POPULATION BASED SELF-REPORTED ACUTE GASTRO-INTESTINAL INFECTION IN SLOVENIA: MULTIPLIER STUDY

POPULACIJSKA ŠTUDIJA AKUTNIH ČREVESNIH OKUŽB V SLOVENIJI: OPREDELITEV MULTIPLIKATORJA

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Abstract

Background: *The assessment of the incidence of acute gastrintestinal infections (AGI) derived from the notifications underestimates the real burden of AGI. The symptoms of AGI are usually not severe enough for consultation with a physician. The more exact data on the burden of AGI are gained through cross sectional population-based studies. To estimate the burden of AGI in Slovenia, a period prevalence study was conducted.*
Methods: *A simple random sample consisting of 5000 Slovenian inhabitants was chosen to whom a questionnaire was sent in July 2011. The participants were asked if they experienced AGI in June 2011 according to a symptom-based case definition. The participants were asked to fill in the questionnaire on a paper or via a web page created for study purposes.*
Results: *Out of 5000 participants, 1500 filled out the questionnaire, giving a response rate of 33%. The number of women responding out-numbered men – there were 58% female and 42% male responders. 66 (4.4%) of the responders claimed to have had AGI in June 2011. The incidence rate of acute AGI was therefore 4400 per 100,000 inhabitants. Comparatively, the incidence rate of notified cases in the same month was 78.9 per 100,000 inhabitants. The difference between the incidence of AGI, based on notified cases and incidence, calculated in the first Slovenian cross sectional study, showed that one out of 56 cases of AGI in the community has been notified.*
Conclusion: *the incidence of AGI among the Slovenian population, based on data from our cross sectional study, is as expected higher than the incidence calculated from notification data from the same period.*

Key words: acute intestinal infection, notification, multiplier, population-based study

Izvirni znanstveni članek
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Izvleček

Izhodišče: *Incidenco akutnih črevesnih okužb (AČO) običajno ocenjujemo na osnovi prijav. S takšnim pristopom pogosto podcenimo dejansko breme AČO v populaciji. Simptomi AČO so redko tako resni, da sta potrebna obisk in nasvet zdravnika. Podatek o dejanskem bremenu AČO pridobimo s presečnimi študijami na vzorcu populacije, zato smo za oceno bremena v slovenski populaciji zasnovali periodično prevalenčno študijo.*
Metode: *V raziskavo smo povabili 5.000 prebivalcev Slovenije, ki so bili izbrani s pomočjo preprostega naključnega vzorčenja. Na preiskovance smo v začetku julija 2011 naslovili vprašalnik. Osrednje vprašanje raziskave je bilo, ali so v juniju 2011 preboleli AČO. Dodatna vprašanja smo postavili tistim preiskovancem, ki so odgovorili, da so imeli v juniju 2011 simptome in znake, ki so se skladali z definicijo AČO. Preiskovanci so imeli možnost odgovoriti prek spletne ankete ali izpolniti vprašalnik v papirnati obliki.*
Rezultati: *Natanko 1.500 preiskovancev je vrnilo izpolnjen vprašalnik (delež odgovorov: 33-odstoten). Vprašalnik je izpolnilo več žensk (58 %) kot moških (42 %). Akutno okužbo prebavil je po lastnih navedbah v juniju 2011 prebolelo 66 (4,4 %) preiskovancev. Incidenčna stopnja AČO je bila 4.400/100.000 prebivalcev Slovenije, kar je bistveno več kot prijavna incidenčna stopnja v istem mesecu (78,9/100.000). Na osnovi prve slovenske presečne študije AČO v populaciji ocenjujemo, da je na vsak prijavljen primer 56 zbolelih v populaciji.*

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Zaključek: *Rezultati presečne študije kažejo, da je incidenca AČO slovenskega prebivalstva pričakovano višja od incidence na osnovi prijav v istem obdobju.*

Ključne besede: akutne črevesne okužbe, prijava, multiplikator, populacijska študija

1 INTRODUCTION

Acute gastrointestinal infection (AGI) continues to be an important cause of morbidity and mortality in the developing world as well as in developed countries, accounting for an estimated 1.78 million deaths and 58.7 million disability-adjusted life years (DALYs) (1). To measure the exact burden of AGI by means of epidemiological studies is a demanding task (2).

Assessments of disease burden are often based on singular health metrics such as incidence, prevalence or mortality data alone (3). The incidence of AGI is usually estimated on the basis of notifications. The assessment derived from the notifications underestimates the real burden of AGI. The fact is that many patients with diarrheal diseases do not seek medical help, as vomiting or diarrhoea are mostly self-limiting and of short duration. The second problem is underreporting and under-ascertainment: even when the patient consults a doctor, e.g. suffering from more severe disease or simply in need of certificate for a sick-leave, it is not uncommon that the obligation to notify is overlooked by the physician. The incidence rate of AGI based on notifications is therefore mostly smaller than the real burden of the disease.

The global burden caused by food-borne pathogens remains largely unknown. Importantly, data indicating trends in food-borne infections are limited to a few industrialised countries and even fewer pathogens (4). It has been predicted that the importance of diarrheal disease, mainly due to contaminated food and water, as a cause of death will decline worldwide. However, evidence for such a downward trend is insufficient. This prediction presumes that improvements in the production and retail of microbiologically safe food will be sustained in the developed world and, moreover, will be rolled out to those countries of the developing world increasingly producing food for a global market. In fact, AGI caused by some bacterial pathogens (e.g. salmonellosis in developed countries) have decreased, others have even increased or re-emerged and the epidemiological situation remains dynamic (1). The real burden of all AGI can be assessed only through burden of disease studies.

Many cases of AGI, especially those with a mild clinical picture, are not captured by routine data sources, because they don´t seek medical advice or they do but are not notified. This is a part of a pattern described as the surveillance pyramid (5). Routinely available surveillance data thus underestimate the total AGI burden.

The aim of our study was to reveal part of the burden of AGI in the Slovenian population and to estimate the multiplier for notified cases.

2 METHODS

2.1 Survey case definition

According to the International Collaboration on Enteric Disease "Burden of Illness" (6), a case of AGI is defined as a person reporting three or more loose stools or any vomiting in a 24-hour period that was not due to the consumption of drugs or alcohol, excluding those with cancer of the bowel, irritable bowel syndrome, Crohn's disease, ulcerative colitis, cystic fibrosis, celiac disease or other chronic illnesses with symptoms of diarrhoea or vomiting (7).

2.2 The survey

A study was designed as a period prevalence study using a self-administrated questionnaire. The invited participants were chosen by a simple random method from the Central Population Registry. In 2011, Slovenia had 2,050,189 residents (8). In developed countries, estimates of monthly prevalence of AGI ranges from 4.5% to 11% (6). A minimum of 3754 individuals was required to reach the target sample size. This was calculated based on 11% expected monthly prevalence of AGI and 95% level of confidence, using the formula from the Epi Info 2000 program, Statcalc. The sampling method was simple random sampling, which included 5000 residents from Slovenia. The sampling was performed by the Statistical Office of the Republic Slovenia (SURS) from demographic data for Slovenia in 2011.

The questionnaire, along with the accompanying letter explaining the aim of the study, was sent to the home addresses of all randomly chosen participants on the first of July 2011. The accompanying letter was referred to parents of children and adolescents (less than 18 years of age). The participants (or their parents or guardians) were asked to complete the self-administrated questionnaire. The participants

could choose one of two options given: to answer the questionnaire on a paper and return it by ordinary mail or to give their answers on a webpage. It was clearly stated that they had to answer only once.

The participants answered the questionnaire anonymously. They were asked to disclose their age, gender, level of education, employment status, environment of their permanent residence (urban, rural and the size of the settlement), having a pet in the household or living on a farm, habits of drinking water from the tap and visiting spas.

The main question was whether they experienced AGI in June 2011 according to the "symptoms compatible" with the case definition. There were no additional questions for patients with AGI in June 2011. The participants without AGI were reminded to return the questionnaire anyway. Those who had symptoms of AGI were invited to answer additional questions regarding the possible source of infection, course of the disease and recourse of healthcare.

2.3 National notification system of communicable diseases

Surveillance of acute gastrointestinal infections (AGI) in Slovenia is based on passive notification according to the Law on Communicable Diseases (Official Gazette No. 33/06) and Act on Registration (Official Gazette No. 16/99). A case with AGI classified as A00-A09 (gastrointestinal infection with or without specified microorganisms) according to International Classification of Diseases, 10th revision (ICD-10), has to be notified by a treating physician on a standard notification form. Data collected on the notification form are: name, surname, date of birth, permanent address, date of the beginning of the illness, notification date and the results of microbiological testing (if available).

2.4 Statistical analysis

Data were expressed as mean, median and modus for continuous variables. Categorical variables were described using counts and percentages. Association was assessed by the χ^2 (Chi square test) method or, when appropriate, Fisher's exact test (p value < 0.05 was considered significant).

The formula for incidence rate calculation used was the one described by Rothman & Greenland (9). We calculated incidence rate of AGI as the number of cases that reported episodes of AGI during the 30 days of June 2011 divided by the total number of participants of the study multiplied by 100,000. Incidence rate derived from regular surveillance of communicable diseases in Slovenia was defined as the number of notified AGI cases in June 2011 divided by the total number of residents in June 2011 multiplied by 100,000.

Chi square analysis was applied to identify the factors associated with the occurrence of AGI. We compared the characteristics of AGI cases with those of respondents who did not meet the criteria for classification as cases of AGI.

3 RESULTS

3.1 The survey

Out of 5000 invited participants, 1500 (848 female in 602 male responders (50 did not answer the question about gender), 58% and 42% respectively) answered the questionnaire by mail (1399 or 93%) or via the web page (101 or 7%), giving a total response rate of 33%. Sixty-six (4.4%) responders reported having AGI in June 2011. There were 19 male and 47 female responders with AGI.

In this study, the incidence rate of AGI cases was 4400/100,000 inhabitants. The mean age of AGI cases was 37 years, median 35 years and modus 63 years. The mean age of AGI cases was lower than in healthy participants, whose mean age was 44, median 48 and modus 65 years ($p=0.000$). A much higher percentage of AGI cases was among children aged < 1 year as shown in Table 2.

Table 1. *Characteristics of survey responders with and without acute gastrointestinal illness in June 2011.*
Tabela 1. *Značilnosti preiskovancev z ali brez akutne črevesne okužbe (AČO) v juniju 2011, ki so posredovali izpolnjen vprašalnik.*

	Responders without AGI/ Preiskovanci brez AČO	Responders with AGI/ Preiskovanci z AČO	p-value/ p-vrednost
Mean age (years)/ Povprečna starost	44	37	0,000
Gender – male (%)/ Spol -moški (%)	40 %	28,7 %	0,030
The highest level of education accomplished*, graduation (%)/ Najvišja stopnja dosežene izobrazbe, končana fakulteta	30%	38%	0,191
Employed*– yes (%)/ Zaposlen – da (%)	48 %	44%	0,002
**Permanent residence – living in smaller settlement/ Stalno prebivališče – živi v manjšem naselju	51%	47%	0,478
Habit of drinking tap water – yes (%/)/ Pije vodo iz pipe - (da)	100%	82%	0,520
Visiting spas – yes (%)/ Obiskuje kopališča – da (%)	0%	10%	0,632
pets in the household/ Živi s hišnimi ljubljenčki	52%	48%	0,338
Living on farm/ Živi na kmetiji	0%	10%	0,000

*for responders over 25 years/ za preiskovance, ki so starejši od 25 let
** responders who live in small villages with less than 4000 inhabitants/ preiskovanci, ki živijo v vaseh z manj kot 4000 prebivalcev

Table 2. *Number of cases with acute gastro-intestinal infection and number of responders by age groups.*
Tabela 2. *Število preiskovancev, ki so imeli akutno črevesno okužbo in število tistih, ki so posredovali vprašalnik po starostnih skupinah.*

Age/ Starost	Number of AGI cases/ Število primerov z akutno črevesno okužbo	Number of responders from the population sample/ Število sodelujočih iz vzorca populacije
< 1 year/ < 1 leto	4	22
> 1 to 6 years/ >1 do 6 let	3	66
> 7 to 15 years/ >7 do 15 let	5	101
> 16 to 30 years/ > 16 do 30 let	27	368
> 31 to 60 years/ >31 do 60 let	10	458
> 60 years/ >60 let	17	407
Unknown/ Neznano	0	12
All/ Vsi	66	1422

The most common clinical symptom described by AGI cases was pain in abdomen (49 cases, 79%), abdominal cramps (39 cases, 59%), vomiting (19 cases, 29%) and fever (17 cases, 26%). Bloody diarrhoea was described by two patients (3%). Fifteen responders with AGI suspected a specific food or water to be associated with the disease. Twenty-four (36%) responders reported that household contacts had similar symptoms. Fifteen responders with AGI travelled abroad just before signs and symptoms of AGI started. Most frequently visited countries were Croatia (6), Italy (3), Spain (2) or others (Turkey, Tunisia, Egypt, Austria).

A physician was consulted by 13 (19.6%) respondents with AGI one to 21 days after AGI started, on average after 3.7 days. Only 3 were asked to provide a stool sample for which there was full compliance. In one case, rotavirus was confirmed; other tests were negative. Three patients with AGI were treated with antibiotics (1.5%). Those who consulted the physician for AGI were on average younger than those who did not (27 versus 36). Half of the patients who visited a doctor were expectedly younger than 10 years (the age ranged from 0.5 to 83 years, median 17.5 years and modus 1 year). One patient, a 2-year-old boy with AGI, was hospitalised. Chi square test showed that the visit to the doctor's office was associated with longer duration of diarrhoea (p=0,000) and fever (higher than 37 °C, p=0.000). The duration of diarrhoea is significantly associated with age of patients (p=0.007) as shown in Table 3.

Table 3. *Age of the AGI cases and the duration of the illness – cross sectional study, June 2011, Slovenia.*
Tabela 3. *Starost bolnikov in trajanje akutne črevesne okužbe prebavil – presečna študija, junij 2011, Slovenija.*

Duration of diarrhea/ Trajanje driske	Preschool children/ Predšolski otroci	School children/ Šolski otroci	Adults 26-64 years/ Odrasli od 26-64 leta	Adults ≥65/ Odrasli nad 65 let	Total/ Skupaj
≤3 days/ ≤3 dni	1 (20%)	16 (72,7%)	21 (80,8%)	2 (28,6%)	40 (66,7%)
≥ 4 days/ ≥4 dni	4 (80%)	6 (27,3%)	5 (19,2%)	5 (71,4%)	20 (33,3%)
All/ Vsi	5 (100%)	22 (100%)	26 (100%)	7 (100%)	60 (100%)*

* Data on duration of diarrhoea was available only for 60 out of 66 cases with AGI.
*Podatki o trajanju driske so bili na voljo samo za 60 od 66 primerov z akutnim gastroenterokolitisom.

From 66 patients reporting AGI in the month of June 2011, almost half (48%) lived in small villages or in remote houses out of settlements. We created the hypothesis that the quality of drinking water coming from local wells in small villages is not of the same quality compared to well-controlled drinking water from big urban systems. Therefore, the inhabitants of small villages might have a greater possibility to become ill with AGI. There was no association found between living in a small settlement and occurrence of AGI (Chi square test; $p > 0.05$).

3.2 AGI multipliers

In the year 2011, there were 22,335 notified AGI cases, the incidence was 1088.2/100,000 inhabitants. Approximately 70% of reported AGI cases were coded as A0.9 according to ICD-10 – AGI of unknown aetiology. Rotavirus and *Campylobacter* were the most frequent confirmed agents causing AGI (Annual epidemiologic report 2011; National Institute of Public Health, Slovenia). 1606 notified cases were reported in June 2011 (incidence rate 78.9/100,000 inhabitants).

The age-specific AGI incidence rates derived from the cross-sectional study and notification system are presented in Table 4 with multipliers for age group calculated. The multipliers were calculated by dividing the incidence rate from the cross sectional study with the incidence rate from national surveillance of communicable diseases.

Table 4. *Acute gastrointestinal infection incidence rates (per 100,000) by age groups derived from cross sectional study and surveillance system with the multipliers for age groups.*
Tabela 4. *Incidenčna stopnja (na 100.000) akutnih črevesnih okužb v presečni študiji in prijavljenih primerov z multiplikatorji po starostnih skupinah.*

Age group (years)/ Starostna skupina (leta)	Incidence rate per 100.000 inhabitants (cross sectional survey)/ Incidenčna stopnja na 100.000 prebivalcev (presečna študija)	Incidence rate per 100.000 inhabitants (notification in June 2011) / Incidenčna stopnja na 100.000 prebivalcev (junij 2011)	The multipliers for age group/ Multiplikatorji po starostnih skupinah
≤ 1	18181	83	219
1-6	7777	351	22
7-14	5882	151	39
15- 29	6250	303	21
30-59	3059	432	7
> 60	3703	219	17

4 DISCUSSION

The data derived from regular surveillance of communicable diseases showed that AGI causes a considerable burden in Slovenia. Due to underreporting and under-ascertainment, the burden is still underestimated. To move toward the real burden of AGI, the first population based period prevalence study was carried out in Slovenia.

The response rate was 33%, which is slightly lower compared to a previously published study from Canada (8). There were 66 (4.4%) AGI cases among responders. Only 13 (19%) of them consulted a primary care physician. The estimated incidence rate of acute gastroenteritis in June 2011, based on the cross sectional study, was 4400/100,000 inhabitants. As expected, the estimated incidence rate was much higher in children of ≤6 years (7500/100,000) than in elderly aged ≥61 years (3703/100,000).

The results of the survey showed that AGI incidence rate was 56 times higher than the incidence rate recorded through the passive surveillance system. The multipliers derived from different age groups ranged from 7 to 219. The highest multiplier was in children aged less than one year, the lowest from the 30 to 59 years age group. However, the incidence in the cross sectional study is the estimation of the incidence of all AGI cases in the community. Most of them do not seek medical advice and are therefore not registered.

In studies from New Zealand and Canada, the multiplier was found to be 222 and 347 respectively (10, 11). The study of AGI in the general population in Great Britain showed that along with every notified case of AGI that seeks medical help, there are at least six AGI cases that are not notified (4). In a cross sectional telephone survey in New York, residents were asked about diarrhoea during the 30 days before the interview. Estimated numbers of citywide illnesses were compared to emergency department (ED) visits for AGI that were recorded. One ED visit for AGI represented approximately 250 illnesses in the community (12). The readiness to report and timeliness of notification of communicable diseases depend on the severity of the disease and its public health implications.

There is general awareness that diseases important from a public health point of view and/or causing outbreaks are to be reported (13). The probabilities of visiting a doctor having stool tested and notification of disease are likely to be greater when the illness is more severe, which is dependent on causative agent (13). Most of cases with mild clinical AGI do not seek medical advice and are not notified. The multipliers were calculated for some pathogens (mostly for bacteria), e.g. by determining the average incidence of laboratory-confirmed *Salmonella* infection and adjusting for under-ascertainment using values from the literature. *Salmonella*-specific multipliers range from 3.2 in England, 7 in Australia, 14.3 in the Netherlands, 25 in Canada and 38 in the United States to 64 in Japan (14). An even higher multiplier was found in Jordan: for each person with laboratory-confirmed *Shigella* or *Salmonella* infection, there are about 273 infected persons in the community (15). The multipliers for viruses are probably even higher.

There are some less sensitive options (in comparison to cross sectional multiplier studies) to estimate the burden of AGI. Over the counter (OTC) medications sales of antidiarrheal medication increased during fall and peaked during early winter (16). The increase better

correlated with noroviral outbreaks than the increase of AGI caused by rotaviruses.

We assume that the burden of AGI in Slovenia is probably higher during summer than winter due to the seasonal pattern of AGI. In temperate climates, AGI typically alternate periods of low endemic levels with periods with outbreaks, forming a typical seasonal pattern depending on etiologic agent. *Salmonella* or *Campylobacter* spp. AGI rise in the summer and decline in the winter. Enteric infections caused by the protozoans *Giardia* and *Cryptosporidium* also exhibit seasonal variation, but it is shifted towards autumn (17). In contrast, seasonality is not marked for hepatitis A and shigellosis (17). Infections caused by *Salmonella* and *Campylobacter* closely follow the ambient temperature curve of the environment. Food contamination is believed to be the most significant mode of transmission for *Salmonella* and *Campylobacter*. In contrast, the seasonal increase in *Giardia*, *Shigella* and *Cryptosporidium* infections form a separate cluster peaking a month after the temperature peak, strongly suggesting different route(s) of exposure than for *Salmonella* or *Campylobacter* (17).

The question to be answered is: which pathogen caused the most AGI in our study? Most AGI cases in the present study did not seek medical help due to mild course of the illness and did not have a sample taken. We can only assume that noroviruses and rotaviruses were the most prevalent pathogens causing AGI. According to notification data in Slovenia, the majority of AGI with known pathogen are caused by rotaviruses (26% in the year 2010) and noroviruses (34% in 2010) (18). The same has been found in previous studies – the largest part of the burden in the community is caused by viruses, especially noroviruses, in last few years (19). In a UK study, the incidence rate of norovirus-associated AGI in the community showed a slight peak in the winter and autumn months, while general practice consultations were reasonably constant throughout the year. In the same study in the UK, they found that norovirus is the most common cause of AGI across all age groups in the community (20).

Noroviral gastroenterocolitis has been long considered the second most frequent cause of AGI, far behind rotaviral gastroenteritis. Development of molecular-based diagnostic techniques has provided clearer insight into the epidemiological impact of noroviruses that are now recognised not only as the leading cause of non-bacterial gastroenteritis outbreaks but also as an important cause of sporadic gastroenteritis in both children and adults. The virus is able to survive in the environment for many days, which enables outbreaks to be prolonged (20). Actually, noroviruses are also recognised as the major causes of waterborne illnesses worldwide (21).

In this study, there were more female than male responders (58% vs. 42%). It seems that women were more willing to answer the survey, which could be a source of bias. Nevertheless, the percentage of males and females with AGI was not statistically significantly different (males 3.1% versus females 5.5%, p-value 0.066), therefore we assume that higher response rate in females had no impact on multiplier assessment. The age structure of responders did not differ significantly from Slovenian age structure and the age distribution of AGI cases was similar as in routine surveillance data.

The study population was surveyed in just one month of the year, which is the major limitation of the present study. As the same intestinal pathogens are much more often found during summer and others in cooler months of the year, it might be anticipated that an all year-round study might show more realistic multipliers of AGI. Therefore, extrapolation based on a one month study might be questionable. Multiplier studies in which the selected study population was surveyed for 12 months have been published and give much better insight into multiplier of AGI than one-month studies (22, 23). The main drawback of a one-year multiplier study is high cost. The results gained through such studies done in (usually) wealthier countries cannot be easily translated to other countries and different social environments. WHO explicitly discourages countries from using data from other countries to develop multipliers for extrapolating from reported to true incidence and encourage them to base such estimates on their own studies and case selection (24).

5 CONCLUSION

The incidence of AGI among the population, who mostly did not seek medical advice, based on data from our cross sectional study, is expectedly higher than the incidence calculated from notification data from the same period.

We assume that like in other countries in temperate climates the frequency of AGI during summer is probably higher than in winter due to the seasonal patterns of most AGI. However, to confirm that we should repeat the study in winter.

Furthermore the number of cases and responders in different age groups in our study were quite different, which also influenced the multipliers. We expect that higher percentages of responders enable better

estimates of the multipliers, which is one of the limitations of this study.

Diarrhoea continues to be a major global health problem and there is an ongoing debate over identifying research priorities and effective interventions given the limited funding. Whereas standard clinical trial procedures are often adequate to assess the effect of a vaccine or drug on diarrhoea in individuals, environmental interventions aiming at diarrhoea control are often much more complex and more difficult to evaluate with randomised trials (2).

We assume, like in most countries, that probably most AGI cases in the community are caused by viruses. According to that assumption, if the burden of norovirus and rotavirus infections increased, the multiplier between notified and community based cases of AGI would also rise.

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