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Identification of the novel Kawasaki 2014 GII.17 human norovirus strain in Italy, 2015

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Surveillance of noroviruses in Italy identified the novel GII.17 human norovirus strain, Kawasaki 2014, in February 2015. This novel strain emerged as a major cause of gastroenteritis in Asia during 2014/15, replacing the pandemic GII.4 norovirus strain Sydney 2012, but being reported only sporadically elsewhere. This novel strain is undergoing fast diversification and continuous monitoring is important to understand the evolution of noroviruses and to implement the future strategies on norovirus vaccines.

During the winter season 2014/15, a novel GII.P17-GII.17 norovirus (NoV) strain emerged in Asian countries [1-4]. Since its emergence, this novel NoV strain, named Kawasaki 2014, has replaced the previously dominant GII.4 genotype Sydney 2012 variant in Asia, and it has been detected in a limited number of cases on other continents [1-5]. This epidemiological trend is also reflected in the GenBank database, with the vast majority of the Kawasaki 2014 GII.17 NoV sequences generated in studies from the Asian continent.

Here we report the detection of the Kawasaki 2014 GII.17 strain during the 2014/15 winter season in Italy. As sequence information on Kawasaki 2014 GII.17 NoVs detected outside the Asian continent is limited [5], we determined the sequence of a large portion of the genome, including the full-length capsid gene of the GII.17 Kawasaki NoV strain circulating in Italy, and analysed the virus sequence with similar GII.17 NoV sequences available in the GenBank database.

Genotyping

The NoV genome contains three open reading frames (ORFs). ORF1 encodes non-structural proteins including the RNA-dependent RNA polymerase (RdRp), while ORF2 and ORF3 encode the major capsid protein VP1 and a minor structural protein VP2, respectively [6]. NoVs are classified in at least six genogroups, GI to GVI [6]. NoV genogroups are further divided in various genotypes based on differences in the RdRp region (polymerase genotype, or pol type) and in the VP1 (capsid genotype, or cap type) [7]. NoV genotyping was performed using standardised sequence analysis web-based tools developed and maintained by the NoroNet [8].

Surveillance of noroviruses in Italy

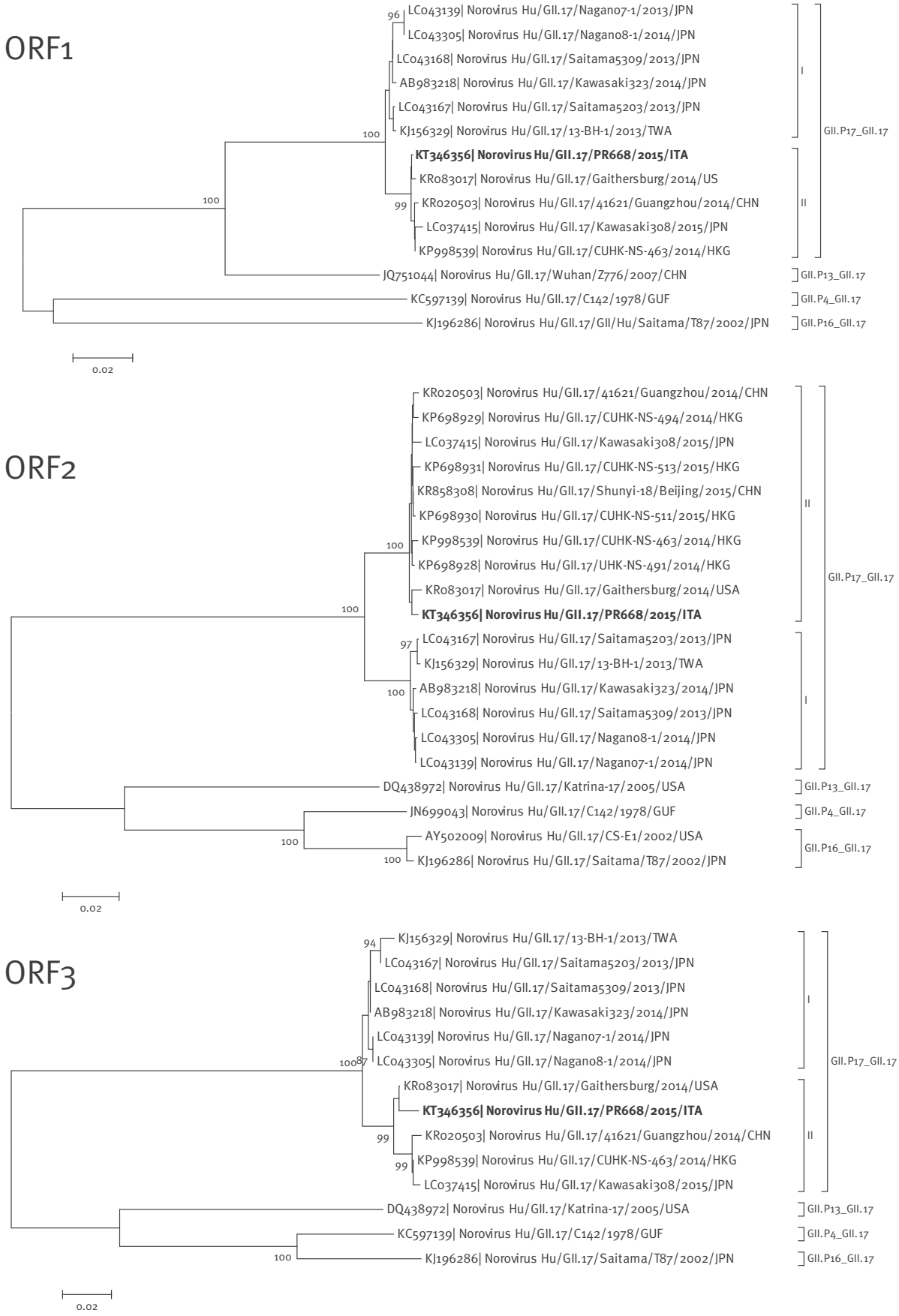
The Italian Study Group for Enteric Viruses (ISGEV; http://isgev.net) monitors the epidemiology of enteric viruses in children through hospital-based surveillance. A subset of about half of the NoV-positive samples is systematically genotyped in both region A (ORF1, RdRp) and region C (ORF2, capsid). From September 2014 to March 2015, NoV prevalence was 12% (137/1,144) and NoVs were typed in 81 cases (59%). GII.P17-GII.17 NoV strains were detected in two sporadic cases of acute severe gastroenteritis in young children hospitalised in February 2015 in two distinct Italian regions.

Sequence analysis

Upon direct sequencing of the RT-PCR amplicons, the two strains, PR668/2015/ITA and BA603–6/2015/ITA, were found to be identical in the short diagnostic regions A and C. We determined the sequence of a large portion (3.2 kb) of the genome at the 3' end for strain PR668/2015/ITA. Viral RNA was extracted from 140 µl of stool suspension using the QIAmp viral RNA kit (Qiagen, GmbH, Hilden, Germany). A 3'-rapid amplification of cDNA ends (RACE)-PCR) protocol was used to generate the 3.2-kb amplicon encompassing the 3' end of ORF1, the full-length ORF2 and ORF3, and the 3' untranslated region (UTR) until the poly(A) tail, using the reverse primer VN3T20 [9] and the forward primer JV12Y [10]. The RACE product was cloned and the

Figure 1

Phylogenetic analysis based on partial ORF1, full ORF2 and full ORF3 sequences of GII.17 NoV, Italy, February 2015



The Italian GII.P17_GII.17 strain is indicated in bold. Trees were built with the maximum-likelihood method, and bootstrapped with 1,000 repetitions. Bootstrap values›80% are indicated. The scale bar indicates the number of nucleotide substitutions per site.

Figure 2

Amino acid substitutions in the VP1 sequence of norovirus GII.17 norovirus strains, 1978–2015

Strain	Country	Year	Amino acid number (P2 domain amino acids 279-405)																																															
								A		A	A	A					B																		D	D							E							
			22	173	174	256	293	294	295	296	297	298	299	313	314	330	333	343	344	345	346	348	354	356	357	360	362	374	375	377	378	379	383	384	394	395	396	397	399	400	402	404	407	410	414	440	444	447	449	517
LC043168 Saitama5309	Japan	2013	G	N	S	V	E	-	-	-	D	H	R	T	Y	K	V	G	N	D	A	G	E	V	Y	Y	P	R	-	N	D	N	-	-	I	N	-	-	G	D	P	R	E	D	L	F	S	Y	Q	Y
LC043167 Saitama5203	Japan	2013	.	.	.	.	.	-	-	-	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	-	.	.	.	-	-	.	.	-	-	.	.	.	.	.	.	.	.	.	.	.	.
KJ156329 13-BH-1	Taiwan	2013	.	.	.	.	.	-	-	-	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	-	.	.	.	-	-	.	.	-	-	.	.	.	.	.	.	.	.	.	.	.	.
LC043139 Nagano7-1	Japan	2014	.	.	.	.	.	-	-	-	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	-	.	.	.	-	-	.	.	-	-	.	.	.	.	.	.	.	.	.	.	.	.
LC043305 Nagano8-1	Japan	2014	.	.	.	.	.	-	-	-	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	-	.	.	.	-	-	.	.	-	-	.	.	.	.	.	.	.	.	.	.	.	.
AB983218 Kawasaki323	Japan	2014	.	.	.	.	.	-	-	-	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	.	-	.	.	.	-	-	.	.	-	-	.	.	.	.	.	.	.	.	.	.	.	.
KP998539 CUHK-NS-463	Hong Kong	2014	.	.	.	.	Q	-	-	-	N	Q	.	.	.	.	.	.	.	.	.	.	Q	W	.	.	.	.	I	D	N	D	-	-	V	.	D	D	D	G	.	.	.	N	E	.	.	.	.	H
KR020503 Guangzhou	Hong Kong	2014	.	.	.	.	Q	-	-	-	N	Q	.	.	.	.	.	.	.	.	.	.	Q	W	.	.	.	.	I	D	N	D	-	-	V	.	D	D	D	G	.	.	.	N	E	.	.	.	.	H
KP698928 CUHK-NS-491	Hong Kong	2014	.	.	.	.	Q	-	-	-	N	Q	.	.	.	.	.	.	.	.	.	.	Q	W	.	.	.	.	I	D	N	D	-	-	V	.	D	D	D	G	.	.	.	N	E	.	.	.	.	H
KP698929 CUHK-NS-494	Hong Kong	2014	.	.	.	.	Q	-	-	-	N	Q	.	.	.	.	.	.	.	.	.	.	Q	W	.	.	.	.	I	D	N	D	-	-	V	.	D	D	D	G	.	.	.	N	E	.	.	.	.	H
KR083017 Gaithersburg	USA	2014	.	.	.	.	Q	-	-	-	N	Q	.	.	.	.	.	.	.	.	.	.	Q	W	.	.	.	.	I	D	N	D	-	-	V	.	D	D	D	G	.	.	.	N	E	.	.	.	.	H
LC037415 Kawasaki308	Japan	2015	.	.	.	.	Q	-	-	-	N	Q	.	.	.	.	.	.	.	.	.	.	Q	W	.	.	.	.	I	D	N	D	-	-	V	.	D	D	D	G	.	.	.	N	E	.	.	.	.	H
KP698931 CUHK-NS-513	Hong Kong	2015	.	.	.	.	Q	-	-	-	N	Q	.	.	.	.	.	.	.	.	.	.	Q	W	.	.	.	.	I	D	N	D	-	-	V	.	D	D	D	G	.	.	.	N	E	.	.	.	.	H
KP698930 CUHK-NS-511	Hong Kong	2015	.	.	.	.	Q	-	-	-	N	Q	.	.	.	.	.	.	.	.	.	.	Q	W	.	.	.	.	I	D	N	D	-	-	V	.	D	D	D	G	.	.	.	N	E	.	.	.	.	H
KR858308 Shunyi-18	China	2015	.	.	.	.	Q	-	-	-	N	Q	.	.	.	.	.	.	.	.	.	.	Q	W	.	.	.	.	I	D	N	D	-	-	V	.	D	D	D	G	.	.	.	N	E	.	.	.	.	H
KT346356 PR668/2015	**Italy**	**2015**	.	.	.	.	**Q**	-	-	-	**N**	**Q**	.	.	.	.	.	.	.	.	.	.	**Q**	**W**	.	.	.	.	**I**	**D**	**N**	**D**	-	-	**V**	.	**D**	**D**	**D**	**G**	.	.	.	**N**	**E**	.	.	.	.	**H**
JN699043 C142	USA	1978	I	A	N	N	D	V	H	Q	S	.	D	P	F	T	L	-	-	S	N	N	.	.	T	T	S	G	-	T	S	D	L	Q	.	K	-	-	S	G	D	D	A	R	H	N	A	V	D	.
AY502009 CS-E1	USA	2002	I	A	N	N	D	V	D	G	S	.	D	P	F	T	L	-	-	S	N	N	.	.	T	T	S	G	-	T	S	T	L	Q	.	K	-	-	S	G	E	D	A	R	H	N	A	V	D	.
KJ196286 Saitama/T87	Japan	2002	I	A	N	N	D	V	D	G	S	.	D	P	F	T	L	-	-	S	N	N	.	.	T	T	S	G	-	T	S	T	L	Q	.	K	-	-	S	G	E	D	A	R	H	N	A	V	D	.
DQ438972 Katrina-17	USA	2005	I	S	E	N	D	V	Q	N	S	.	Q	P	F	T	L	.	G	T	G	N	.	.	T	T	T	G	-	E	S	E	V	G	.	K	-	-	T	G	S	.	D	N	A	N	A	V	E	.

The putative blockade epitopes A–E are indicated. Dots indicate sequence conservation. Dashes indicate deletions/insertions of the amino acid residues. Amino acid numbering is based on the sequence of the C142 strain (JN699043).

sequence was determined. Phylogenetic analysis was performed using MEGA v. 6.0 [11].

The 3.2-kb sequence of the Italian NoV GII.P17-GII.17 strain has been deposited in GenBank under accession number KT346356. The partial sequence of ORF1 (807 nt), and the full-length sequences of ORF2 (1,621 nt) and ORF3 (849 nt) of strain PR668/2015/ITA were analysed with NoV GII.P17-GII.17 sequences available in the GenBank database (Figure 1).

The topology of the trees in the multi-target phylogenetic analysis was conserved, with the GII.P17-GII.17 Kawasaki 2014 NoV forming a monophyletic branch and further segregating into two genetic subclades. The first subclade containing the Italian PR668/2015/ITA strain clustered with GII.P17-GII.17 NoVs detected in China and Hong Kong during 2014 and 2015, and was genetically related (99.9%) to a GII.P17-GII.17 strain detected in the United States (US) in November 2014. The second subclade included GII.P17-GII.17 NoV detected in Japan and Taiwan during 2013 and 2014. The viruses of the two subclades showed a moderate degree of nucleotide and amino acid divergence in the ORF2 and ORF3 sequences (1–1.9% nucleotide and 0–0.4% amino acid differences in ORF1, 0.4–4.1% nucleotides and 0.9–6.2% amino acids in ORF2, and 0.5–3.3% nucleotides and 1–4.9% amino acids in ORF3). Interestingly, the GII.17 capsid sequences of the two genetic subclades differed markedly from the oldest GII.17 capsid sequence available in GenBank database, dating back to 1978 (23.3–24.8% nucleotide and 14.2–16.6% amino acid differences in ORF2, and 19.4–27% nucleotide and 22.1–22.9% amino acid differences in ORF3).

Several changes in the VP1 sequence were observed between the two Kawasaki 2014 subclades, mostly, but not exclusively, affecting the antibody blockade sites, i.e. the putative epitopes (A-E) located in the capsid protruding hypervariable P2 domain (Figure 2). In the 543 amino acid VP1 protein, 17 amino acid changes (3.1% divergence) and four insertions separate the two Kawasaki 2014 subclades, while 38 amino acid changes (7% divergence) and several insertions/deletions separate the Kawasaki 2014 GII.17 NoV and the former GII.17 recombinant forms.

Discussion

NoVs are a major cause of acute gastroenteritis in both children and adults, with sporadic cases and outbreaks in various epidemiological settings [6]. Although more than 30 cap genotypes within genogroups GI, GII, and GIV may infect humans [7], a single genotype, GII.4, has been associated since the mid-1990s with the majority (ca 70–80%) of NoV-associated cases of gastroenteritis worldwide [12]. GII.4 NoV strains undergo a continuous process of genetic/antigenic diversification and periodically generate new strains via accumulation of point mutations or recombination, with one novel GII.4 variant emerging every two to three years [12,13] and becoming predominant globally. NoV vaccines based on GII.4 NoV strains are currently under development [14].

In the winter season 2014/15, the GII.P17-GII.17 NoV strain Kawasaki 2014 emerged in Asia, replacing the previously dominant GII.4 genotype Sydney 2012 variant [1-4]. A signature of the Kawasaki 2014 variant is a novel pol type GII.P17, combined with a GII.17 ORF2 gene. Previously, NoVs with a GII.17 cap genotype possessed a GII.P4, GII.P3, GII.P13 or GII.P16 pol genotype [15-18]. Although being predominant in several Asian countries, this novel GII.P17-GII.17 strain has been detected in a limited number of cases on other continents [1-5]. The epidemiological trends exhibited by the Kawasaki 2014 NoV variant are considered unique, as, so far, this is the only non-GII.4 NoV strain to have shown such epidemic pattern. The emergence of the novel GII.P17-GII.17 NoV strain in the Asian countries has been associated with increased NoV activity, i.e. with increased incidence of NoV-induced acute gastroenteritis, in the 2014/15 winter season, compared to the previous (2013/14) winter season [1-3]. This pattern has been observed, but not consistently, during the worldwide spread of NoV GII.4 variants [19]. Based on current literature on GII.17 NoVs, there is no indication on the clinical severity of the novel GII.17 virus [1-5]. Likewise, our study did not assess whether Kawasaki 2014 NoVs are associated with increased severity of the clinical symptoms.

Hospital-based surveillance for NoV identified the emergence of GII.P17-GII.17 strains in Italy at the end of the 2014/15 winter season, in February 2015. The viruses were genetically closely related to GII.17 NoVs identified in the US and Asia in 2014 and 2015 [3,5], forming a distinct subclade of the Kawasaki 2014 GII.17 NoV variant. Co-circulation of two subclades of Kawasaki 2014 GII.17 NoV with several amino acid changes in the putative capsid epitopes could suggest that this novel strain is undergoing fast diversification, mirroring what was seen globally for the epidemic GII.4 variants [12].

In addition, the emergence and spread of the novel GII.17 variant Kawasaki 2014 could represent a challenge for the efficacy of the candidate NoV vaccines [14], that target the globally predominant GII.4 NoV, as it is not known whether vaccine immunity elicited to GII.4 NoV is cross-reactive with GII.17 viruses. Continuous monitoring of the epidemiology of human NoV is important to understand the evolution of NoV and to implement the future strategies on NoV vaccines.

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Conflict of interest

None declared.

Authors' contributions

Conceived and designed the experiments: MCM, FT, VM; analysis of samples: MCM, FT, MC, GMG, SDG, VM; analysed and interpreted the data: MCM, FT, VM; wrote the manuscript: MCM, FT, VM; critical revision of the manuscript: AC, MC, GMG, SDG, MCA, FDC, CC; approved the final version: MCM, FT, AC, MC, GMG, SDG, MCA, FDC, CC, VM.

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Research article

Hepatitis B virus, hepatitis C virus and human immunodeficiency virus infection in undocumented migrants and refugees in southern Italy, January 2012 to June 2013

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Screening of undocumented migrants or refugees for hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections has been offered free of charge and free from bureaucratic procedures since 2012 at four primary-level clinical centres in Naples and Caserta, Italy. Of 926 undocumented migrants and refugees visiting one of the primary-level clinical centres from January 2012 to June 2013, 882 (95%) were screened for hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (anti-HBc) and antibodies against HCV and HIV. Of the 882 individuals enrolled, 78 (9%) were HBsAg positive, 35 (4%) anti-HCV positive and 11 (1%) anti-HIV positive (single infections); seven (1%) had more than one infection (three were HBsAg positive). Of the 801 HBsAg-negative patients, 373 (47%) were anti-HBc positive. The HBsAg-positivity rate was high (14%; 62/444) in individuals from sub-Saharan Africa and intermediate in those from eastern Europe (6%; 12/198), northern Africa (2%; 2/80) and Bangladesh, India, Pakistan and Sri Lanka (the 'India-Pakistan area') (3%; 4/126). Anti-HCV was detected in 9/126 (7%) individuals originating from the India-Pakistan area, in 12/198 (6%) from eastern Europe, in 17/444 (4%) from sub-Saharan and in 2/80 (2%) from northern Africa. The HBV, HCV and HIV infections in the undocumented migrants and refugees screened serve as a reminder to the Italian healthcare authorities to carry out extensive screening and educational programmes for these populations.

Introduction

Around 350–400 million worldwide people carry hepatitis B virus (HBV), 140–170 million hepatitis C virus (HCV) and 30–50 million human immunodeficiency virus (HIV) [1-5]. In spite of the decrease in the prevalence and incidence of HBV and HCV infections in young people (aged under 30 years) in industrialised countries after 1990s [1-5], these infections remain a major health problem in most countries due to their associated morbidity and mortality [3-9].

As a consequence of socio-economic and political crises in certain parts of the world, mostly due to war and civil war in recent decades, countries of western Europe have received migrants and refugees from areas that have a level of endemicity higher than 2% for HBV, HCV and HIV infections [10]. Surveillance data from 2014 showed that nearly 4.9 million legal migrants lived in Italy, making up 8% of the resident population [11]. The Italian immigration authorities estimate that nearly 500,000 migrants without a residence permit ('undocumented migrants') or refugees were living in Italy in 2014 [11], originating mainly from northern and sub-Saharan Africa, eastern Europe and central and eastern Asia [11,12]. Once in Italy, these individuals – with a low income most frequently from casual day-to-day work, broken family ties and of no fixed abode [11] – have limited access to healthcare services [11]. Despite the intermediate or high level of endemicity of HBV, HCV and HIV infections in their geographical area of

origin, the majority of them are unaware of their HBV, HCV and HIV status [11].

According to Italian policy, refugees should be regularly admitted to all healthcare facilities of the national healthcare system, whereas access of undocumented migrants is limited to minors, pregnant women, patients with serious pathological conditions and to individuals with transmissible diseases including HBV, HCV and HIV infections [11]. In our experience, shared by numerous other investigators in Italy, undocumented migrants and refugees prefer primary-level clinical centres with proven experience in the clinical, psychological and legal management of vulnerable groups, operating with the help of cultural mediators (Asli Ahmed Abdulle, personal communication, September 2013).

Prospective screening of migrants and refugees for HBV, HCV and HIV infection started in January 2012 in Naples and Caserta and is still ongoing. It involves a large number of people (more than 1,200 participants up to December 2014) and is monitored by individuals outside the programme. Our study involved six participating centres: four primary-care clinical centres (two in Naples and two in Caserta) and two tertiary units in infectious diseases (one in Naples and one in Caserta). These two cities are located in the Campania region in southern Italy, 30 kilometres from each other, have a large population of refugees and undocumented migrants from Africa, central and eastern Asia, eastern Europe and Latin America [11].

In this article, we present the results of screening carried out from January to June 2013 for HBV, HCV and HIV infections in undocumented migrants and refugees living in Naples and Caserta, Italy. The study was carried out to help undocumented migrants and refugees to attend to the screening and to assess the extent to which these vulnerable groups take part in the screening.

Methods

Study protocol and setting

Senior investigators from the six participating centres prepared the study protocol and an anonymous questionnaire; they also established all screening and post-screening procedures.

The questionnaire was used to record age, sex, geographical origin, date (month and year) of migration, level of education, religion, family history, cohabitation details, sexual orientation and practices including condom use, history of HBV vaccination, surgery, dental care, tattooing, body piercing, use of drugs, blood transfusion, tribal rituals, abortion and information on previously documented personal and family HBV, HCV and HIV infections.

During clinical consultations, asked for by the patient, a physician from the clinical centre and a cultural mediator explain to the undocumented migrants and refugees the importance of being tested for HBV, HCV and HIV infection and offer testing free of charge, in anonymity (recording only the centre number and patient's number), in full accordance with Italian privacy law regarding observational studies [13]. In each case, the clinical history was obtained with the help of a physician and a cultural mediator during a prolonged, in-depth clinical consultation and counselling. All questionnaires were checked by the senior investigators of the primary-care clinical centres and found suitable for the study, as they had been correctly completed.

The study population consisted of all the undocumented migrants (including the citizens from other European countries who might not qualify for the right of residence for more than three months in Italy) and refugees seen consecutively for clinical consultation at one of the four primary-care clinical centres from January 2012 to June 2013, who agreed to participate in the investigation. The most frequent clinical conditions leading the patients to seek care at one of these centres were lumbago, headache, pruritus, cough, high blood pressure and allergy symptoms.

Written informed consent to participate in the study, in the person's native language, was obtained on a voluntary basis. As explained in the informed consent form, a serum sample would be taken from study participants. All participants received the results of their serological screening and information on preventing infection and transmission of HBV, HCV and HIV.

The primary-level clinical centres involved in our study were hospitals in the national healthcare system or clinical centres (general outpatient clinics) of international charity organisations such as Caritas and the Sisters of Mother Teresa of Calcutta.

Participants who were positive for total hepatitis B core antibody (anti-HBc), positive or negative for hepatitis B surface antigen (HBsAg), anti-HCV positive or anti-HIV positive were referred to one of the two tertiary units of infectious diseases for further investigation, monitoring and possible treatment. These tertiary units offer refugees and undocumented migrants with serum markers of HBV, HCV or HIV infection the same clinical management given to legal migrants and to Italian citizens. These two tertiary units of infectious diseases are both affiliated with the Second University of Naples and have cooperated for nearly 15 years in several clinical investigations on HIV, HBV and HCV infections using the same clinical approach and the same laboratory methods [14-18].

The study was approved by the Ethics Committee of the Azienda Ospedaliera Universitaria of the Second University of Naples.

Table 1

Characteristics of study participants, Caserta and Naples, Italy, January 2012–June 2013 (n=882)

Characteristic	Total	Undocumented migrants[b]	Refugees	P value Undocumented migrant vs refugee
	n (%)[a]	n (%)[a]	n (%)[a]	
Number of patients	882	625	257	NC
Median age in years(range)	34.5 (14–74)	34 (14–74)	35 (18–71)	0.8
Number who were male (%)	638 (72.3)	425 (68.0)	213 (82.9)	<0.001
Mean length of time living in Italy in months (SD)	58(55)	60(54)	57(62.6)	0.6
Serological status, n (%)				
HBsAg positive	78 (8.8)	55 (8.8)	23 (8.9)	0.2
Anti-HCV positive	35 (4.0)	28 (4.5)	7 (2.7)	0.3
Anti-HIV positive	11 (1.2)	9 (1.4)	2 (0.8)	0.3
HBsAg/anti-HIV positive	2 (0.2)	0(0)	2 (0.8)	0.08
HBsAg/anti-HCV/anti-HIV positive	1 (0.1)	1 (0.2)	0 (0)	0.7
Anti-HCV/anti-HIV positive	4 (0.5)	4 (0.6)	0 (0)	0.2
HBsAg negative/anti-HBc positive	373 (42.3)	254 (40.6)	119 (46.3)	0.1
Any of these serological markers	474 (53.7)	319 (51.0)	155 (60.3)	<0.001
No serological marker	408 (46.3)	306 (49.0)	102 (39.7)	0.01

Anti-HBc: total hepatitis B core antibody; HBsAg; hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; NC: not calculated, SD: standard deviation.

[a] Unless otherwise stated.

[b] The group of 625 undocumented migrants included 105 individuals from Romania, Bulgaria 35 and Poland with no right of residence in Italy for more than three months, but living there for at least two years.

Testing procedure

Serum samples were tested for HBsAg, total anti-HCV, anti-HIV, anti-HBc and hepatitis B surface antibodies (anti-HBs) by commercial immunoenzymatic assays (Abbott Laboratories, North Chicago, IL, United States: AxSYM HBsAg (V.2) M/S for HBsAg, AXSYM HCV 3.0 for anti-HCV, AXSYM HIV 0.5 COMBO for anti-HIV, AXSYM core for anti-HBc and AXSYM AUSAB for anti-HBs). Anti-HIV reactivity was always confirmed by a western blot assay (Genelabs Diagnostics, Science Park Drive, Singapore) that identifies both HIV-1 and HIV-2 strains. Circulating HCV RNA was quantified by real-time polymerase chain reaction (PCR) in a Light cycler 1.5 (Roche Diagnostics, Branchburg, NJ, United States) as previously described [15].

Statistical analysis

Continuous variables were summarised as mean and standard deviation, and categorical variables as absolute and relative frequencies. Differences in mean values were evaluated by Student's t-test and chi-squared test was applied to categorical variables. A p value < 0.05 was considered to be statistically significant.

Results

Of the 926 undocumented migrants and refugees who attended one of the four primary-care clinical units during the study period, 882 agreed to participate in the study: 625 undocumented migrants and 257 refugees. The group of 625 undocumented migrants includes 105 citizens from Romania (n = 63), Bulgaria (n = 35) and Poland (n = 7) with no right of residence in Italy for more than three months, but living there for more than two years. The demographic and serological data of the patients obtained at the time of enrolment in the study are shown in Table 1. These participants were relatively young (median age: 34.5 years; range: 14–74), mostly male (72%) and had been living in Italy for a mean period of 58 months (standard deviation (SD): 55). A total of 444 (50%) came from sub-Saharan Africa, 198 (22%) from eastern Europe, 80 (9%) from northern Africa, 126 (14%) from Bangladesh, India, Pakistan and Sri Lanka (the 'India-Pakistan area'), 25 (3%) from other areas of Asia and 9 (1%) from South America (Table 2). Details of the country of origin of these 882study participants are shown in Table 2.

Table 2a

Country of origin of study participants, Caserta and Naples, Italy, January 2012–June 2013 (n = 882)

Area and countries	Number of participants
Eastern Europe	
Albania	3
Belarus	2
Bosnia and Herzegovina	3
Bulgaria	35
Georgia	4
Former Yugoslav Republic of Macedonia	1
Moldova	1
Poland	7
Romania	63
Russia	19
Ukraine	60
Northern Africa	
Algeria	22
Libya	1
Mauritania	4
Morocco	36
Tunisia	17
Sub-Saharan Africa	
Angola	1
Benin	4
Burkina Faso	35
Cameroon	4
Cape Verde	2
Chad	3
Congo	2
Côte d'Ivoire	27
Democratic Republic of the Congo	2
Ethiopia	1
Gambia	9
Ghana	89
Guinea	10
Liberia	13
Mali	25
Mauritius	1
Niger	4
Nigeria	89
Rwanda	1
Senegal	84
Sierra Leone	1
Somalia	6
South Africa	1
Sudan	14
Tanzania	4
Togo	12

Table 2b

Country of origin of study participants, Caserta and Naples, Italy, January 2012–June 2013 (n = 882)

Area and countries	Number of participants
India-Pakistan area	
Bangladesh	48
India	6
Pakistan	46
Sri Lanka	26
Other Asian countries	
China	11
Iraq	1
Kazakhstan	1
Kyrgyzstan	11
Syria	1
South America	
Brazil	2
Dominican Republic	4
El Salvador	3

Serological screening

Of the 882 individuals enrolled, 78 (9%) were HBsAg positive, 35 (4%) anti-HCV positive and 11 (1%) anti-HIV positive (single infections); seven (1%) had more than one infection. Of these seven with multiple infections, two were HBsAg/anti-HIV positive, four anti-HCV/anti-HIV positive and one HBsAg/anti-HCV/anti-HIV positive (Table 1). Of the 801 HBsAg-negative patients, 373 (47%) were anti-HBc positive, of whom 20 were also positive for anti-HCV and five for anti-HIV. Thus, 454 of the 882 participants screened (51%) had a serum marker of HBV infection.

All participants with a detectable serum marker of HBV, HCV or HIV infection were unaware of their serological status. The differences between the 625 undocumented migrants and the 257 refugees were small (Table 1), and were of no or limited clinical value.

Of the 882 study participants, 638 were male and 244 female (Table 3). Compared with those who were male, female participants were generally older (38 years (SD: 12.2) vs 34 years (SD: 9.0); $p<0.001$), more frequently from eastern Europe (55% vs 10%; $p<0.0001$) and less frequently from sub-Saharan Africa (32% vs 58%; $p<0.001$) (Table 3). In addition, female participants had fewer serum markers of HBV infection (HBsAg positivity: 6% vs 10%; $p=0.07$; anti-HBc positivity: 31% vs 46%; $p<0.0001$). Other differences shown in Table 3 are of lesser demographic or epidemiological impact.

The characteristics of participants grouped according to the four major geographical groups (northern Africa,

Table 3

Characteristics of study participants by sex, Caserta and Naples, Italy, January 2012–June 2013 (n = 882)

Characteristic	Male n (%)[a]	Female n (%)[a]	P value Male vs female
Number of patients	638	244	NC
Mean age in years (SD)	34 (9.0)	38 (12.2)	‹0.001
Mean length of time living in Italy in months (SD)	58 (57)	57 (41.5)	0.8
Mean number of years of schooling (SD)	6.7 (5)	8.5 (6)	0.01
Number using alcohol[b] (%)	127 (19.9)	30 (12.3)	‹0.001
Status in country, n (%)			
Undocumented migrant [c]	426 (66.8)	199 (81.5)	‹0.0001
Refugee	212 (33.2)	45 (18.4)	‹0.0001
Area of origin, n (%)			
Northern Africa	72 (11.3)	4 (1.6)	‹0.0001
Sub-Saharan Africa	370 (58.0)	78 (32.0)	‹0.0001
Eastern Europe	65 (10.2)	133 (54.5)	‹0.0001
India-Pakistan area[d]	117 (18.3)	9 (3.7)	‹0.0001
Other	14 (2.2)	20 (8.2)	‹0.0001
Reported risk factors[e], n (%)			
Use of drugs	3 (0.5)	0 (0)	0.8
Unsafe sexual intercourse[f]	187 (29.3)	34 (13.9)	‹ 0.0001
Surgery/dental care/illegal abortion	304 (47.6)	104 (42.6)	0.4
Blood transfusion	9 (1.4)	7 (2.9)	0.7
Other parenteral exposure[g]	522 (81.8)	232 (95.1)	‹ 0.001
Not stated	3 (0.5)	2 (0.8)	0.5
Serological status, n (%)			
HBsAg positive	66 (10.3)	15 (6.1)	Any serological marker vs none 0.001
HBsAg negative/anti-HBc positive	297 (46.5)	76 (31.1)	
Anti-HCV positive	31 (4.8)	9 (3.7)	
Anti-HIV positive	13 (2.0)	5 (2.0)	
Any serological marker	378 (59.2)	96 (39.3)	
No serological marker	261 (40.9)	148 (60.6)	

Anti-HBc: total hepatitis B core antibody; HBsAg; hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; NC: not calculated; SD: standard deviation.

[a] Unless otherwise indicated.

[b] Defined as consumption of alcohol exceeding 30g per day for women and 40g per day for men over the last six months.

[c] The group of 625 undocumented migrants included 105 individuals from Romania, Bulgaria 35 and Poland with no right of residence for more than three months, but living in Italy from at least two years.

[d] Bangladesh, India, Pakistan, Sri Lanka.

[e] Both in the country of origin and in Italy.

[f] No use of condoms with more than two sexual partners.

[g] Unsafe intravenous or intramuscular injections, acupuncture, tattoo, body piercing or tribal practices.

sub-Saharan Africa, eastern Europe and India-Pakistan area) are shown in Table 4. These four geographical groups comprised 96% of the study participants. The rates of HBsAg, anti-HBc, anti-HCV and anti-HIV positivity according to these geographical groups and the participants' age are shown in Figures 1, 2, 3 and 4. Five age groups (0–15, 16–30, 31–45, 46–60 and 61–75 years) were considered; however, the age group 0–15 years included only one person and was therefore not included.

Compared with the other geographical groups, the 198 individuals from eastern Europe were older ($p<0.0001$) and mostly female ($p<0.00001$). The majority (n = 78) of the 80 individuals from northern Africa were men and, compared with other geographical groups, were more frequently refugees (41% (33/80); $p=0.05$) and had had a longer stay in Italy ($p<0.0001$). The 444 individuals from sub-Saharan Africa were mostly male (n = 366; 82%) and, compared with the other geographical groups, had fewer years of schooling ($p<0.0001$). The 126 individuals in the India-Pakistan group were mostly male (n = 117 (93%)), with the most years of

Table 4

Characteristics of study participants by geographical area of origin, Caserta and Naples, Italy, January 2012–June 2013 (n = 848)

Characteristic	Northern Africa n (%)[a]	Sub-Saharan Africa n (%)[a]	Eastern Europe n (%)[a]	India-Pakistan area[b] n (%)[a]
Number of patients	80	444	198	126
Mean age in years (SD)	37 (8.6)	33 (8)	40.4 (12.7)	33 (11)
Number who were male (%)	76 (95.0)	366 (82.4)	66 (33.3)	117 (81.9)
Mean length of time living in Italy in months (SD)	91.8 (77.2)	53 (46.7)	61.8 (46.4)	43 (48)
Number of years of schooling (SD)	8.2 (4.7)	5.4 (5.1)	9.3 (5)	8.7 (4.5)
Number using alcohol[c] (%)	21 (26.3)	81 (18.2)	24 (12.1)	4 (3.2)
Status in country, n (%)				
Undocumented migrants[d]	47 (58.8)	304 (68.5)	154 (77.8)	97 (77.0)
Refugees	33 (41.2)	140 (31.5)	44 (22.2)	29 (23.0)
Reported risk factors[e] , n (%)				
Use of drugs	1 (1.2)	0 (0)	2 (1.0)	0 (0)
Unsafe sexual intercourse[f]	20 (25.0)	40 (9.0)	19 (9.6)	7 (5.5)
Surgery/dental care/ abortion	60 (75.0)	226 (50.1)	166 (83.8)	10 (7.9)
Blood transfusion	1 (1.2)	8 (1.8)	7 (3.5)	0 (0)
Other parenteral exposure[g]	54 (67.5)	353 (79.5)	154 (77.8)	8 (6.3)
Not stated	0 (0)	0 (0)	0 (0)	101 (80.2)
Serological status, n (%)				
HBsAg positive	2 (2.5)	62 (14.0)	12 (6.1)	4 (3.2)
HBsAg negative/anti-HBc positive	15 (18.7)	253 (57.0)	60 (30.3)	37 (29.4)
Anti-HCV positive	2 (2.5)	17 (3.8)	12 (6.1)	9 (7.1)
Anti-HIV positive	0 (0)	12 (2.7)	5 (2.5)	1 (0.8)
Any serological marker	19(23.7)	320 (72.1)	89 (44.9)	51 (40.5)
No serological marker	61 (76.3)	124 (27.9)	115 (58.1)	75 (59.5)

Anti-HBc: total hepatitis B core antibody; HBsAg; hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; SD: standard deviation.

[a] Unless otherwise indicated.

[b] Bangladesh, India, Pakistan, Sri Lanka.

[c] Defined as consumption of alcohol exceeding 30g per day for women and 40g per day for men over the last six months.

[d] The group of the undocumented migrants included 105 individuals from Romania, Bulgaria and Poland with no right of residence for more than three months, but living in Italy from more than two years.

[e] Both in the country of origin and in Italy.

[f] No use of condoms with more than two sexual partners.

[g] Unsafe intravenous or intramuscular injections, acupuncture, tattoo, body piercing or tribal practices.

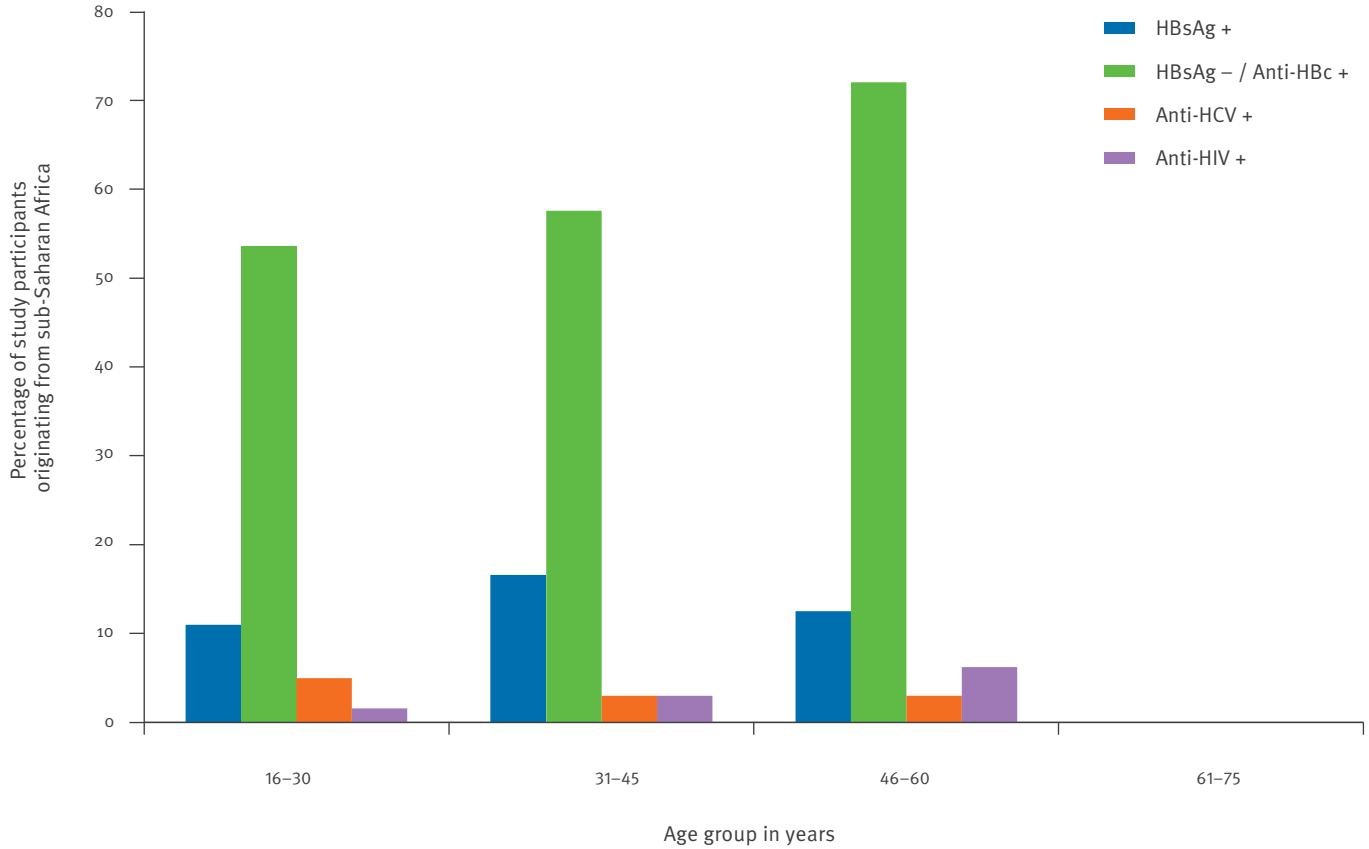
schooling (mean: 8.7; SD: 4.5) and the shortest stay in Italy (mean: 43 months; SD: 48).

The number of HBsAg-positive cases was very high (62/444 (14%)) in the individuals from sub-Saharan Africa and intermediate in those from eastern Europe (12/198 (6%)), northern Africa (2/80 (2%)) and the India-Pakistan area (4/126 (3%)), reflecting the level of HBV endemicity in the countries of origin [1,2,19], (Table 4). Similarly, an HBsAg-negative/anti-HBc-positive status, identifying individuals with occult or past HBV infection, was more frequently observed in individuals from sub-Saharan Africa (253/444 (57%)) than in those from eastern Europe (60/198 (30%); $p<0.0001$, northern Africa (15/80 (19%); $p<0.0001$) and the India-Pakistan area (37/126 (29%); $p<0.001$).

In individuals from sub-Saharan Africa, the cumulative prevalence of markers of ongoing or past HBV infection was very high (more than 50%) in the age groups 16–30, 31–45 and 46–60 years, with a tendency to increase with age, from 98/183 in the youngest age group to 23/32 in those aged 46–60 years (Figure 1); this differed from that seen in individuals from the

Figure 1

Serological status of study participants originating from sub-Saharan Africa, by age, Caserta and Naples, Italy, January 2012–June 2013 (n = 444)



Anti-HBc: total hepatitis B core antibody; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus. + : positive; – : negative.

other geographical groups (Figures 2, 3 and 4), but it should be borne in mind that the numbers per age group were sometimes small.

We used anti-HCV positivity as an index of both ongoing and previous HCV infection, an index particularly indicated for epidemiological investigations of HCV infection [20]. We tested for the presence of HCV RNA, a marker of ongoing HCV infection [21], in samples from 34 of the 40 anti-HCV positive individuals: 33 were positive. HCV infection was more frequent in individuals from eastern Europe (12/198 (6%)) and in those from the India-Pakistan area (91/126 (7%)) than in those from sub-Saharan (17/444 (4%)) and northern Africa (2/80 (2%)) (Table 4). In individuals from eastern Europe, anti-HCV positivity was high in people aged 16–30 years (6/57) and 31–45 years (6/66), whereas no positive individual was observed in the older age groups (Figure 3). A high prevalence of anti-HCV positivity was also found in all age groups of individuals from the India-Pakistan area: 2/56 in those aged 16–30 years, 5/49 in the 31–45 year-olds and 1/20 in the 46–60 year-olds (Figure 4). The prevalence of anti-HCV-positivity was 9/183 (5%) in individuals from sub-Saharan Africa aged 16–30 years, 7/229 (3%) in those aged 31–45 years and 1/32 in those aged 46–60 years (Figure 1). Of the 68 individuals from northern Africa tested for anti-HCV, only two were positive, both in the 31–45 age group (Figure 2).

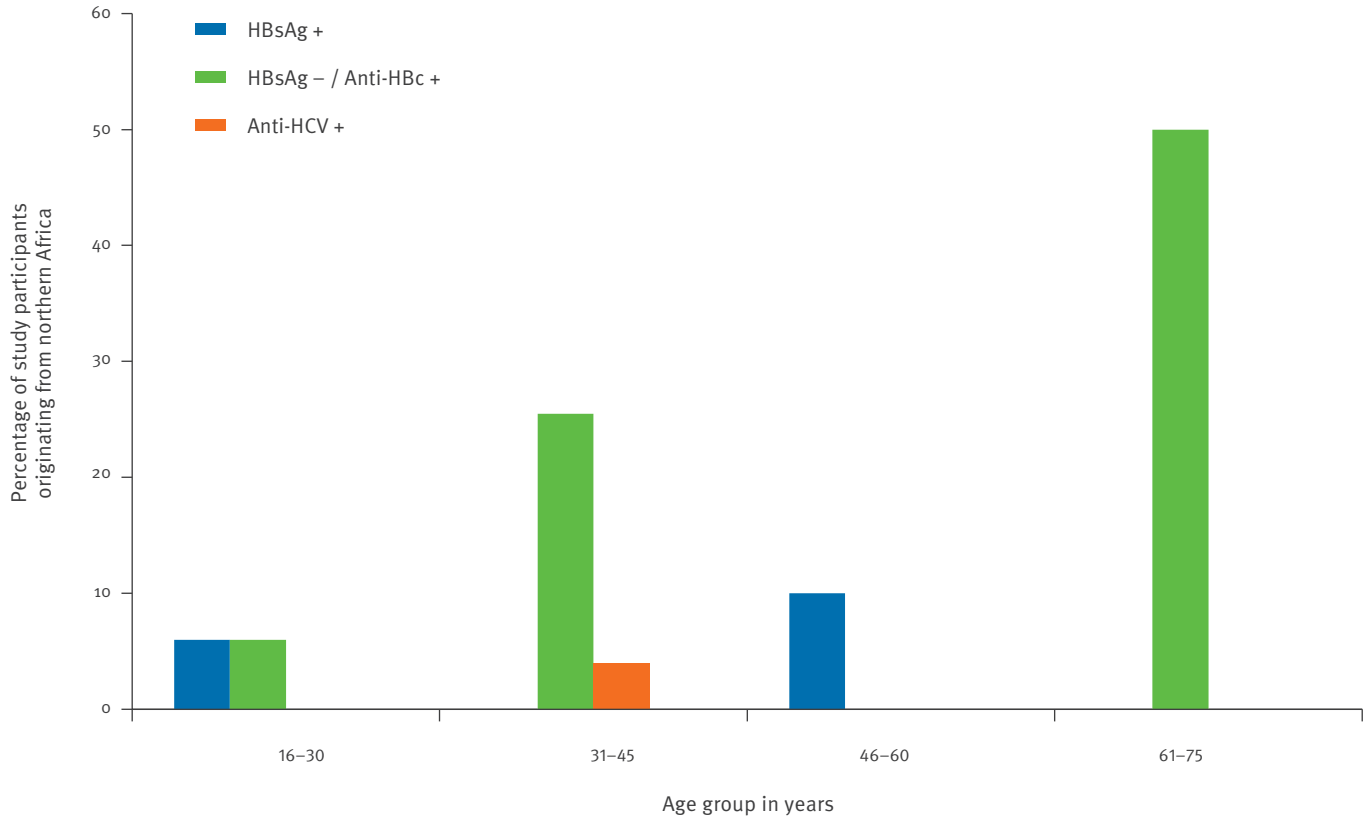
HIV antibodies were detected in 12 (3%) of the 444 migrants from sub-Saharan Africa: 3/183 (2%) were among those aged 16–30, 7/229 (3%) in 31–45 year-olds and 2/32 in 46–60 year-olds (Figure 1), whereas none of the 68 individuals from northern Africa tested positive (Figure 2). Anti-HIV positivity was also detected in individuals from eastern Europe (5/198, with a peak of 3/66 in the age group 31–45 years (Figure 3).

Serological markers of infection and demographic and epidemiological characteristics

Correlation between the presence of serological markers of HBV, HCV and HIV infection and the demographic and epidemiological characteristics of the 882 migrants enrolled in the study is shown in Table 5. The individuals who were either HBsAg positive, HBsAg negative/anti-HBc positive, anti-HCV positive or anti-HIV positive (aetiological subgroups), compared with those with no serum marker, had fewer years of schooling, were more frequently male and more frequently came from sub-Saharan Africa (Table 5). The percentages of migrants

Figure 2

Serological status of study participants originating from northern Africa, by age, Caserta and Naples, Italy, January 2012–June 2013 (n = 80)



Anti-HBc: total hepatitis B core antibody; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus.
+ : positive; – : negative.

reporting the risk factors stated in Table 5 were similar in the four aetiological groups and the group with no serum marker of HBV, HCV or HIV infection. A total of 701 (80%) of the study participants reported 'other parenteral exposure', including unsafe intravenous or intramuscular injections, acupuncture, tattoo, piercing or tribal practices, 532 (60%) invasive medical procedures such as surgery, dental care and abortion, and 217 (25%) unsafe sexual intercourse (defined as no use of condoms with more than two sexual partners). Use of drugs and blood transfusion were infrequently reported.

These analyses were performed also for the two most numerous geographical groups (individuals from sub-Saharan Africa and eastern Europe). In the former, the individuals in each aetiological group and those in the group with no serum marker reported other parenteral exposure in 353 (80%) of the 444 cases, invasive medical procedures in 226 (51%) and unsafe sex in 40 (9%); no individual reported use of drugs. In individuals from eastern Europe, only a few (n = 7) reported having had a blood transfusion, 166/198 (84%) reported invasive medical procedures and 154 (78%) other parenteral exposure. Unsafe sex was reported by 10% (n = 19) and use of drugs by only a few (n=2) individuals from this area.

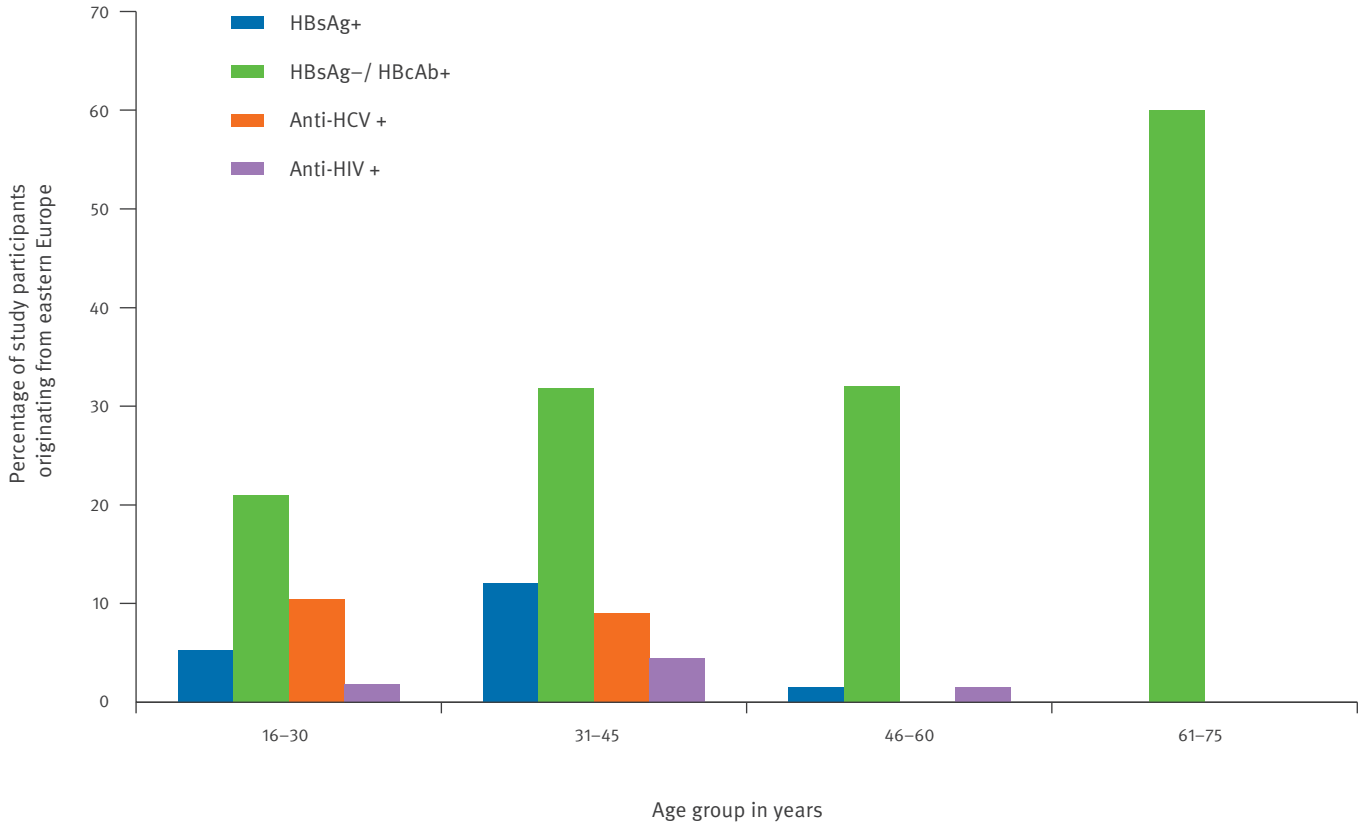
None of the 882 undocumented migrants or refugees had been vaccinated against HBV. This is supported in part by the observation that 68 (17%) of the 408 anti-HBc negative individuals were tested for anti-HBs and found negative.

Discussion

The socio-economic and cultural backgrounds of the undocumented migrants and refugees in our study made their access to the Italian healthcare services difficult. Nevertheless, the presence of a skilled physician and a cultural mediator in the four centres overcame any language or cultural barrier and allowed successful screening, with an over-95% acceptance rate. Indeed, the rate of the interviewed undocumented migrants and refugees who agreed to be screened seems a useful parameter to evaluate the effectiveness of the screening. The success of screening to identify serum markers of HBV, HCV or HIV infection in undocumented migrants or refugees varies from one study to another, mainly due to the different composition of the populations studied according to their place of origin, legal status, length of stay in the foreign country and the quality of the strategies used to improve the access of these vulnerable populations to a screening programme [22-31].

Figure 3

Serological status of study participants originating from eastern Europe, by age, Caserta and Naples, Italy, January 2012–June 2013 (n = 194)



Anti-HBc: total hepatitis B core antibody; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus. + : positive; – : negative.

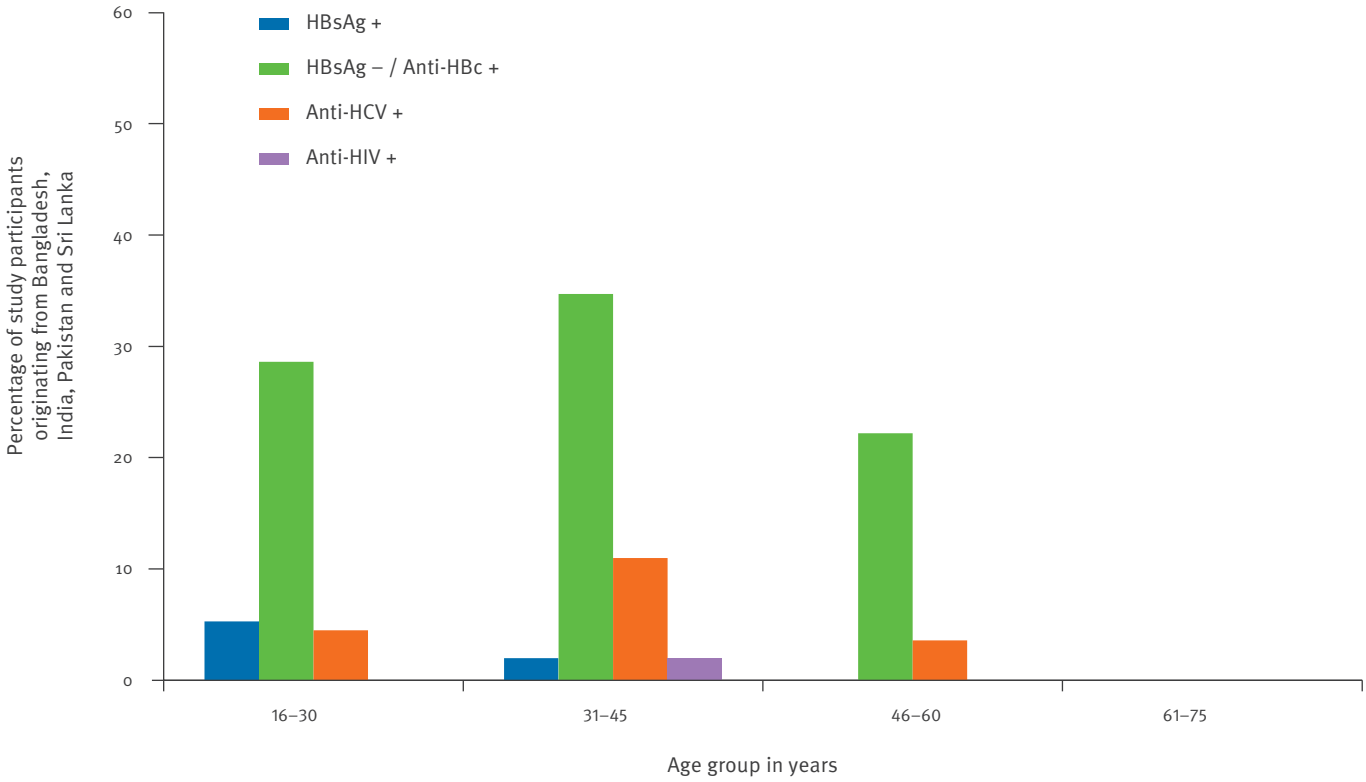
In our study, individuals who were HBsAg positive, HBsAg negative/anti-HBc positive, anti-HCV positive and anti-HIV positive were referred to a tertiary-level clinical centre to complete the diagnostic course and if necessary to receive therapeutic follow-up. In addition, all those participating in the screening had the opportunity to improve their knowledge of the transmission and prevention of HBV, HCV and HIV infections. Consequently, our screening strategy may be an example of how to overcome language and cultural barriers in a population of undocumented migrants and refugees.

In agreement with recommendations of the United States Centers for Disease Control and Prevention, the data from our study underscore the need for universal screening for HBV infection in people from countries with HBsAg prevalence higher than 2% [23]. Our data also suggest the need for universal screening for HCV and HIV infections in people from countries with anti-HCV or anti-HIV prevalences higher than 2%.

An ongoing or past/occult HBV infection was frequently detected in the population in our study: nearly 9% of the undocumented migrants and refugees were HBsAg positive and nearly 40% HBsAg negative/anti-HBc positive. The HBsAg positivity prevalence ranged from 2.2% to 13.6% in other studies carried out in Italy investigating undocumented migrants in Verona (northern Italy) in 2004–05 [24] and in the Campania region (southern Italy) from 1999 to 2008 [22] and refugees in Bari in 2001–10 [25-28] and Foggia [29] in 2005 in southern Italy. The highest prevalence of HBsAg positivity was observed in refugees from Albania (13.6%), and the lowest (2.9%) in refugees from Kosovo under UN Security Council Resolution 1244 and in a Kurdish refugee population from Iraq (2.2%) in Apulia in 2000–03 [26-28]. These high prevalences most probably reflect widespread HBV infection in the countries of origin, as the rate of HBsAg positivity is under 1% in Italy, a country with an ongoing mass vaccination programme currently covering Italian citizens aged 0–34 years [32]. HCV infection was identified in 4.8% of the population in our study: it was 2.7% in undocumented migrants enrolled in 2004–05 in Verona [23], 4.3% in refugees in 2008 in Bari [25] and 3.6% in migrants, frequently undocumented, from 1999 to 2009 the Campania region [22]. HIV infection was identified in 2% of the individuals in our study, whereas it was 5% of those investigated in the Campania region [22] and 1.5% of those investigated in Bari [25]. Thus the prevalence of HBV, HCV or HIV infection in the populations investigated in the studies performed in Italy to date

Figure 4

Serological status of study participants originating from eastern Europe, by age, Caserta and Naples, Italy, January 2012–June 2013 (n = 194)



Anti-HBc: total hepatitis B core antibody; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus. + : positive; – : negative.

is high, but this provides an incomplete picture on a national scale due to the limited number of published papers and the lack of a systematic survey.

Individuals from sub-Saharan Africa accounted for just over half of the people enrolled in our study, one eighth of whom had an ongoing infection and more than a half had a past or occult HBV infection. These very high rates, with wide variation in the country subgroups (data not shown), indicate acquisition of HBV at birth from infected mothers or in early youth from parents or siblings [30]. The HBsAg positivity rates were intermediate in individuals from eastern Europe and the India-Pakistan area, again with wide variation in the country subgroups (data not shown). In agreement with the information available on the epidemiology of HIV infection [6,31,33,34], the highest prevalence of anti-HIV-positivity was seen in the individuals from sub-Saharan Africa, with some variations between single countries (data not shown).

The data in our study suggest that healthcare strategies for screening should differ by sex, as the prevalence of individuals with an ongoing or past HBV infection was higher among those who were male. Compared with individuals in the subgroup with no serum markers, those in the four aetiological subgroups were less frequently female, had fewer years of schooling and more frequently came from sub-Saharan Africa. In these aetiological subgroups, the percentages of individuals reporting risk factors for acquiring HBV, HCV or HIV were very high but similar to those found in the subgroup with no serum marker and, therefore, infection-associated risk factors may be difficult to determine. It is noteworthy that many of the infections were detected in individuals who had experienced unsafe healthcare practices and that only a few individuals reported drug use or having had a blood transfusion in all the aetiological subgroups.

Only individuals aged 16–30, 31–45 and 46–60 years were numerous enough to be analysed by age. Widespread HBV infection (ongoing or past) in individuals from sub-Saharan Africa (65% aged 16–30 years and a progressive increase in older age groups up to 80% in individuals aged 45–60 years) should alert the Italian healthcare authorities to implement measures to control parenteral infections in undocumented migrants and refugees. Universal HBV vaccination has been mandatory in Italy since 1991 [32,35] and nearly all Italian citizens aged 0–34 years have been vaccinated [36]. In contrast, none of the 882 undocumented migrants or refugees in our study had been vaccinated against HBV or tested for HBV markers after a mean stay in Italy of 58 months. Thus extending HBV

Table 5

Demographic and other characteristics at enrolment of study participants according to serum markers of HBV, HCV and HIV infection (n = 882)

Characteristic	Number of patients (%)[a]				
	HBsAg positive	HBsAg negative/ anti-HBc positive	Anti-HCV positive	Anti-HIV positive	No serological marker
Number of patients (%)	81 (9.2)	373 (42.3)	40 (4.5)	18 (2.0)	408 (46.3)
Mean age in years (SD)	34 (8.3)	35 (10)	32.5 (8)	37 (7)	36 (11)
Number who were male (%)	66 (81.5$_A$)[b]	297 (79.6$_B$)[b]	31 (77.5)	13 (72.2)	261 (64.0$_C$)[b]
Mean length of time living in Italy in months (SD)	47 (54)	54 (50)	61.6 (55)	63 (38)	56.5 (57)
Mean number of years of schooling, (SD)	3.6 (4.2$_D$)[c]	6.7 (5.4$_E$)[c]	7.3 (4$_F$)[c]	7 (5)	8.5 (3.5$_G$)[c]
Number using alcohol[d] (%)	13 (16.0)	63 (16.9)	13 (32.5)	4 (22.2)	83 (20.3)
Legal status, n (%)					
Undocumented migrant[e]	58 (71.6)	254 (68.1)	33 (82.5)	14 (77.8)	293 (71.8)
Refugee	23 (28.4)	119 (31.9)	7 (17.5)	4 (22.2)	115 (28.2)
Area of origin, n (%)					
Eastern Europe	12 (14.8)	60 (16.1)	12 (30.0)	5 (27.8)	120 (29.4)
Northern Africa	2 (2.5)	15 (4.0)	2 (5.0)	0 (0)	62 (15.2)
Sub-Saharan Africa	62 (76.5$_G$)[f]	253 (67.8$_H$)[f]	17 (42.5)	12 (66.7$_I$)[f]	126 (30.9$_J$)[f]
India-Pakistan area[g]	4 (4.9)	37 (9.9)	9 (22.5)	1 (5.5)	78 (19.1)
Other	1 (1.2)	8 (2.1)	0 (0)	0 (0)	22 (5.4)
Reported risk factors[h] , n (%)					
Use of drugs	0 (0)	1 (0.3)	2 (5.0)	0 (0)	1 (0.2)
Unsafe sexual intercourse[i]	21 (25.9)	82 (22.0)	12 (30.0)	3 (16.7)	99 (24.3)
Surgery, dental care, abortion	43 (53.1)	202 (54.2)	24 (60.0)	13 (72.2)	250 (61.3)
Blood transfusion	1 (1.2)	7 (1.9)	1 (2.5)	0 (0)	8 (2.0)
Other parenteral exposure[j]	66 (81.5)	285 (76.4)	35 (87.5)	18 (100)	297 (72.8)
Not stated	5 (6.2)	2 (0.5)	5 (12.5)	0 (0)	3 (0.7)

HBc: total hepatitis B core; HBsAg; hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; SD: standard deviation.

[a] Unless otherwise specified.

[b] P value for $_A$ vs $_C$ = 0.003; $_B$ vs $_C$ <0.0001.

[c] P value for $_D$ vs $_G$ < 0.0001; $_E$ vs$_G$ < 0.0001; $_F$ vs$_G$ = 0.042.

[d] Defined as consumption of alcohol exceeding 30 g per day for women and 40 g per day for men over the last six months.

[e] The group of the undocumented migrants included 105 individuals from Romania, Bulgaria and Poland with no right of residence for more than three months, but living in Italy from more than two years.

[f] P value for $_G$ vs $_J$<0.0001; $_H$ vs $_J$=0.0001; $_I$ vs $_J$=0.003.

[g] Bangladesh, India, Pakistan, Sri Lanka.

[h] Both in the country of origin and in Italy.

[i] No use of condoms with more than two sexual partners.

[j] Unsafe intravenous or intramuscular injections, acupuncture, tattoo, piercing, or tribal practices.

vaccination to legal and undocumented migrants and refugees living in Italy should be considered, especially for those who stay in the country a long time. Of course, some undocumented migrants and refugees will chose another country as their final destination, but some may remain in Italy for years or forever, as shown by the length of stay in our study (mean: 58 months; SD: 55). Indeed, taking care of this vulnerable group of individuals should be a moral duty of the governments of all countries [37-39].

The prevalence of anti-HCV positive individuals reached 10% in those aged 16–30 and 31–45 years from eastern Europe, whereas no positive individual was seen in the older age group. This finding possibly indicates spread of HCV infection in young adults in the countries of origin in recent years. Also of epidemiological importance was the percentage of individuals who were anti-HIV positive among those from sub-Saharan Africa: the prevalence increased with increasing age, with prevalence doubling (from 1.6% to 3%) in the 16–30 year-olds to the 31–45 year-olds and from the 31–45 year-olds to the 45–60 year-olds (from 3% to 6.2%).

It is difficult to assess the representativeness of the refugees and undocumented migrants in our study, but the percentages of cases with HBV, HCV or HIV infection in the different geographical groups in our study do not differ substantially from those reported in the literature for the corresponding areas of origin [1,2,5,6]. Although the individuals investigated in this study may not be representative of the whole population in their geographical area of origin, the observed rates of HBV, HCV and HIV infection may be useful to help to devise appropriate healthcare strategies for undocumented migrant and refugee populations from different geographical areas.

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Conflict of interest

None declared.

Authors' contributions

NCo, GP and ES were responsible for the conception and design of the study and wrote the manuscript; LA, LG, MP, NCa, RF enrolled the individuals and followed the individuals. CS and IFA participated in the conception of the study and interpreted the data; MS performed the serological tests.

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