35$ for GI norovirus and $Ct \leq 37$ for GII norovirus) and found that the odds of norovirus detection were 2.7 (95% CI: 1.9–3.8) times higher among AGE cases than among healthy controls.

DISCUSSION

Among participants in this multiyear, active surveillance cohort in Cusco, Peru, the overall AGE incidence was 26.3 events/100 PY, and the norovirus AGE incidence was 4.4 events/100 PY. Incidences of both overall AGE and norovirus AGE were highest in children younger than 2 years of age and lowest in adults ages 18–64 years. After the initial norovirus AGE case in the household, approximately one third of household contacts subsequently tested positive for norovirus. Of those, a large majority (87%) were asymptomatic. Although asymptomatic infection with norovirus was also common among non-AGE control households (8%), the odds of norovirus detection were significantly higher among AGE cases compared with non-AGE controls. There was no distinct seasonal pattern for norovirus detections (i.e., no consistent increases/decreases in the number of detections during certain months of the year).

This study used the same methodology and protocol as another community cohort conducted in Puerto Maldonado, Peru.⁸ Higher overall AGE incidence (52 events/100 PY) and norovirus AGE incidence (7 events/100 PY) were observed in Puerto Maldonado than described here for San Jeronimo. However, the difference in norovirus AGE incidence may be largely explained by demographic differences, with a younger population in Puerto Maldonado compared with San Jeronimo; children younger than 5 years of age contributed 12% of person-time in the Puerto Maldonado cohort compared with 8% in San Jeronimo. Age-stratified norovirus incidence was similar across the two study sites. The higher overall AGE incidence observed in Puerto Maldonado compared with San Jeronimo in Cusco aligns with regional reports from the Peruvian Ministry of Health that show higher clinically attended AGE incidence in Puerto Maldonado than in Cusco.¹³

Our study found that young children had the highest incidence of both AGE and norovirus AGE and that 30% of specimens from AGE events among children younger than 2 years of age tested positive for norovirus. The high burden of norovirus AGE among children is supported by several other studies conducted in Peru. A birth cohort near Lima found that 70% of children experienced at least one episode of norovirus AGE by 2 years of age, with norovirus detected in 23% of diarrheal stool and 13% of nondiarrheal stool.⁷ Norovirus is also a leading cause of childhood AGE elsewhere in Latin America.¹⁴ A community cohort in Nicaragua found a norovirus AGE incidence of 23 events/100 PY among children younger than 5 years old.¹⁵ In a birth cohort in Ecuador, norovirus AGE incidence was 17 events/100 PY among children younger than 3 years old.¹⁶ In comparison, norovirus AGE incidences in this study population were 60.9 events/100 PY among children younger than 2 years old and 9 events/100 PY among children 2–4 years old.

When identifying target populations for norovirus interventions, it may be important to consider the age structure in a given country or setting. Although AGE and norovirus AGE incidences were lowest among adults ages 18–64 years, this age group still accounted for the most observed cases in crude numbers. Illnesses in this age group can lead to missed work and subsequent losses in economic productivity. Although epidemiological studies of norovirus disease burden in other countries have observed a higher burden of disease among both younger children and older adults, we did not find a high burden of norovirus among

older adults.^{17,18} However, our population did not include a large number of adults older than 65 years, so we may have been underpowered to accurately measure incidence in this age group.

No consistent seasonal pattern was observed from year to year. Although norovirus has a distinct winter seasonality in temperate climates, a lack of seasonal pattern has been reported elsewhere in Latin America, including most notably in the study conducted previously in Puerto Maldonado.^{5,8} Yearly norovirus incidence was slightly higher during the latter half of the study period, but this difference was not statistically significant.

Numerous genotypes were detected among both AGE and control specimens. GII.4 noroviruses typically comprise about half of norovirus detections worldwide¹⁹; however, this was not observed in this study, with only 20% of both case and control specimens typed as GII.4. This highlights the need for norovirus vaccines to provide crossprotection against non-GII.4 strains and for continued norovirus surveillance across settings to fully document genotype diversity. Notably, GII.27 viruses, which were first described in Peru, also comprised 20% of detections among AGE specimens. Overall, GII noroviruses made up the majority of detections, and among those with repeat norovirus AGE events, multiple detections of GII norovirus were common. Multiple detections of the same genotype occurred only once; because of the short time frame between events, it is likely that the second detection in this instance was because of convalescent shedding, which can occur for several weeks in norovirus-infected individuals.^{20,21}

Asymptomatic norovirus infection was common in this cohort. The prevalence of asymptomatic norovirus infection among controls without a known household exposure was 8%, which aligns with global estimates.²² Around one third of the household contacts of norovirus cases were positive for norovirus; however, there were few symptomatic secondary household cases. This underlines the importance of testing all household contacts when studying the transmission of norovirus. Interaction with a symptomatic or asymptomatic infected household member as well the presence of a child in the household have both previously been described as risk factors for norovirus transmission.^{23,24} We did not observe statistically significant differences in household transmission of norovirus by age of the index cases or age of the household contacts. This may suggest that the high burden of circulating norovirus infections in the community and subsequent exposure may offset the effects of certain risk factors, such as age of household contacts. However, the role of asymptomatic infections in transmission is not well understood.

These results were subject to some limitations. Approximately 9% of norovirus detections among AGE cases had a Ct value of >35, suggesting low viral loads. However, we could not assess coinfections or potential alternate causes of AGE among the participants as stool specimens were not systematically tested for other gastrointestinal pathogens. Future studies may consider further examination of the role of asymptomatic infection in transmission.

CONCLUSION

Our study provides multiple years of data on norovirus incidence among all ages and among both symptomatic and asymptomatic individuals. As norovirus vaccines progress through clinical trials, robust baseline incidence estimates are needed to inform evidence-based policies and assess future impacts of vaccination. The findings of this study support young children as the group most likely to benefit from vaccination and public health interventions.

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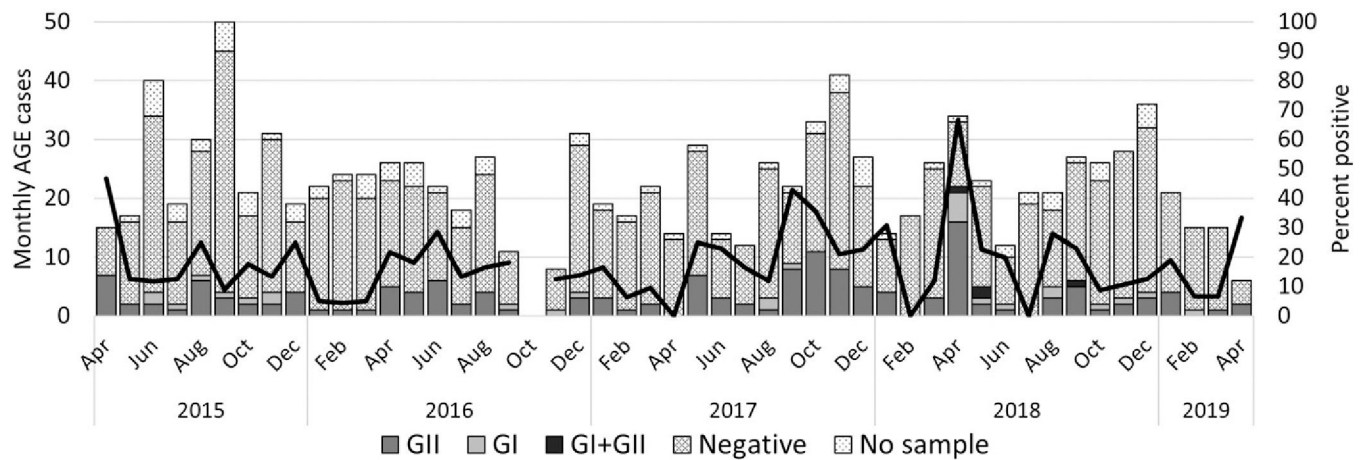


FIGURE 1.

Detection of AGE and norovirus AGE by genogroup and month of illness onset in San Jeronimo, Cusco, Peru from April 2015 to April 2019. The line represents the percent of AGE specimens that were norovirus positive. The bars represent the monthly AGE cases broken down by norovirus genotype. An AGE event was defined as any of the following in a 24-hour period: 1) three or more loose or liquid stools, 2) two or more vomiting episodes, or 3) one or more vomiting episodes and one or more loose or liquid stools. Surveillance was not conducted during October 2016 for administrative reasons. AGE = acute gastroenteritis; GI = genogroup I; GII = genogroup II.

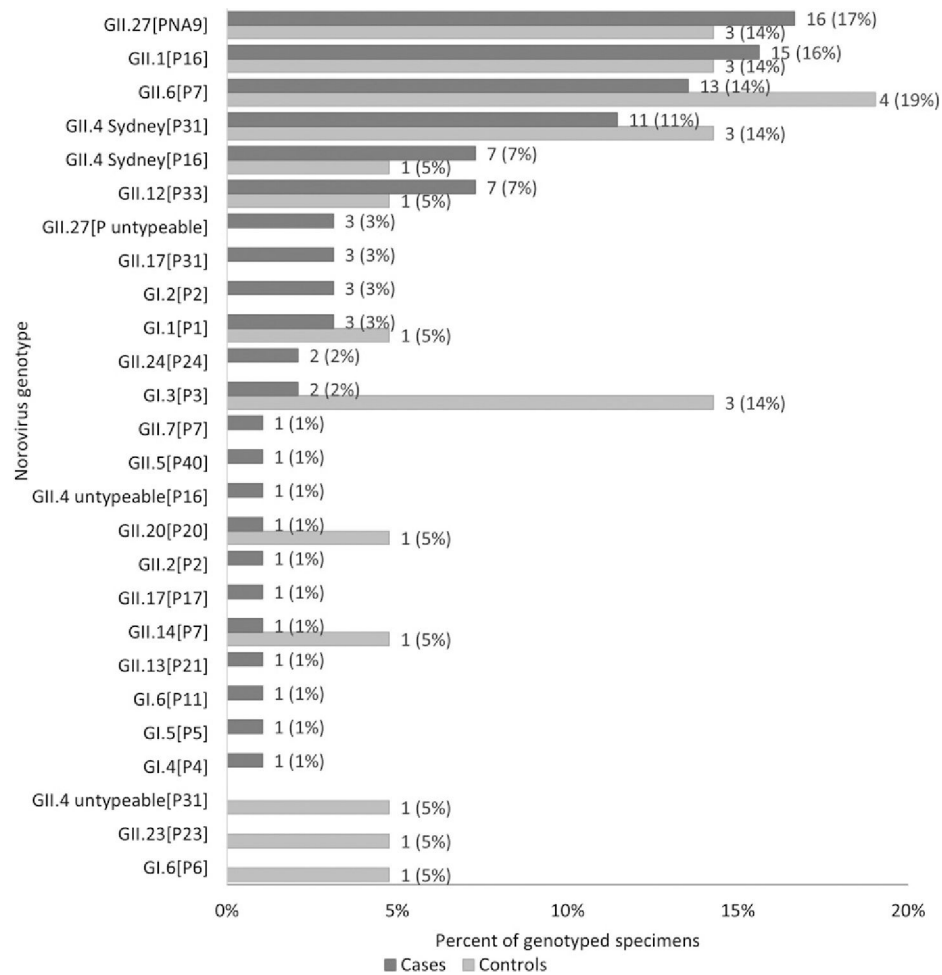


FIGURE 2.

Distribution of genotypes detected among acute gastroenteritis case and asymptomatic control specimens in San Jeronimo, Cusco, Peru from April 2015 to April 2018. Percentages for each genotype are among the number of specimens typed for cases and controls, respectively. Specimens collected after March 2018 were genogrouped but not genotyped.

TABLE 1

Cohort characteristics in San Jeronimo, Cusco, Peru from April 2015 to April 2019

Characteristic	No.
Household participation	
Mean number of enrolled households per year (range)	247 (235–273)
Median duration of household participation in months (IQR)	36 (22–43)
Median number of household members (IQR)	6 (4–9)
Participant	
Mean number of participants enrolled per year (range)	1,555 (1,242–1,667)
Median duration of participation in months (IQR)	24 (11–29)
Mean age of participants in years (range)	30 (0–99)

IQR5 interquartile range.

TABLE 2

Incidence of AGE and norovirus AGE events by participant age, participant sex, and surveillance year in San Jeronimo, Cusco, Peru from April 2015 to April 2019

Characteristic	Person-Years	All-Cause AGE		Norovirus AGE	
		Events	Incidence (95% CI)	Events	Incidence (95% CI)
Age group (years)					
<2	90.2	181	200.6 (173.4–232.0)	55	60.9 (46.8–79.4)
2–4	254.5	186	73.1 (63.3–84.4)	23	9.0 (6.0–13.6)
5–17	1,074.4	246	22.9 (20.2–25.9)	34	3.2 (2.3–4.4)
18–64	2,531.7	432	17.1 (15.5–18.8)	66	2.6 (2.0–3.3)
≥65	225.5	54	24.0 (18.3–31.3)	8	3.6 (1.8–7.1)
Sex					
Male	1,926.9	505	26.2 (24.0–28.6)	94	4.9 (3.9–5.9)
Female	2,249.5	594	26.4 (24.4–28.6)	92	4.1 (3.3–5.0)
Surveillance year					
April 2015–March 2016	1,138.3	311	27.3 (24.5–30.5)	40	3.5 (2.6–4.8)
April 2016–March 2017	921.5	227	24.6 (21.6–28.1)	34	3.7 (2.6–5.2)
April 2017–March 2018	1,035.2	274	26.5 (23.5–29.8)	55	5.3 (4.1–6.9)
April 2018–April 2019	1,081.4	287	26.5 (23.6–29.8)	57	5.3 (4.1–6.8)
Overall	4,176.4	1,099	26.3 (24.8–27.9)	186	4.4 (3.9–5.1)

AGE 5 acute gastroenteritis. Incidence is per 100 person-years.