

R E V I E W

HCV and immigration in Italy

Massimo Galli, Annalisa Ridolfo, Lorena van denBogaart, Cristina Negri, Andrea Giacomelli

Department of Infectious Disease, ASST Fatebenefratelli Sacco, Milan, Italy

Summary. Aim of this survey is to examine the current situation regarding the various migrant populations in Italy, their consistency, their distribution and the known data in terms of prevalence of HCV infection in the countries of origin, possibly distinguishing by age groups, and evaluate the presumed prevalence of HCV infection in the different areas of Italy in relation to the place of departure, in relation to any comparative data already present in Italy. This in order to construct a sort of Italian geographic map - detailed by Regions or by Provinces - of an estimated or predictable number of migrant people, according to the various groups, who carry the HCV infection, in order to provide a summary of information not yet available and which may constitute the starting point for further studies. This is a rather ambitious work because it intends to reason on a composite reality - making it an instrument of dissemination - such as the multifaceted reality of the presence in Italy of migrant populations who arrive or have already arrived from countries of South America, Africa, Eastern Europe of Asia; this in a vision not linked to the current dramatic arrival of immigrants by sea but which falls within a more general context. (www.actabiomedica.it)

Key words: HCV, immigration, Italy

Introduction

Hepatitis C (HCV) is a major cause of liver cirrhosis and hepatocellular carcinoma (1).

The global prevalence of anti-HCV was estimated at 2.0% (1.7-2.3%) among adults and 1.6% (1.3-2.1%) for all ages corresponding to 104 (87-124) million and 115 (92-149) million infections, respectively. The viraemic prevalence was 1.4% (1.2-1.7%) among adults and 1.1% (0.9-1.4%) in all ages corresponding to 75 (62-89) million and 80 (64-103), respectively (2).

A study conducted in 2013 in Europe has estimated that the prevalence of HCV varies between 2,4% for western and Central Europe and 2,9% for Eastern Europe. The global population of this area is approximately 740,000,000 persons leading to an estimation of the HCV infected pool of more than 19,000,000 person. The shortcomings of this and other study reside in the fact that evidence is based on surveys often conducted in selected groups, or excluding high risk

population such as prison inmates and groups of persons living in social exclusion. The attributable fractions of cirrhosis for HCV are 38% for Western and 34% for Eastern Europe while those for hepatocellular carcinoma are, respectively, 44% and 15% (3).

Despite the burden HCV imposes on national healthcare systems and budgets, HCV has failed to attract the type and level of attention it calls for from health policy makers, healthcare workers, and indeed the public at large. WHO resolutions (5) and guidelines (6), as well as a meeting by the Viral Hepatitis Prevention Board (7) have all called for more attention to the problem. All these calls for action have mentioned the growing role of migration as a possible driver of the epidemic.

In 2015 alone, over one million migrants, refugees and asylum seekers arrived in Europe, (7) adding to an existing migrant population of around 72 million people (8). Many of them are from countries where both HBV and HCV are significantly more prevalent than

in Europe. The contribution of migrants to the changing epidemiology of HCV in Europe has been referred to in several studies (3, 9-11).

Proportionately high rates of HCV in migrant populations have been reported in Italy, the Netherlands, Sweden and the UK10-13 and in 2014 the ECDC reported that in Spain the prevalence of HCV ranged between 0.4% and 0.9% among migrants from Latin America, 1.9% among migrants from North Africa and between 9% and 15% among migrants from sub-Saharan Africa and Eastern Europe.¹⁴ Similarly in Germany, where between 23 and 37% of all reported HCV is in people of foreign nationality, migration from Turkey and Eastern Europe is thought to be an important factor in changing patterns of HCV (17).

Although rates of HCV among migrant populations typically reflect the prevalence of the disease in countries of origin, there are also reports that HCV rates among migrants in Europe are higher than in home countries (18). This suggests that the migration process itself may prompt behaviors that expose migrants to a higher risk of HCV (19-23). Migrants are also represented in other known HCV risk groups, such as prisoners, (24) and men who have sex with men (25).

A common feature among migrants and refugees is also self perceived loss of power and difficulty in making key decisions on health and healthcare seeking (26). Culturally defined attitudes to disease prevention and treatment vary widely and this can easily complicate public health initiatives. Mass migration into Europe is changing the epidemiology of HCV. To what extent countries are prepared to respond to the challenge is not clear. The public health sectors' response to migration has been slow, and in the case of HCV there is little evidence of concerted action. Although studies have shown the cost effectiveness of screening migrants for HCV, only four countries in the EU have adopted migrant screening policies and while there have been some advances in the form of migrant friendly hospitals, migrants on the whole continue to be ignored as a group that has special psychosocial as well as medical needs. If the goal of HCV eradication is to be achieved much more inclusive policies and practices will be required (26). An imperative need now exists for new thinking, increased resources, and

better training of health-care staff working with these new populations (27).

Analysis of literature

The starting point of this analysis is represented by the prevalence data of HCV infection in the places of origin of the migrants (being the local ones relative to Italy scarcely available) from which any problems can be extrapolated (a lower prevalence of infection in one present population with greater consistency on our territory implies a greater impact, in absolute numerical terms, of a higher prevalence in immigrants of another nationality not represented in Italy).

Of particular importance is the analysis of prevalence of HCV infection compared to starting populations also according to age groups, since the clinical condition of a fifty year old compared to that of a thirty year old can be very different. Another aspect to consider, in countries of South America or Africa, is the failure to guarantee the rights to health and care for those not covered by social insurance (a condition that can involve more than half of the less well-off), condition which can promote the transmission of the virus. To this end, after an accurate bibliographic research, an analysis of the costs incurred in health by the most significant epidemiological States of the infection in question is reported.

The HCV seroprevalence among immigrants in Italy

The available data on immigration in Italy of HCV-positive subjects are scarce and not uniformly reported to the entire national territory. However, there are many studies that carefully address individual local realities.

A recent retrospective multicentre study with the aim to evaluate the clinical and epidemiological features of HCV infection in a cohort of immigrants in Italy shown that migrant populations had higher rates of HCV-related chronic hepatitis than the indigenous population; in some cases the infections were contracted in the country of origin, but in others the infection

took place in Italy (Table 1). The most commonly represented genotype, besides 1, was 4, especially among Africans. The therapeutic management of immigrants proved to be very difficult, mostly but not exclusively because of social factors (28).

A series of studies have analyzed the changes in the epidemiology of hepatitis C in the various areas of Italy and how immigration has influenced these changes.

In a study conducted by Chiamonte M. et al. on HBV and HCV infection among non-European Union immigrants in North-East Italy, resulted that among the 933 individuals screened for HCV infection, prevalence of antibody was much lower (0.9%) than that observed in the Italian general population (3.2 in the North-East Italy, 12.6 % in the South Italy). That's why we can consider the risk of HCV spread from non-EU immigrants very low. No significative differences were observed in the prevalence of anti-HCV according to the age group, sex and region of origin (Table 2). The results of this study demonstrate that the prevalence of HCV infection seems to be similar or lower than the host population, while that HBV infection among immigrants from non-UE countries

is still very high because of the high endemicity of HBV in the place of origin. This difference depends on the different way of transmission: iatrogenic for HCV and household or sexual for HBV (29).

Another study, conducted in a community of Sub-Saharan Immigrants living in Verona (Northern Italy) made for analyze the epidemiology of HAV, HBV and HCV, revealed that the HCV positivity rate resulted similar to the prevalence of the Italian population: Of the 182 people enrolled, 5 males (2.7%) who had been in Italy since 2003 were HCV positive. Two of them had a history of HBV infection. No specific parenteral risk factors emerged for these subjects, nor there were any significant differences in their sociodemographic characteristics, though they mostly declared a lower educational level and unemployment (30). The prevalence of HCV infection (2.7%) in this immigrants was a little higher than that reported in a similar study (0.9%) carried out in the mid-1990s by Chiamonte and colleagues, (29) but it is substantially the same as the estimated prevalence in their geographical area of origin (on average around 3.0%) (31). In any case as the most recent Italian data show an HCV incidence rate of 0.5/100,000 and a prevalence rate that ranges from 3% to 26%, (32) there is no evidence of any particular impact of this infection on the autochthonous population.

A study published in 2001 assessed the prevalence of viral hepatitis infections in a sample of Kosovar refugees that arrived in southern Italy as a result of the 1999 war in the Balkans. This study indicate that the level of endemicity of HCV infection in the

Table 1. HCV-RNA positive patients (119) (29)

	No.	%
Sub-Saharan Africa	24	20.2
Asia	17	14.3
East Europe	71	59.6
North Africa	5	4.2
South America	2	1.7

Table 2. Data on the anti-HCV patient subjects (30)

Age (year)	Sex	Region of origin	HBsAg	Anti-HBc ± anti-HBs	Risk factors
21	m	Eastern Europe	–	+	n.i.*
30	m	Latin America	–	+	n.i.
31	f	Eastern Europe	–	+	n.i.
36	m	North Africa/Middle East	–	+	Multiple surgical interventions
19	f	Eastern Europe	–	–	Presence of STD†
29	m	North Africa/Middle East	–	–	Multiple partners
29	f	Eastern Europe	–	–	Occupational
34	m	Latin America	–	–	Multiple partners, HIV +

* n.i., information not available.

† STDs, sexually transmitted diseases.

Kosovar population was low, in fact the prevalence of anti-HCV antibodies was 0.7%, in agreement with the prevalence rates reported in the population of European countries (33).

Another study in 2003 investigated the prevalence of hepatitis infection in a sample of 1005 refugee Kurds from Iraq and Turkey. In this population the HBV infection is moderately endemic, while the prevalence of HCV infection is low. Only the subject that was confirmed positive for anti-HCV (0.1%) and HCV-RNA showed a 4c/4d genotype (34).

In Italy in 2002 was performed a retrospective multicenter study to evaluate the prevalence of hepatitis in hospitalized immigrants in Italy. It was evinced that 282 of the 2255 immigrants analyzed were affected by hepatitis (12.5% of total hospitalised patients). The prevalent form was HBV-related (41.6% in chronic forms and 48.4% in acute), while the rate for HCV were less frequent (37.5% in chronic and 3% in acute). The most part of patient were men (59.6%), with a mean age of 34.2 years and come from east-European countries (34.39%). Viral hepatitis are the third infectious diseases evidenced in immigrated population. HBV-chronic hepatitis is the prevalent form in immigrated patients, as expression of absence of vaccine prophylaxis in many countries (35).

A new picture of HCV epidemiology in Northern Italy is instead offered by a study conducted on a cohort of 965 subjects all resident (including 47 immigrants), anonymously tested for HBV and HCV infections: the overall prevalence of anti-HCV was 2.6%, with a bimodal distribution characterized by the highest prevalence (12%) in subjects over 75 years old; none of the subjects under 25 years old was anti-HCV positive; anti-HCV positivity was similar in males and females (2.4% vs. 2.7%); HCV-RNA was positive in 40% of cases and genotype 1 was the most common. A cohort effect showing a reduction of HCV infection in the elderly, possible due to age-related mortality (36).

A huge study based on screening of undocumented migrants or refugees for HBV, HCV and HIV was conducted from January 2012 to June 2013 at four primary-level clinical centers in Naples and Caserta, in Southern Italy: Of the 882 individuals enrolled, 35 (4%) were anti-HCV positive and seven (1%) had more than one infection (Table 3). All participants

with a detectable serum marker of HBV, HCV or HIV infection were unaware of their serological status. HCV infection was more frequent in individual from Eastern Europe 12/198 (6%), and in those from India-Pakistan area 91/126 (7%) then in those from sub-Saharan 17/144 (4%) and Northern Africa 2/80 (2%). In individual from Eastern Europe, anti-HCV positivity was higher in people aged 16-30 years and 31-45 years, whereas non positive individual was observed in older age group. A high prevalence of anti-HCV positivity was also found in all age groups of individuals from the India-Pakistan area. 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. Of the 68 individuals from Northern Africa tested for anti-HCV, only two were positive, both in the 31-45 age group. 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 experience unsafe healthcare practice and that only a few individuals reported drug use or have a blood transfusions. 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 (37).

A research conducted among refugees hosted in the Bari Palese CARA (Asylum Seeker Centres) in Southern Italy (Apulian Model) to study seroprevalence of viral hepatitis and HIV in 2008, involving 529 refugees, found that 44 individuals (8.3%) were HBsAg positive, 24 (4.5%) anti-HCV positive, and 8 (1.5%) HIV positive. In the opinion of the authors, these results - such many others - confirmed some traditional concerns about migrant health and especially about the control of infectious diseases among these populations and the need to strengthen screening to

Table 3. Characteristics of study participants by geographical area of origin, Caserta and Naples, Italy, January 2012–June 2013 (n = 848) (37)

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)

aid the development of trust between migrants and resident population (38).

In a previous study, also conducted in a population of refugees of various nationalities, living in forementioned Asylum Seeker Centre in Bari Palese, was assessed the prevalence of HIV, HBV and HCV serological markers and the prevalence of VDRL positive subjects. The study was carried out in the period May–July 2008 and recruited only voluntarily enrolled healthy refugees. A total of 529 refugees, 442 males and 87 females, aged between 7 and 52 years, were studied. Of these, 510 were from Africa and 19 from Asia. A total of 24 (4.5%) individuals, 23 males and 1 female were anti-HCV positive. In detail, the figures were 4.3% for African refugees and 10.5% for Asians.

A significant proportion (12.3%) of asymptomatic refugees presented with at least one condition potentially associated with long-term complications and risk of secondary transmission (39).

In another study was assessed the seroprevalence of hepatitis B, C and D markers in a sample of 670 Albanian refugees in Apulia, in 1997: the prevalence of anti-HCV antibodies resulted low (0.3%, 95% CI: 0.0–0.7) (40).

Another study aimed to describe the prevalence of HBV, HCV, and HIV infections in a cohort of immigrants living in Palermo, Sicily. The study was carried out in the period May 2006–June 2010 and recruited a total of 393 patients. Overall, 22/393 (5.6%) immigrants were anti-HCV positive and 13/327 (4.0%)

were infected with HIV. Findings from this study suggest that a suitable screening protocol for the viral blood/sexually transmissible diseases is recommended on entering Italy, and the adoption of health control strategies should also be considered to safeguard the health of the local population (41).

Another study was conducted in three areas of Southern Italy on undocumented migrants and refugees, it was a screening performed from 2012 to 2015, involved 1,727 immigrants in the Campania and Apulia. 70 (4,1%) of 1727 subjects screened were anti-HCV-positive and 55,7% of this resulted positive to HCV RNA. Patients in the anti-HCV/HCV-RNA-positive subgroup compare with those in the other two subgroups more frequently came from Northern Africa and more frequently declared risk factors associated with parental transmission of HCV infection (Tab.4). The 35,5% of cases showed HCV-genotype 1a or 1b, 23,8% genotype 2 and 22,6% genotype 3. Clinically: 11 (35,5%) HCV-RNA-positive cases were HCV inactive chronic carriers, 18 (58,1%) had chronic hepatitis and 2 (6,4%) liver cirrhosis (42).

The prevalence data of HCV infection in the places of origin of the migrants

According to WHO estimates, an estimated 500 million are living with chronic viral hepatitis, making HBV and HCV one of the top 10 infectious diseases killers globally (43). A recent review that have analyzed data between 2000 and 2015 showed that globally the prevalence and number of HCV infected patients, if compared to a similar study concerning the period 1990-2005, has decreased from 2,8% to 2,5% and from 185 to 177 millions. It's interesting to note that the most relevant decrease has been observed in the high income zones, especially in Western Europe, Southern Africa and Australasia, whereas a massive increase it's reported in some of the low income areas of Central Africa and Central Asia (44).

A meta-analysis published in 2015 that have evaluated seroprevalence of Hepatitis C Antibodies suggest that migrants from intermediate or high HCV prevalence countries represent an important risk group for HCV infection. The overall pooled anti-HCV seroprev-

Table 4. Demographic and initial characteristics of the 1727 immigrants according to HCV serology and viraemia (42)

	Anti-HCV-positive/ HCV-RNA-negative subjects (A)	Anti-HCV/ HCV-RNA-positive subjects (B)	Anti-HCV- negative (C)	P value
Patients (n)	39	31	1,657	
Age, years, mean \pm SD	30 \pm 8.2	32.9 \pm 7.8	32.1 \pm 10.3	0.432
Males, n (%)	35 (89.7)	25 (80.6)	1,315 (79.4)	0.133
Legal status, n (%):				
Undocumented migrants	22 (56.4)	25 (80.6)	1,076 (65)	0,10
Low-income refugees	17 (43.6)	6 (19.3)	581 (35)	
Country of origin, n (%):				0.0306
Eastern Europe, 261 cases	4 (10.2)	11 (35.5)	246 (14.8)	A -> B: 0.02653
Northern Africa, 94 cases	1 (2.6)	1 (3.2)	92 (5.5)	
Sub-Saharan Africa, 990 cases	26 (66.7)	9 (29.0)	955 (57.6)	A -> C: 0.0017
India-Pakistan area, 353 cases	7 (17.9)	9 (29.0)	337 (20.33)	B -> C: 0.0001
Other countries, 29 cases	1 (2.6)	1 (3.2)	27 (1.6)	
In Italy for months, mean \pm SD	32.2 \pm 41.1	49.5 \pm 52.7	38.9 \pm 50	0.237
Years of schooling, mean \pm SD	7 \pm 3.6	6.4 \pm 3.9	6.7 \pm 4.8	0,520
Declared risk factors,* n (% by column)				0,0001
Drug addiction	0	3 (9.7)	5 (0.3)	A -> B = 0,001
Unsafe sexual intercourse	11 (28.2)	6 (19.3)	408 (24.6)	A -> C: 0,02
Surgery, dental care, abortion	10 (25.6)	27 (87)	774 (46.7)	B -> C: 0,001
Blood transfusion	0	0	21 (1.3)	
Other parenteral exposure**	16 (41.0)	31 (100)	1,216 (73.3)	
Not declaring risk factors	5 (12.8)	0	88 (5.3)	

* Not mutually exclusive. ** The term other parenteral exposure includes unsafe therapy injection, acupuncture, tattoo, piercing and tribal practices.

alence in migrants in this study was 1.9% (1.4%-2.7%). Globally, anti-HCV prevalence is highest in Asia, Africa, Eastern Europe, and North Africa & the Middle East, ranging from 2-4%, whereas in North America, Latin American & the Caribbean, most Western European countries and Australia, the anti- HCV prevalence is less than 1.5%. The regional HCV seroprevalence estimates for migrants from this meta-analysis were similar or slightly lower than the corresponding HCV seroprevalence estimates from the WHO in the general population in their regions of origin with the exception of Sub-Saharan Africa and South Asia (Fig.1) (45).

Globally, Egypt has the highest prevalence of HCV, with some studies reporting HCV antibody positive rates of up to 15%, with an estimated 10% with chronic viremia.

The largest population of HCV patients worldwide resides in East Asia and the Indian subcontinent, with at least 100 million HCV positive individuals in this region.

The prevalence of HCV in North America and Western Europe is comparatively lower. HCV transmission in Europe and North America is predominantly through IDU. At least 7.3 million people (1.1%) are estimated to be living with HCV in Europe. Estimates suggest that 5.2 million people are anti-HCV positive in the United States. These figures likely underestimate the true prevalence in both regions. These data reveal large differences in the prevalence of these chronic liver diseases among migrant groups and the host nations. In an era of increasing migration, these differences in HBV and HCV prevalence between regions have important implications for public health agencies in host nations. According to UN estimates, the total number of international migrants in 2013 was 231.5 million, making this group larger than the 5th most populous nation. In 1990, 154 million people, or 2.9% of the global population were migrants, whereas the corresponding figure for 2013 was 3.2%. These numbers do not include undocumented migrants of

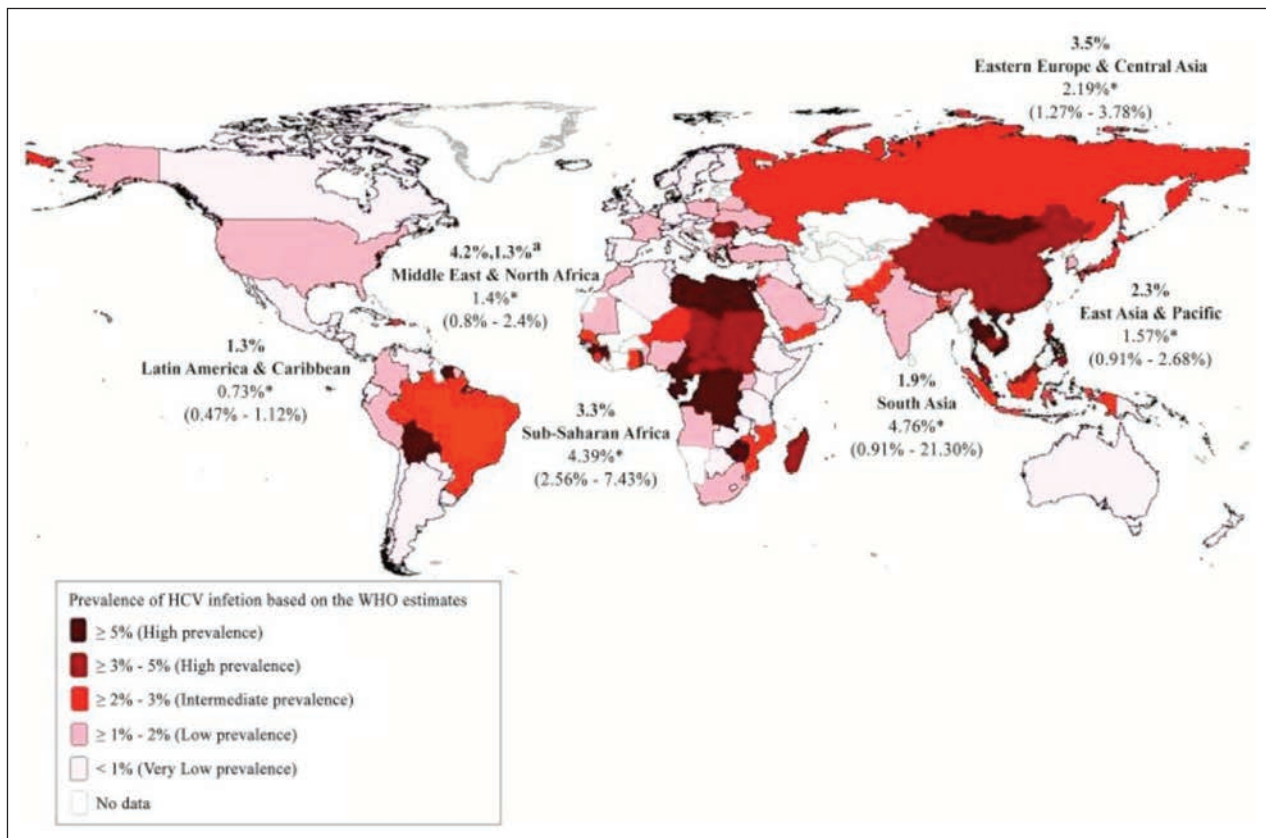


Figure 1. Anti HCV Seroprevalence stratified by region of origin (map) (45)

trafficked persons, and therefore likely underestimate the global migrant population. Many of these migrants move into and remain part of ethnic minority groups where traditional social and cultural behaviors that may have adverse implications for exposure to HBV and HCV are reinforced and persist (16).

Szabo et al. systematically reviewed 25 articles presenting population-based estimates of HCV prevalence from general population or blood donor samples, and supplemented those with publically-available data, to estimate the total number of persons infected with HCV in Latin America at 7.8 million (2010) (46). Of these, 4.6 million would be expected to have genotype 1 chronic HCV. Finally, they calculated that between 1.6 and 2.3 million persons with genotype 1 chronic would potentially benefit from current treatments, based on published estimates of genotype-epidemiologic burden of HCV (46).

Studies focused only on the presence of HCV antibodies generally overestimate the disease burden because they include also patients who have been cured, either spontaneously or through treatment. So, although antibodies to HCV (anti-HCV) are at present the most commonly available marker of HCV infection, used both to estimate its prevalence and to compare HCV infection levels globally, the most important indicator of HCV diffusion seems to be its classification into different genetic variants. At present, in fact, the length of the therapy and the opportunity to associate interferon and/or ribavirin with the new direct-acting antiviral (DAA) therapies still remain partially dependent on HCV genotype. Up to now, HCV is classified into seven recognized genotypes on the basis of sequence of the viral genome.

A recent review of the 2016 tried to quantify global anti-HCV prevalence, viraemic rate and genotype distribution to generate a global estimate of HCV burden disease. From this study results that total global HCV prevalence is nearly 2,5% (ranging from 2,9% in Africa and 1,3% in Americas), the global viraemic rate is 67% and the most prevalent HCV genotype is 1 (49,1%) followed by genotype 3 (17,9%). While genotypes 1 and 3 are common worldwide, the largest proportion of genotypes 4 and 5 is in low-income countries. Below we report tabs (Tab.5-7) and graphics that show the results of this study (44).

In particular the graphics below show the situation in Europe.

An European Study contributes to secondary prevention planning in the European Union/

European Economic Area (EU/EEA) by estimating the number of CHC (anti-HCV positive and viraemic) cases among migrants living in the EU/EEA and born in endemic countries, defining the most affected migrant populations, and assessing whether country of birth prevalence is a reliable proxy for migrant prevalence. Anti-HCV prevalence in the general population in the EU/EEA is estimated at 1.4% (range of 0.7-2.2%). However, prevalence estimates range from 0.2% in the Netherlands to 4.4% in Italy and 14 EU/EEA countries are considered endemic by the definition adopted in our study ($\geq 1\%$ anti-HCV prevalence). So Italy was considered both endemic area and host country. The migrant populations account for approximately 10.7% of the total adult population in the EU/EEA although the proportion in each country varies. Nearly 80% of the total migrant population were born in HCV endemic countries. The number and propor-

Table 5. Global Anti-Hepatitis C virus prevalence and numbers of infected individuals (44)

Continent	Anti- HCV prevalence (%)	Viraemic rate (%)	2013 population (millions)	Anti- HCV infected (millions)	Viraemic HCV infected (millions)
Africa	2.9	70.5	927.0	26.9	19.0
North Africa/Middle East	2.7	68.8	469.0	12.7	8.7
America	1.3	74.0	953.7	12.4	9.2
Asia	2.8	64.4	3985.0	111.6	71.9
Australasia	1.8	74.8	28.0	0.5	0.4
Europe	1.8	72.4	742.5	13.4	9.7
Total	2.5	67.0	7105.2	177.5	118.9

HCV: Hepatitis C virus.

Table 6. Regional estimates of Hepatitis C virus seroprevalence and viraemia (44)

Regions	Anti-HCV prevalence (%)	Viraemic rate (%)
Central Sub-Saharan Africa	6.0	68.5
EastSub-Saharan Africa	2.4	65.0
Southern Sub-Saharan Africa	0.9	69.0
WestSub-Saharan Africa	2.4	79.6
North Africa and Middle East	2.7	68.8
North America, High Income	1.2	75.7
Caribbean	1.5	70.0
Andean Latin America	1.2	70.0
Central Latin America	1.4	75.8
Southern Latin America	1.5	79.5
Tropical Latin America	1.6	80.2
Central Asia	5.8	48.7
East Asia	2.8	63.6
Pacific Asia, High-income	1.1	70.5
South Asia	2.5	78.5
Southeast Asia	1.6	60.5
Australasia	1.8	74.8
Europe, Central	1.3	76.6
Europe, Eastern	3.1	69.6
Europe, Western	0.9	71.0

tion of all migrants that come from endemic countries, at country level and in the EU/EEA as a whole are shown in Graphic below (Graphic 2) (47).

Across the EU/EEA, the overall anti-HCV prevalence among migrants from endemic countries is es-

timated at 2.3%, which corresponds to a CHC prevalence of 1.6% and an estimated 580,000 CHC infections. Table 8 lists the ten migrant populations with the highest estimated number of CHC cases and the host EU/EEA countries with the largest populations of migrants born in these countries.

The relative proportion (and range) of infected migrants from endemic countries within the overall CHC burden in EU/EEA countries is shown in the Graphic below (Graphic 3).

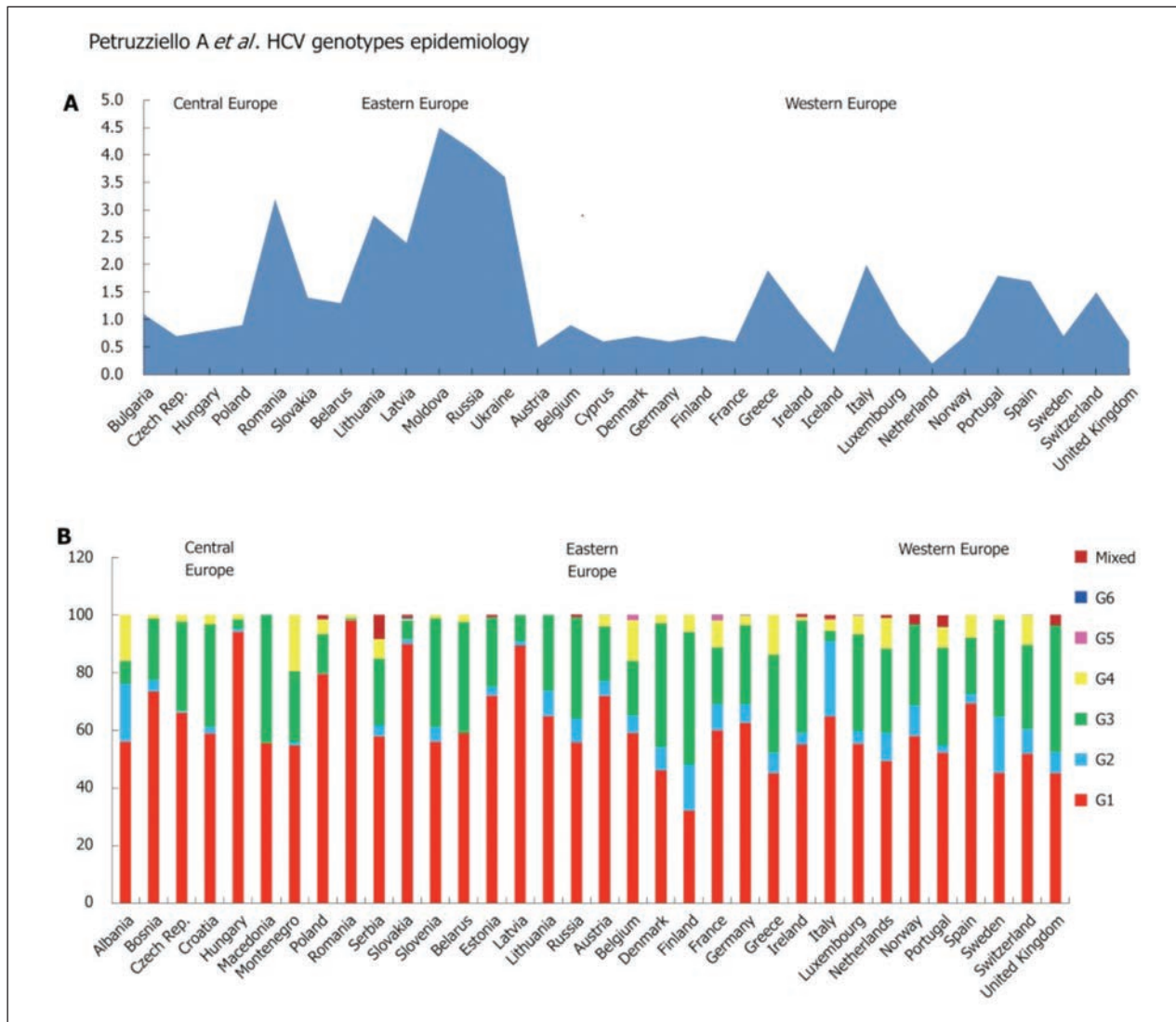
In particular, considering Italy like host country, from this study result that, nearly 10% of migrant population is born in endemic countries; the migrant groups accounting for the highest number of CHC cases are Egypt, Romania, Russia, Polonia, Morocco, Pakistan, Ukraine, Kazakhstan, Nigeria; the relative contribution of migrants to the total number of CHC cases is nearly 4-5% (47).

Discussion

From the data of this work (and from the review on HCV and drug addiction), it is possible to identify the extent of interventions that can be envisaged in the

Table 7. Regional estimates of hepatitis C virus Genotype

Regions	G1 (%)	G2 (%)	G3 (%)	G4 (%)	G5 (%)	G6 (%)	Mixed
Central Sub-Saharan Africa	12.3	4.0	0.8	82.9	-	-	-
East Sub-Saharan Africa	36.2	26.8	7.4	16.6	13.0	-	-
Southern Sub-Saharan Africa	31.4	1.2	12.6	12.4	35.7	-	6.7
West Sub-Saharan Africa	25.5	62.9	4.4	0.6	-	-	6.6
North Africa and Middle East	27.3	0.8	6.3	65.3	0.3	-	-
North America	66.3	13.1	15.7	4.3	-	0.6	-
Caribbean	83.0	7.2	2.1	0.6	-	0.1	7.0
Andean Latin America	86.0	2.0	10.0	-	-	-	2.0
Central Latin America	74.6	21.6	3.3	0.1	0.1	-	0.3
Southern Latin America	72.0	13.3	13.5	0.9	0.1	0.1	0.1
Tropical Latin America	64.8	4.6	30.2	0.2	0.1	-	0.1
Central Asia	70.4	8.6	19.6	-	-	-	1.4
East Asia	53.5	31.7	5.4	0.1	-	3.3	6.0
Pacific Asia, High-Income	58.7	39.7	0.4	0.1	-	0.5	0.6
South Asia	15.5	1.9	66.7	3.7	0.1	0.5	11.6
Southeast Asia	35.2	11.1	19.9	0.9	0.4	30.8	1.7
Australasia	55.0	6.5	36.0	1.2	-	1.3	-
Central Europe	70.0	3.2	21.0	4.9	-	0.1	0.8
Eastern Europe	68.1	4.3	26.6	0.5	-	-	0.5
Western Europe	55.1	8.9	29.0	5.8	0.2	0.1	0.8



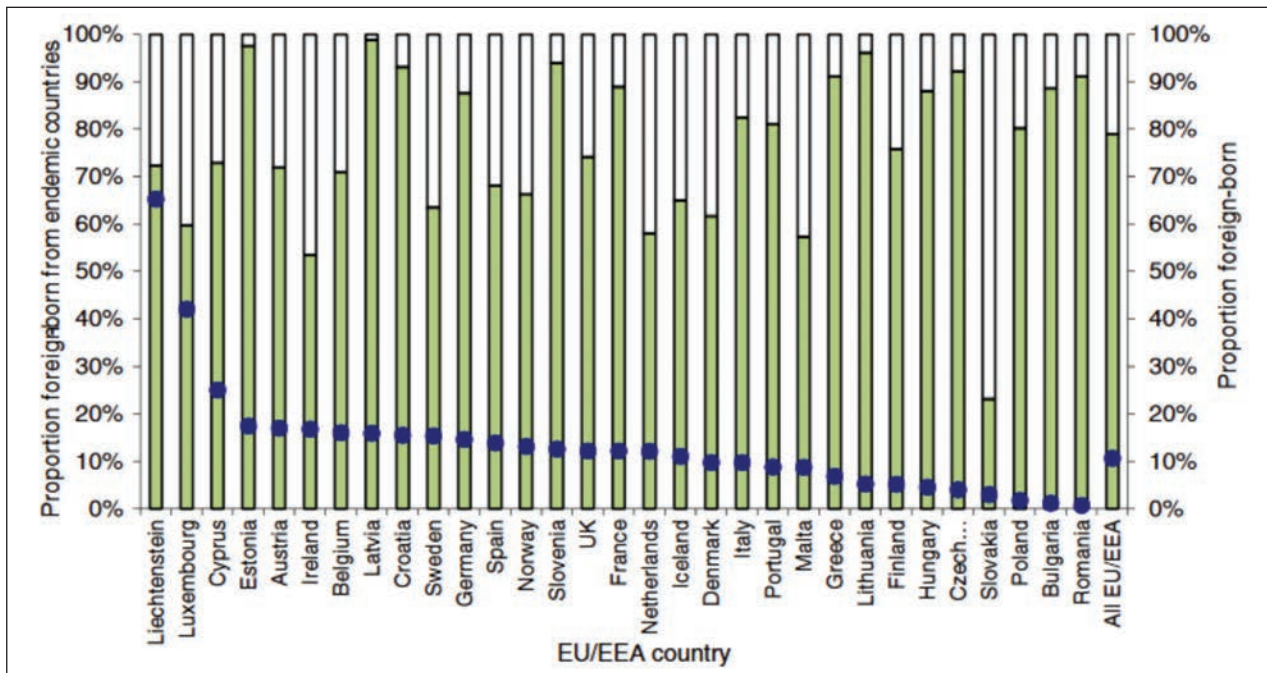
Graphic 1. Anti-Hepatitis C virus prevalence (a) and genotype distribution(b) in Europe (44)

general view of elimination of HCV from the country, which can be substantially theoretically implemented the use of eradicating drugs. In this sense it is possible to proceed with a general population or with a view of a special population. The special populations, precisely because they are delimited, could be an element of intervention from a more immediate part, because they investigate where HCV is expected and a survey is also made to evaluate the emergence of the submerged, on the other they can being an element of greater refractoriness for a number of reasons (many migrant populations, as well as drug addicts, are not easy to manage).

To this, in relation to this specific work, other considerations must be added.

Although many data suggest that HCV infection could be eliminated in the next 15-20 years with focused therapeutic strategies, a good understanding of HCV infection should be required to develop strategies to prevent new infections (44).

To achieve the ambitious elimination targets set out by the WHO of a 90% reduction in new infection and a 65% reduction in mortality from viral hepatitis by 2030, significant scale up of our current effort will be required. Effective therapy was critical to even con-



Graphic 2. Total (%) migrant population in each EU/EEA country and the proportion born in endemic countries (47)

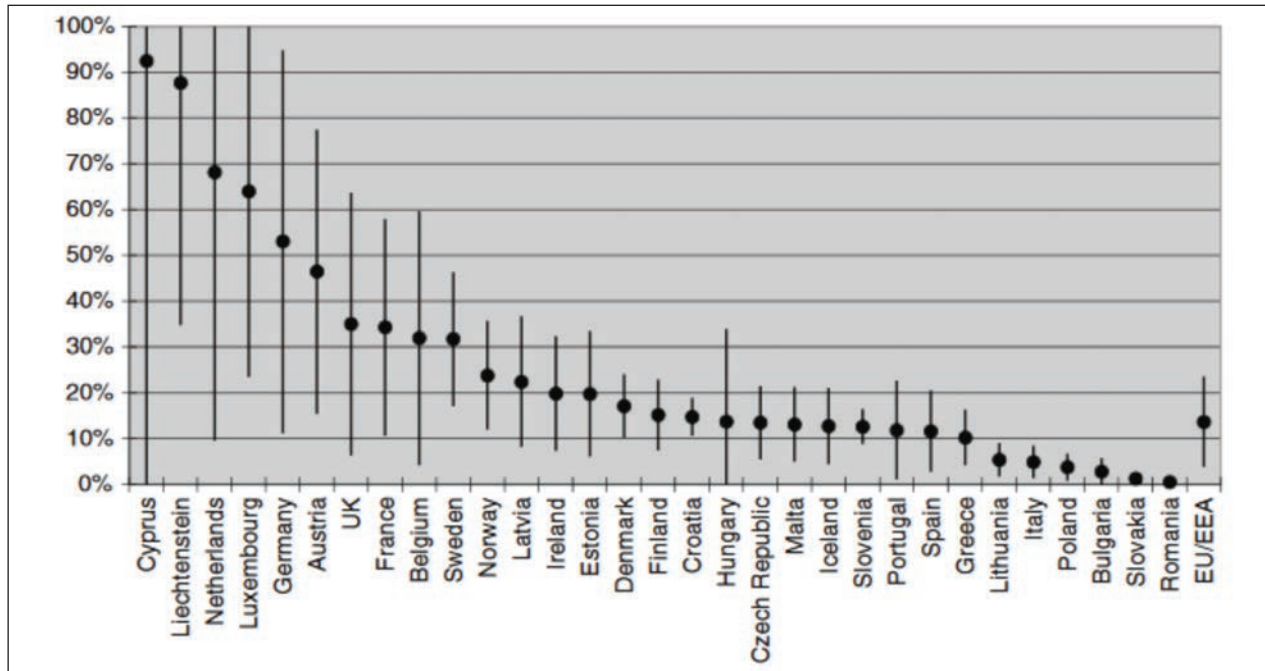
Table 8. The ten migrant groups (from endemic countries) accounting for the highest number of CHC cases (47)

Migrant country of birth	Total adult migrant population	Anti-HCV prevalence	Number (rounded) of CHC cases	Host countries (first 6 with largest populations) ^a
Romania	2,646,392	3.2	59,000	Italy, Spain, Germany, Hungary, UK, Austria
Russia	1,713,636	4.1	49,000	Germany, Latvia, Estonia, Italy, Lithuania, Spain
Italy	1,114,683	4.4	34,000	France, Germany, UK, Belgium, Spain, The Netherlands
Poland	4,103,409	1.1	32,000	Germany, UK, Italy, France, Ireland, The Netherlands
Morocco	2,418,072	1.6	27,000	France, Spain, Italy, Belgium, The Netherlands, Germany
Pakistan	756,170	5.0	27,000	UK, Italy, Spain, Germany, Greece, France
Ukraine	993,459	3.6	25,000	Poland, Germany, Italy, Czech Republic, Spain, Latvia
Egypt	194,852	15.7	21,000	Italy, UK, France, The Netherlands, Austria, Greece
Kazakhstan	807,781	3.3	19,000	Germany, Latvia, Czech Republic, Poland, Lithuania, Estonia
Nigeria	313,212	8.4	18,000	UK, Italy, Spain, Ireland, Austria, The Netherlands

^aif migrant population is at least 1000

sider elimination but it is important to recognize that therapy is necessary but entirely insufficient on its own to achieve elimination. HCV disproportionately affects marginalized people, like migrants and refugees, but high quality data from such populations are very limited. Such individuals often have very limited or no access to primary health care (48).

Patients in early stages of the disease are generally asymptomatic, and therefore most patients present in the late stages of HCV disease, when treatments are less effective and complications or death are unavoidable. In recent years, highly effective but very expensive curative treatments have emerged. Early diagnosis and treatment may limit the burden



Graphic 3. Estimated relative contribution (upper/lower range) of migrants to the total number of CHC cases (47)

of the disease in the EU/EEA, for example is necessary to screen migrants when HCV prevalence in their countries of origin is higher than those of European settlement countries. Defining high prevalence regions and determining the effectiveness, acceptability, cost and affordability of screening and treatment from both an EU/EEA migrant and a public health perspective are necessary (49).

A recent review supports the effectiveness and cost-effectiveness of HCV screening in populations at risk for HCV infection, including migrants from intermediate and high HCV prevalence countries (anti-HCV $\geq 2\%$ and $\geq 5\%$, respectively). Migrant populations in the EU/EEA face difficulties accessing care and treatment as a result of numerous barriers at the patient, provider, and health system level. To reach HCV elimination goals in the EU/EEA dramatic scale up of HCV testing with diagnosis of all groups at HCV risk, including migrants, and linking those found to be positive to care and treatment will be required. Migrants living in the EU/EEA bear a disproportionate burden of HCV. They are older and more likely to have advanced liver disease and hepatocellular carcinoma compared to non-migrants at the time of

HCV diagnosis. The data suggest that early screening of migrants based on the HCV prevalence in the country of origin with linkage to care and treatment could prevent liver related sequelae in the migrant population and would be cost-effective (50).

Other authors, already mentioned, say that in countries where HCV prevalence is high in the general population and the contribution of migrants is low, it may be more cost-effective to implement population-based screening (47).

Conclusion

Italy is a country that has fought hard to allow the diagnosis of HIV free of charge but the infectivologists are now also struggling to ensure the free diagnosis of HCV to the general population since, on this front, foreigners are more likely to be present temporarily in our country while a citizen must pay the exam. Therefore, also to act in a ministerial context in this field, the contained here constitute a possible basis for discussion, since we are able to tell the decision-makers of the health policies the reality we know and, broadly

speaking, what can be expected from the epidemiological profile as a consequence of the implemented interventions.

References

- Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, et al. Global and regional mortality from 235 causes of death for 20 agegroups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012; 380: 2095-2128.
- Erin Gower, Chris Estes, Sarah Blach, Kathryn Razavi-Shearer, Homie Razavi. Global epidemiology and genotype distribution of the hepatitis C virus infection. *Journal of Hepatology* 2014 vol. 61 j S45-S57
- Christina Greenaway, Iuliia Makarenko, Claire Nour Abou Chakra, Balqis Alabdulkarim, Robin Christensen, Adam Palayew, Anh Tran, Lukas Staub, Manish Pareek, Joerg J. Meerpohl, Teymur Noori, Irene Veldhuijzen, Kevin Pottie, Francesco Castelli, and Rachael L. Morton. The Effectiveness and Cost-Effectiveness of Hepatitis C Screening for Migrants in the EU/EEA: A Systematic Review. *Int J Environ Res Public Health*. 2018 Sep; 15(9): 2013.
- World Health Organization. Hepatitis C FactSheet No.164. 2015.
- World Health Organization. Call to action to scale up Global hepatitis response: Global Partners' meeting on hepatitis. 2014.
- World Health Organization. Guidelines for the screening, care and treatment of persons with hepatitis C infection. World Health Organization, Geneva. April 2014.
- ViralHepatitis Prevention Board. Highlight underserved screening, prevention and treatment of viral hepatitis B and C in Europe. March 2016, Ljubljana.
- Call to Action 2010. Conference on Hepatitis B and C in Europe, Brussels.
- Hepatitis B&C Public Policy Association. Call to Action 2012. Conference on Hepatitis B and C in Mediterranean and Balkan countries, Cyprus.
- Hepatitis B&C Public Policy Association. Elimination Manifesto.
- World Health Organization. Call to action to scale up Global hepatitis response: Global Partners' meeting on hepatitis. 2014.
- World Health Organization. Guidelines for the screening, care and treatment of persons with hepatitis C infection. World Health Organization, Geneva. April 2014.
- ViralHepatitis Prevention Board. Highlight underserved screening, prevention and treatment of viral hepatitis B and C in Europe. March 2016, Ljubljana.
- UNHCR. "Over one millions ea arrivals reach Europe in 2015". 30 December 2015.
- UNDESA. "Number of international migrants rises above 232 million". 11 September 2013.
- Carballo M, Cody R, O-Reilly E, Felici AP. Migration, Hepatitis B and Hepatitis C. International Centre for Migration Health and Development. 2010.
- ECDC. Hepatitis B and C in the EU neighborhood: prevalence, burden of disease and screening policies. 2010.
- Hatzakis A, Van Damme P, Alcorn K, Gore C, Benazzouz M, Berkane S, et al. The State of Hepatitis B and C in the Mediterranean and Balkan Countries. *J ViralHepat*. 2013; 20:1-20.
- Hahne S. et al. Infection with Hepatitis B and C virus in Europe a Systematic Review of Prevalence and Cost-Effectiveness of Screening. *BMC Infectious Diseases*. 2013; 13: 181-197.
- Vriend HJ, Van Veen MG, Prins M, Urbanus AT, Boot HJ, Op De Coul EL. Hepatitis C virus prevalence in The Netherlands: migrants account for most infections. *Epidemiol Infect*. 2013; 141: 1310-1317.
- Duberg A, Janzon R, Bäck E, Ekdahl K, Blaxhult A. The Epidemiology of Hepatitis C Virus Infection in Sweden. *Euro Surveill*. 2008; 13: 18882.
- Uddin G1, Shoeb D, Solaiman S, Marley R, Gore C, Ramsay M, et al. Prevalence of chronic viral hepatitis in people of south Asian ethnicity living in England: the prevalence cannot necessarily be predicted from the prevalence in the country of origin. *J ViralHepat*. 2010; 17: 327-335.
- ECDC. Assessing the burden of key infectious diseases affecting migrant populations in the EU/EEA. 2014.
- Semaille C, Le Strat Y, Chiron E, Chemlal K, Valantin MA, Serre P, et al. Prevalence of human immunodeficiency virus and hepatitis C virus among French prison inmates in 2010: a challenge for public health policy. *Euro Surveill*. 2013; 18: pii=20524.
- Schmidt et al. Prevalence of hepatitis C in a Swiss sample of men who have sex with men: whom to screen for HCV infection? *BMC Public Health*. 2014; 14: 3.
- Carballo M, Maclean C, Godumac I, Van Damme P. Hepatitis C and Migration: A Public Health Challenge. *J Family Med*, 2016, June 28.
- Carballo M, Hargreaves S, Gudumac I, Maclean EC. Evolving migrant crisis in Europe: implications for health systems. *Lancet Glob Health*. 2017 Mar; 5(3):e252-e253.
- Scotto G, Armignacco O, Starnini G, et al. Hepatitis C and immigration: a multicentre study. *Le infezioni in medicina*, 2016; 3:210-216.
- Chiaromonte M, Pupo A, Menegon T, et al. HBV and HCV infection among non-European Union immigrants in North-East Italy. *Epidemiol Infect*, 1998; 121:179-183.
- Majori S, Baldo V, Tommasi I, et al. Hepatitis A, B, and C Infection in a Community of Sub-Saharan Immigrants Living in Verona (Italy). *Journal of Travel Medicine*, 2008; 15(5):323-327.
- Madhava V, Burgess C, Drucker E. Epidemiology of chronic hepatitis C virus infection in sub-Saharan Africa. *Lancet Infect Dis*, 2002; 2:293-302.
- Mele A, Tosti Me, Spada E, et al. Epidemiology of acute viral hepatitis: twenty years of surveillance through SEIEVA

- in Italy and a review of the literature through the SEIEVA in Italy and a review of the literature. *Rapporti ISTISAN*: 06/12, 2006. Available at: <http://www.iss.it/binary/seie/cont/Rapporto%2020022004.1149599793.pdf>
33. Chironna M, Germinario C, Lopalco PL, et al. Prevalence of Hepatitis Virus Infections in Kosovar Refugees. *Int J Infect Dis*, 2001; 5:209-213.
 34. Chironna M¹, Germinario C, Lopalco PL, Carrozzini F, Barbuti S, Quarto M. Prevalence rates of viral hepatitis infections in refugee Kurds from Iraq and Turkey. *Infection*. 2003 Mar;31(2):70-4.
 35. Scotto G¹, Saracino A, Pempinello R, El Hamad I, Geraci S, Palumbo E, Cibelli DC, Angarano G; Gruppo italiano per lo studio delle malattie infettive negli immigrati. [Epidemiologic multicenter study of the prevalence of hepatitis in hospitalised immigrants in Italy in the year 2002]. *Annali di igiene: medicina preventiva e di comunità*. Jan-Feb (1): 11-18
 36. Fabris P, Baldo V, Baldovin T, et al. Changing Epidemiology of HCV and HBV Infections in Northern Italy A Survey in the General Population. *J Clin Gastroenterol* 2008;42:527-532.
 37. Coppola N, Alessio L, Gualdieri L, Pisaturo M, Sagnelli C, Caprio N, et al. Hepatitis B virus, hepatitis C virus and human immunodeficiency virus infection in undocumented migrants and refugees in southern Italy, January 2012 to June 2013. *Euro Surveill*. 2015.
 38. Germinario C, Gallone MS, Tafuri S. Migrant health: the Apulian model. *EpidemiolPrev*, 2015;39(4) Suppl 1:76-80.
 39. Tafuri S, Prato R, Martinelli D, et al. Prevalence of Hepatitis B, C, HIV and syphilis markers among refugees in Bari, Italy. *BMC Infectious Diseases*, 2010;10:213.
 40. Chironna M, Germinario C, Lopalco PL, et al. HBV, HCV and HDV infections in Albanian refugees in Southern Italy (Apulia region). *Epidemiol infect*, 2000;125:163-167.
 41. Tramuto P, Mazzucco W, Maida CM, et al. Serological Pattern of Hepatitis B, C, and HIV Infections Among Immigrants in Sicily: Epidemiological Aspects and Implication on Public Health. *J Community Health*, 2012;37:543-553.
 42. Sagnelli E, Alessio L, Sagnelli C, Gualdieri L, Pisaturo M, Minichini C, Di Caprio G, Starace M, Onorato L, Scotto G, Macera M, Coppola N. Clinical Findings of HCV Chronic Infection in undocumented immigrants and low-income refugees in three areas of Southern Italy. *Annals of hepatology*. Vol 17, NO1, 2018:47-53
 43. Sharma S, Carballo M, Feld JJ, Janssen HLA. Immigration and viral hepatitis. *Journal of hepatology*, 2015;63:512-522.
 44. Arnolfo Petruzzello, Samantha Marigliano, Giovanna Loquercio, Anna Cozzolino, Carmela Cacciapuoti. Global epidemiology of hepatitis C virus infection: an up-date of the distribution and circulation of hepatitis C virus genotypes. *World J Gastroenterol* 2016 September 14; 22(34): 7824-784
 45. Christina Greenaway, Ann Thu Ma, Lorie A. Kloda, Marina Klein, Sonya Cnossen, Guido Schwarzer, Ian Shrier. The Seroprevalence of Hepatitis C Antibodies in Immigrants and Refugees from Intermediate and High Endemic Countries: A Systematic Review and Meta-Analysis. *PLoS ONE* 10(11): e0141715
 46. Szabo SM, Bibby M, Yuan Y, et al. The epidemiologic burden of hepatitis C virus infection in Latin America. *Annals of Hepatology*, 2012; 11(5):623-635.
 47. A.M. Falla, A. A. Ahmad, E. Duffell, T. Noori and I. K. Veldhuijzen. Estimating the scale of chronic hepatitis C virus infection in the EU/EEA: a focus on migrants from anti-HCV endemic countries. *BMC Infectious Diseases* (2018) 18:42
 48. J.J.Field. Extending a Helping Hand: addressing Hepatitis C in Economic Migrants and Refugees. *Annals of Hepatology*, January-February, Vol 17 NO 1, 2018:8-10
 49. Kevin Pottie, Alain D Mayhew, Rachael L Morton, Christina Greenaway, Elie A Akl, Prinon Rahman, Dominik Zenner, Manish Pareek, Peter Tugwell, Vivian Welch, Joerg Meerpohl, Pablo Alonso-Coello, Charles Hui, Beverley-Ann Biggs, Ana Requena-Méndez, Eric Agbata, Teymur Noori, Holger J Schünemann. Prevention and assessment of infectious diseases among children and adult migrants arriving to the European Union/European Economic Association: a protocol for a suite of systematic reviews for public health and health systems. *BMJ Open* 2017;7:e014608
 50. Christina Greenaway, Iuliia Makarenko, Claire Nour Abou Chakra, Balqis Alabdulkarim, Robin Christensen, Adam Palayew, Anh Tran, Lukas Staub, Manish Pareek, Joerg J. Meerpohl, Teymur Noori, Irene Veldhuijzen, Kevin Pottie, Francesco Castelli, and Rachael L. Morton. The Effectiveness and Cost-Effectiveness of Hepatitis C Screening for Migrants in the EU/EEA: A Systematic Review. *Int J Environ Res Public Health*. 2018 Sep; 15(9): 2013.
 51. F. Negro. Epidemiology of hepatitis C in Europe. *Digestive and Liver Disease* 46(2014) S158-S164.

Received: 18 September 2018

Accepted: 29 October 2018

Correspondence:

Massimo Galli

Department of Infectious Disease,

ASST Fatebenefratelli Sacco, Milan, Italy

E-mail: massimo.galli@unimi.it