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Review

The changing epidemiology of hepatitis C virus infection in Europe☆

Juan I. Esteban[1,2,*], Silvia Sauleda[2,3], Josep Quer[1,2]

[1]*Liver Unit, Department of Medicine, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Po Vall d'Hebron 119-129, 08035 Barcelona, Spain*

[2]*CIBER de Enfermedades Hepáticas y Digestivas (Ciberehd) del Instituto de Salud Carlos III, Spain*

[3]*Banc de Sang i de Teixits, Institut Català de la Salut, Barcelona, Spain*

The epidemic of hepatitis C virus (HCV) infection in Europe is continuously evolving and epidemiological parameters (prevalence, incidence, disease transmission patterns and genotype distribution) have changed substantially during the last 15 years. Four main factors contribute to such changes: increased blood transfusion safety, improvement of healthcare conditions, continuous expansion of intravenous drug use and immigration to Europe from endemic areas. As a result, intravenous drug use has become the main risk factor for HCV transmission, prevalent infections have increased and genotype distribution has changed and diversified. Hence, prevalence data from studies conducted a decade ago may not be useful to estimate the current and future burden of HCV infection and additional epidemiological studies should be conducted, as well as new preventive strategies implemented to control the silent epidemic. This review summarizes recently published data on the epidemiology of HCV infection in Europe focusing on the factors currently shaping the epidemic.

***Keywords*: HCV; Epidemiology; Europe**

1. Search methods

The information in this report is based on peer-reviewed medical articles published up to March 2007. A PubMed search was made using the terms "hepatitis C" or "HCV" in combination with the roots "epidemiol*, "inciden*, "prevalen*, geno*", Europe and each of the European country names. Updates and reviews on HCV epidemiology were also included and bibliographies of the articles retrieved were used to find other references. Several databases (WHO, UN, Eurostat, EMCCDDA, Eurosurveillance and country-specific National Statistics Institutes) were also accessed to retrieve data on population demography, intravenous drug use and HCV rates from each European country.

2. Background

Despite significant geographic and temporal differences in the epidemiology of HCV infection in Europe, it has been suggested that the initial spread of the virus started during the last century through the use of unsafe parenteral injections, invasive medical and surgical procedures and transfusion of blood products. An epidemic explosion of intravenous drug use (IDU) shortly followed the iatrogenic spread. The timing and the extent to which health-care-related transmission or IDU fuelled the epidemic in different countries explain the different epidemiological profiles between North-Western and South-Eastern countries. Despite the limited number of population-based studies on the age-specific prevalence of infection, three patterns of HCV transmission have been recognized in Europe [1]. In Northern Europe the epidemic was mainly transmitted by IDU [1–7]. With an overall prevalence between 0.1 and 1%, in these countries most prevalent infections are found among adults 30–50 years old. In Central Europe HCV prevalence is intermediate, ranging from 0.2% in the Netherlands to 1.2% in

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* Corresponding author. Tel.: +34 932746140; fax: +34 932746068.
E-mail address: jiesteban@vhebron.net (J.I. Esteban).

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France [2,8–10]. In Southern Europe (i.e. Spain, Italy, Greece, Southern France), the overall prevalence ranges between 2.5% and 3.5% [2,8,11–16]. In these countries, an initial epidemic (occurring >50 years ago) of iatrogenic nature led to a high infection prevalence in older people, followed, some 30 years later, by a still-ongoing IDU-related epidemic which spread the infection among younger people [17].

Indeed, using epidemiological data and molecular evolutionary methods, some research groups showed that the spread of genotype 1b in Spain and France, and that of genotype 3a in the former Soviet Union, coincided with local outbreaks of unsafe parenteral treatments [18–20].

In Eastern European countries epidemiological data in the general population are limited. In a review of the epidemiology of HCV in Eastern Europe, based on published and personally communicated data [21], a high prevalence of infection (0.9% to 5%) among blood donors, health care workers (1–10%) and high-risk groups (50–92% in haemophiliacs; 13–48% in haemodialysis patients) was reported. Nosocomial transmission (in-hospital diagnostic or treatment procedures) appeared to play a major role in HCV infection (40% to 70% of prevalent cases). The reported incidence of acute hepatitis C (2.2 – 9 cases per 100,000 population) was already increasing in the mid 1990s among people aged 15 to 29, as a result of the epidemic of IDU that had already started in several Eastern European countries [22–24].

Fig. 1 shows the current estimated prevalence of HCV infection in Europe [2,6,9–11,14–16,21,25–44].

Prevalence of HCV infection in European countries is not homogeneous, with isolated areas in Italy and Greece where 7% to 20% of the general adult population were infected, [13,15,16,45–48], through the widespread use of unsafe medical procedures, in the distant past [1,3,19].

In the early nineties, HCV genotypes 1, 2 and 3 accounted for most infections in blood donors and patients [2,8,49]. After genotype 1, the next most prevalent was genotype 3a, except in Southern Italy, where genotype 2c accounted for 25% to 30% of infections among older adults [2,32,46,50]. Genotype 4 infections were found at low frequencies (4–6%) in Southern Europe [50–53]. It was already known that genotype distribution was associated with the mode of transmission, with subtypes 1a, 3a and 4 being mostly IDU-related and genotypes 1b and 2 associated with blood transfusion and unsafe medical procedures [17,50–53]. Recent studies have reported that HCV genotype 5a, once believed to be restricted to South Africa, had been endemic for a long time in isolated areas of Central France and West Flanders [54,55]. Fig. 2 shows the estimated distribution of HCV genotypes among HCV-infected patients, in different European countries, as reported in studies published after 1999.

The picture described above has changed during the last 15–20 years, due to a combination of several factors: (1) eradication of transfusion-associated infections; (2) improvement in health-care-related standards; (3) continuous expansion of IDU in Western Europe, along with its dramatic increase in Eastern Europe; and, (4) a sharp increase in immigration from endemic areas. How these factors have modified the HCV epidemic in Europe is summarized in Fig. 3, and explained in more detail in the following sections.

3. Blood transfusion safety

Blood transfusions were a leading cause of the spread of HCV in most European countries since World War II. In the late 1980s, 2% to 10% of blood units in developed countries transmitted HCV [12,19,56,57]. Consequently, most chronic transfusion recipients and patients receiving clotting factor concentrates were infected [58–61]. However, implementation of an all-volunteer blood donor system (1980), effective virus-inactivation procedures for blood derivatives (1987), and introduction of first- (1990) and second-generation anti-HCV tests for blood donors (1992) drastically reduced transfusion-associated transmission in developed countries [3,19,58,62,63].

Blood supplies are now very safe in Europe and no cases of HCV transmission due to the administration of plasma-derived products have been reported since 1994 [19]. With the implementation of anti-HCV screening, the residual risk of transfusion-associated hepatitis C was limited to units donated during the serological window period [64]. Using indirect mathematical models [65], such a risk was estimated at <1:200,000 blood units [60,66]. The risk has further decreased with the implementation of HCV RNA testing by nucleic acid technology (HCV-NAT) [67,68]. After 3–6 years of its implementation, risk estimates range between 0.1 and 2.33 per million donations [69–71]. Rare cases of transmission may still occur from recently infected donors with serum HCV RNA level below the detection limit of the tests [64,72,73].

Despite the current levels of blood safety, many European countries are facing the long-term effects of the past epidemic of transfusion-associated hepatitis C. In several cohort studies from Central and Southern Europe, patients with transfusion-associated infection account for 20–30% of patients older than 50 (mostly infected with genotype 1b) with advanced chronic hepatitis, cirrhosis and hepatocellular carcinoma [50,74–81]. With the current blood transfusion safety, and the availability of recombinant clotting factors, newly diagnosed haemophilia and thalassemia patients are no longer at risk for HCV infection. Similarly, blood safety along with the use of erythropoietin (EPO) and improvement

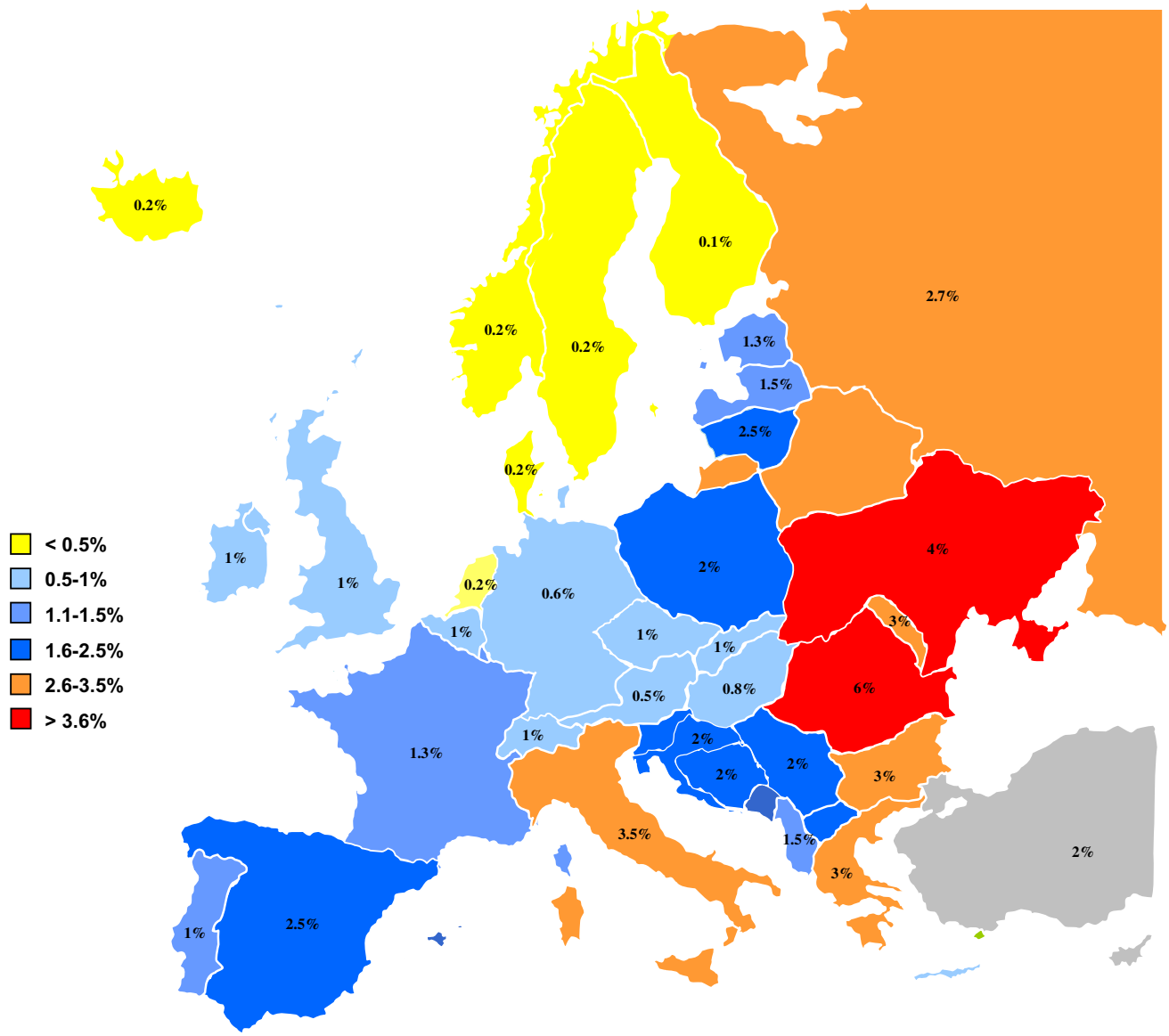

Fig. 1. Estimated current prevalence of HCV infection in different European countries. Data is based on figures reported from large cohorts of blood donors and/or general population [2,6,9–11,14–16,21,25–44].

in infection control practices (see below) has greatly decreased HCV infection among haemodialysis patients. Blood safety has also paved the way for IDU to become the main risk factor for HCV transmission (Table 1) and has switched the HCV genotype distribution (among patients younger than 50) (from 1b and 2 to 1a, 3a and 4d) [31,32,76,78,81–85], and has led vertical transmission to become the almost exclusive source of HCV infection in infants [31,86].

4. Improvement in safety of health-care-related procedures

Use of disposable injection items, improvement of disinfection techniques for non-disposable equipment, and adherence to standard infection control measures [87–90] have likely lowered iatrogenic HCV infection. However, health-care-related infections continue to occur even in countries with high sanitary standards. Such infections are mostly patient-to-patient transmissions (either sporadic or as small outbreaks), and are more common in areas and settings with higher HCV prevalence.

As reviewed elsewhere [1,3,4,19], dialysis units are good examples of hyper endemic health-care settings (with prevalence ranging between 4 and 60% in different countries and centres, in the early 1990s). Subsequently, blood donor screening and use of EPO certainly decreased both prevalence (to <15%) and incidence (to ~2.5 per 100 person/years) [91,92]. New infections, however, indirectly transmitted from patient-to-patient via

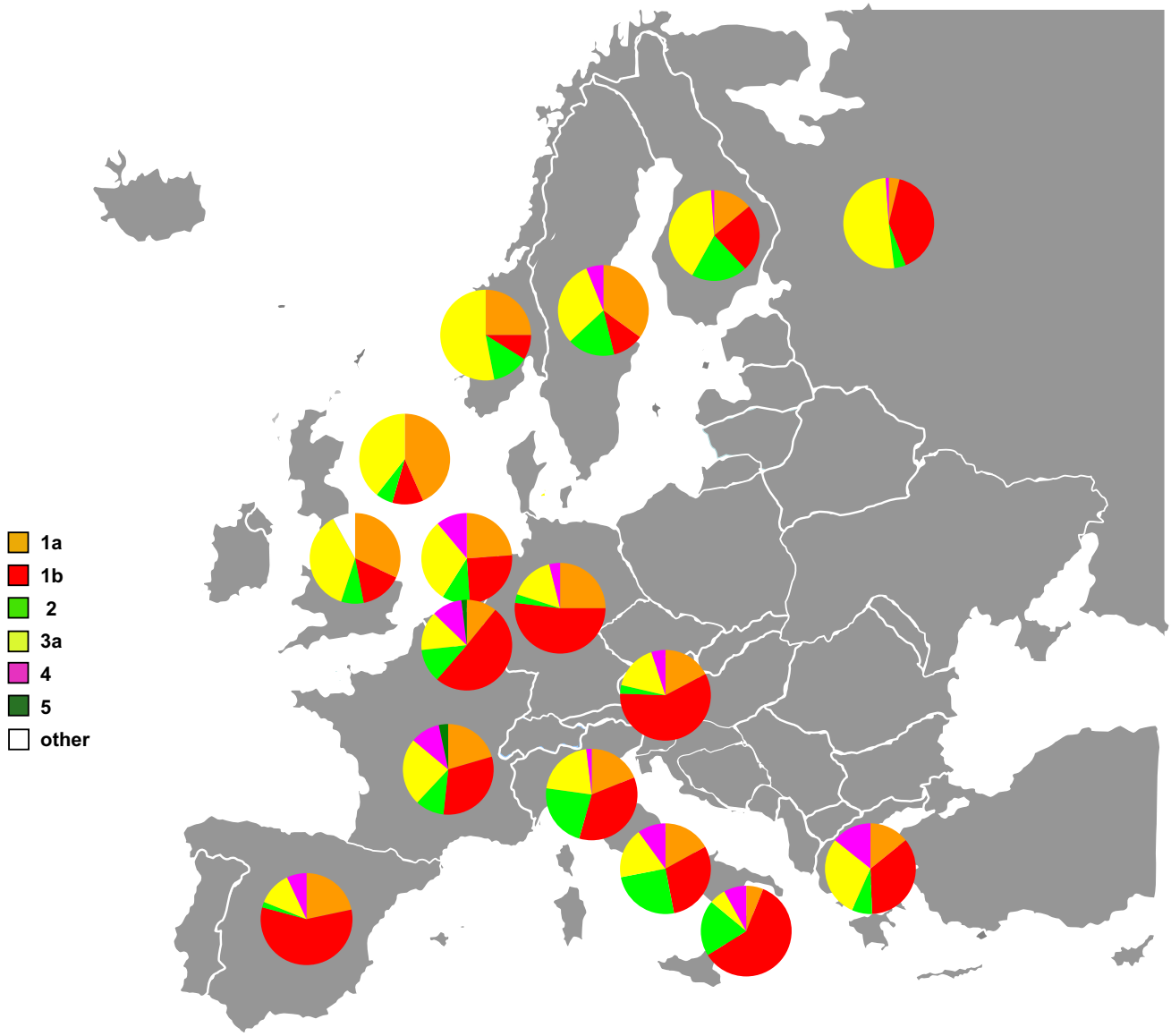

Fig. 2. Estimated HCV genotype distribution among HCV-infected individuals in Europe. Only data from representative cohorts including more than 250 patients evaluated after 1999 are depicted [22,32,76–78,80,83–85,118,119,151,160,161,191–196].

the hands of health-care workers continued to occur, sometimes as large outbreaks involving tens of patients [93]. Hence, scrupulous application of universal hygiene precautions is essential to avoid this type of transmission [94,95]. Although there is no consensus concerning the use of dedicated dialysis machines and staff personnel to prevent nosocomial HCV transmission in dialysis units, countries with a high initial prevalence of infection (36% in Spain in 1991) have widely implemented such measures [96].

Other cases and outbreaks of HCV transmission have been associated with several medical procedures, including the use of contaminated multi-dose vials [97–104]; spring-loaded finger sticks [105,106]; surgical interventions [107,108]; and gastrointestinal endoscopy [109].

Although the relative importance of nosocomial transmission on the current HCV epidemic is probably small, studies of seroconverting blood donors and of patients with acute hepatitis C suggest that such transmission is not uncommon. Medical and surgical invasive procedures were the main risk factors associated with seroconversion and acute hepatitis in Italian blood donors [110] and among patients enrolled in the Italian National Hepatitis Surveillance System [111]. Similarly, among 214 consecutive patients diagnosed with acute hepatitis C at 12 Italian medical centres between 1999 and 2004, an invasive procedure was involved in transmission in 32% [84]. In a prospective study conducted between 2000 and 2002, at a tertiary-care liver unit in Barcelona, six of 1540 hospita-

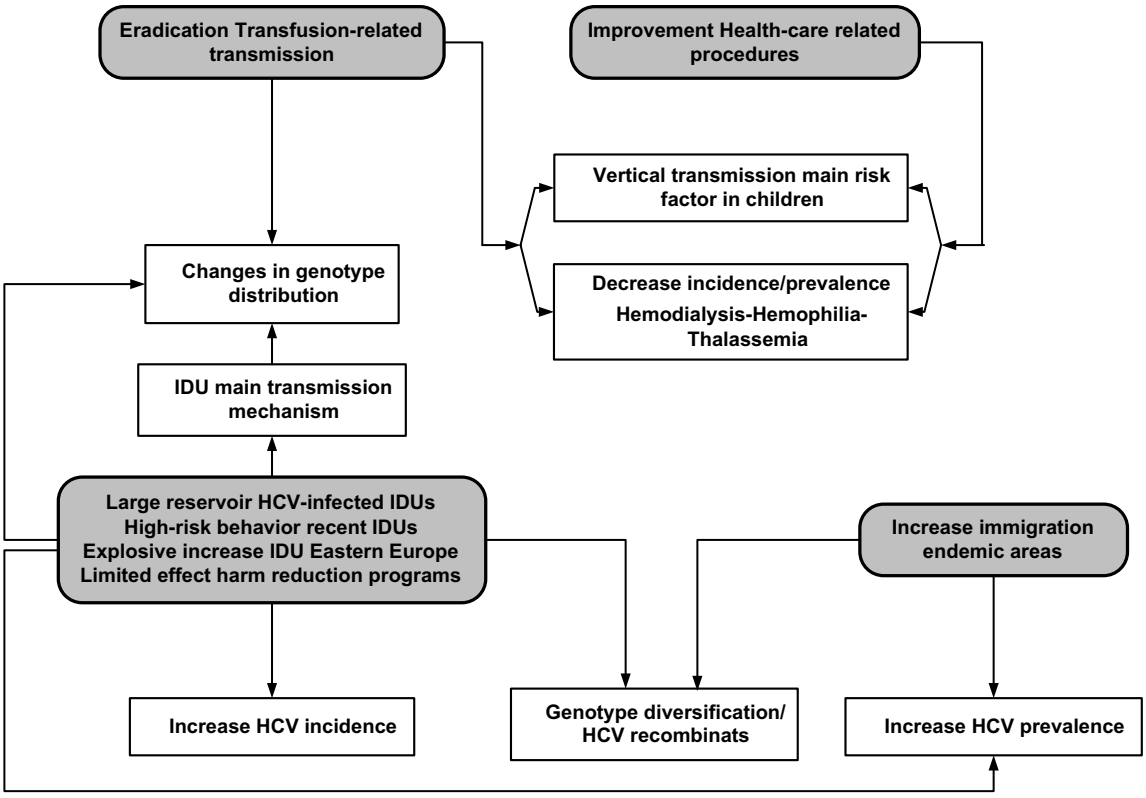

Fig. 3. Relationship between the causes (shaded boxes) and consequences of the changing epidemiology of HCV infection in Europe.

Table 1
Risk factors among patients diagnosed with acute or chronic hepatitis C attending specialized units during recent years in different European countries

Country	Patient setting*	No cases	Years	IDU (%)	BT (%)	Nosocomial (%)	Unknown (%)	Other (%)	Reference
France	CHC	1769	2000–2001	38	27	10	25	0	[76]
France	CHC	1145	1990–2000	45	27	0	10	16	[81]
Germany	CHC	747	2000–2001	23	12	0	54	9	[85]
Belgium	CHC	1726	1992–2002	26[a]	39[a]	9	21	5	[77]
Austria	CHC	250	1999–2000	30	22	0	45	4	[151]
Greece	CHC	1229	1987–2002	30	25	5	37	3	[78]
Sweden	CHC	312	1969–1996	53	21	0	27	9	[118]
Italy	AHC	214	1999–2004	39	0	32	13	18	[84]

[a] Over the 10-year study, blood transfusion decreased 2.7% per year and IDU increased 2.5% per year. In 2001 IDU outnumbered BT.
* CHC, Chronic hepatitis C outpatient GE/Hepatology Unit; AHC, acute hepatitis C; Nacional Surveillance System IDU, intravenous drug use; BT, blood transfusion before 1991; Nosocomial, health-care-related procedure; Other: Dialysis, haemophilia, sexual transmission, vertical transmission, tatooing, piercing.

lised patients seroconverted (incidence: 0.27 per 100 hospital admissions per year), despite the fact that the staff was fully aware of the ongoing study and, hence, adherence to standard safety precautions should have been optimal [112]. In a preliminary report of 103 patients with acute hepatitis C seen at different Spanish hospitals between 2000 and 2005, 70% had been infected during hospitalisation [31]. In a recent French case-control study, a substantial proportion of patients with community acquired chronic hepatitis C had in-hospital or outpatient treatments as the most likely risk factor for infection [113]. Hence, it seems that countries with a higher HCV prevalence are likely to concentrate a significant proportion of HCV carriers in health-care facilities and, when this is associated with insufficient adherence to standard safety measures the risk of nosocomial transmission is considerable. That such measures minimize nosocomial infection rates has been shown in a survey in which no seroconversion was detected among 912 patients undergoing endoscopy with properly disinfected instruments used in HCV-infected patients [114].

A few examples of health-care worker-to-patient transmission have been reported [107,108,115,116].

However, this mode of HCV transmission appears to be very rare [117].

5. Injection drug use as the core of the HCV epidemic

In certain European countries (UK, Sweden, Norway), illegal injection drug use (IDU) has been the dominant mode of HCV transmission during the past 35 years, accounting for 60% to 90% of prevalent infections [42,118–121]. As already stated, IDU has become the main transmission mechanism of HCV in Western Europe [3] and, along with the explosive increase of IDU in Eastern Europe, has placed drug users (IDUs) at the core of the HCV epidemic [122].

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA 2006 report update, available at: http://www.emcdda.europa.eu/) and Eurosurveillance [123] have estimated a median rate of 5.3 IDUs per 1000 population aged 16 to 64 (range: 1.1 to 17). Accordingly, there would be about 1.7 million IDUs in EU countries alone. The real prevalence in Europe is probably much higher, since estimates are based on data provided by EU countries and no data is available from several countries in Southern and Eastern Europe.

Injection drug use is one of the most efficient routes for HCV transmission, which is acquired more rapidly after initiation of IDU than other viral infections, especially during the first year [124], and after 5 years, 50–90% of users have been exposed to HCV [125]. The pooled prevalence of anti-HCV among IDUs during the late 1980s and early 1990s in Western Europe was 79% in studies using second-generation EIA tests and that of HCV RNA, between 27% and 87% [126,127]. More recent estimates have shown a wide variation in anti-HCV prevalence among IDUs in the EU, both within and between countries. Prevalences over 60% are very common (the highest prevalence, >80%, corresponding to countries from the former Soviet Union). Prevalences below 40% have been reported in some regions of Belgium, Greece and the UK, as well as in Austria, the Czech Republic, Cyprus, Finland, Hungary, Malta, the Netherlands and Slovenia [123,128–132].

Factors associated with an increased risk of HCV infection include age, duration and frequency of IDU, sharing equipment, polydrug use, HCV prevalence among experienced IDUs, homelessness and having served a prison sentence [125,132–136]. Differences in the relative contribution of these factors likely explain geographical disparities in HCV prevalence.

Although harm reduction interventions (i.e. needle-exchange and methadone substitution programs) decreased both incidence and prevalence of HCV among IDUs during the 1990s, their impact has been small in most countries [127,129,137–139]. Indeed, with a few exceptions [140], HCV transmission among IDUs remains uncontrolled, with prevalence increasing among young IDUs, and incidence rates ranging between 11 and 42 per 100 person/years [120,132,141,142]. The worst situation is in Eastern Europe where the dramatic IDU-related HCV epidemic started in the early 1990s and harm reduction interventions remain limited [22–24,131,143–146].

Phylogenetic analysis of HCV isolates from IDUs in different European cities shows a typical epidemic profile (large number of isolates per subtype, with a short genetic distance) and lack of site-specific segregation of isolates [147–150], suggesting that HCV exchange between European IDUs has occurred on a large scale.

The IDU-associated HCV epidemic is having several epidemiological consequences. First, most new HCV infections occur in young IDUs and the proportion of patients with IDU-related chronic hepatitis C has surpassed those infected by other routes [76–78,81,85,151], as summarized in Table 1.

Second, IDU-related HCV genotypes (1a, 3a, and 4) have replaced genotypes 1b and 2 among blood donors and young patients [76–78,81,82,85,151,152]. Even among IDUs, relative genotype distribution is rapidly changing [153], with genotype 4 spreading into Central and Northern Europe [76,77,81,140,148,153–156], and increasing in Southern Europe [78–80,157–161].

Third, at least one of the recently described intergenotypic HCV recombinants (a 1b/2k) appears to have arisen during high-risk IDU [162] and is rapidly spreading [24,163]. Whether other recombinants identified in Europe (a 2/5) [164], the Philippines (2b/1b) [165] and Vietnam (a 2i/6h) [166] are related to IDU remains unknown. Despite the limited number of recombinants thus far described, the rapid spread of the 2k/1b and the generation of further hybrids amidst the IDU epidemic might limit the accuracy of genotyping assays and their predictive value for treatment response [167].

Fourth, active HCV infection continues to increase among HIV-infected IDUs (>70%) whose liver disease progresses faster [168] and appear more resistant to current therapy [169], warranting every effort to provide them with optimised treatment strategies [170,171]. In this regard, the increasing spread of genotype 4 among HIV-infected IDUs, may add further difficulties in their therapeutic management [148].

Finally, although there is no reliable data on the extent to which IDUs spread HCV over to the general population, strong evidence supports that such spread occurs. In Southern Spain, 31% of HCV genotype 4-infected individuals have no known risk factor [172]. In cohorts of Greek patients with chronic hepatitis C, HCV genotypes 3 and 4 were detected in a significant proportion of patients with nosocomial or community acquired infection [78,79]. In a French study genotype 3a infection among transfusion recipients increased

almost threefold between 1979 and 1990 [81]. IDU-related subtypes 1a and 3a have also been found in a substantial proportion of non-IDU blood donors in the Netherlands and France [152]. Routes by which HCV infection spread beyond the boundaries of IDU include blood transfusion before 1991, unsafe health-care-related procedures, and to a lesser extent high-risk sexual behaviour and vertical transmission [31,80–82,86,113]. Recent epidemics of acute hepatitis C virus in HIV-positive men who have sex with men have been linked to high-risk sexual behaviours [173].

6. Immigration as part of the epidemiological change

Several European countries have sustained high net migration rates for decades, but uncontrolled migratory flows from developing countries are more recent and a substantial proportion of the estimated 20 million immigrants living in the EU have arrived during the last 15 years. As shown in Table 2, in some countries up to 12% of the population is composed of immigrants. Immigration is a new phenomenon in some EU members like Spain, which, after centuries of net emigration, has become host to the second highest absolute net immigration rate in the World, with 3 million immigrants having entered the country in the last six years. Fig. 4 summarizes current estimates of immigrants living in Spain according to their geographic origin.

The increase in HCV prevalence associated with immigration varies among countries. In Spain, it might be estimated (from data shown in Fig. 4) that about 90,000 new HCV carriers have entered the country during the last 15 years. Although this is a theoretical estimate, recent seroprevalence studies support this assumption. Among recent immigrants attending outpatient health services, anti-HCV has been found in 0.4–0.9% of Latin Americans, 1.9% of Northern Africans and in 9–15% of Sub-Saharan Africans and Asians [174–177]. In a recent study, of 549 immigrants from Pakistan attending a Primary Health Service, 11% were anti-HCV positive[178]. In another study including 1303 non-IDU immigrants who visited for the first time at four Spanish hospitals and an STD clinic, anti-HCV was confirmed in 0.9% of Latin Americans and 6% of Sub-Saharan Africans and Eastern Europeans [179].

In other European countries, the contribution of immigrants to the HCV reservoir is more relevant. Recent estimates suggest that immigrants account for 56% of prevalent infections in the Netherlands [44]. In a recent Dutch study, at least 12% of anti-HCV-positive first-time blood donors were immigrants from endemic areas [152]. In a recent study among 944 underprivileged individuals in Lyon, of whom 5% had anti-HCV, being an immigrant was an independent risk factor for HCV infection [180]. In a nationwide epidemiological survey conducted in Germany, 37% of 5837 chronic hepatitis C patients evaluated at primary health centres originated from 92 countries, mostly (21%) from Eastern Europe [43]. Also, 3% of late German repatriates, returning to Germany from the former USSR, were anti-HCV-positive [181]. Similarly, in a German study among 1176 inmates of a Correctional Centre, anti-HCV was fivefold higher among immigrants from the former USSR than among Germans (31% vs. 6%, respectively) [182]. In Iceland, of 2946 immigrants, 0.8% were found to be anti-HCV-positive (1.2%, among Eastern Europeans), with immigrants accounting for 10% of all reported HCV cases [183].

In Northern Italy, a retrospective evaluation of 2255 immigrants hospitalised during 2002 evidenced acute or chronic HCV infection in 3 and 38% of those with evidence of viral hepatitis infection (13% of the total population), more than one-third of them from Eastern

Table 2
Migrant population and net migration rates in European countries

Country	Total population (millions)	Migrants (*N*)	Migrants (%)	Net migration rate (per 1000 population)
Germany	82.5	8,000,000	9.7	NK
France	64	4,800,000	7.5	NK
United Kingdom	60.6	4,600,000	7.6	NK
Italy	58.9	2,700,000	4.6	9.7
Spain	44.7	4,800,000	10.7	15
The Netherlands	16.5	1,714,000	10.4	NK
Greece	11.3	1,150,000	10.2	NK
Belgium	10.4	985,000	9.5	1.22
Portugal	10.7	560,000	5.2	3.4
Sweden	9.2	1,100,000	11.9	1.7
Denmark	5.5	350,000	6.4	6.1
Austria	8.3	1,000,000	12	NK
Poland	38.1	–	–	−0.69
Romania	22.3	–	–	−0.16
Bulgaria	7.3	–	–	−4.3

Estimates 2006 (data available at: <http://epp.eurostat.ec.europa.eu/portal>).

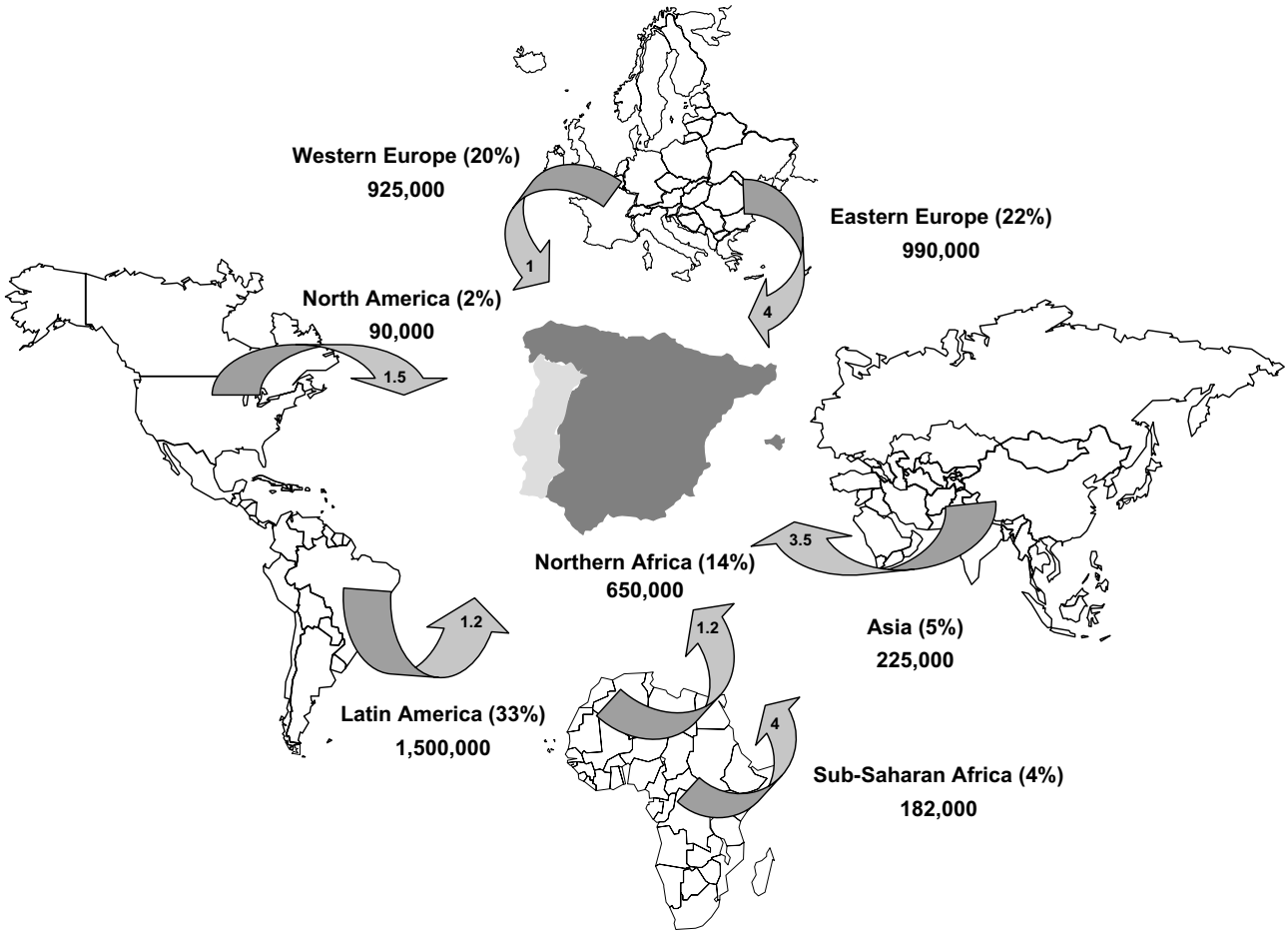

Fig. 4. Estimated number and proportion of immigrants living in Spain according to their geographic origin. Data obtained from the Spanish National Institute of Statistics for 2006. Numbers within arrowheads indicate the average anti-HCV carrier rate corresponding to each region.

Europe [184]. However, because of the high prevalence of HCV infection in the general Italian and Greek populations, immigration may have not changed HCV prevalence. In three Italian seroprevalence studies among non-EU immigrants and Kosovo and Albanian refugees, anti-HCV was found in 0.9%, 0.7%, and 0.3%, respectively, prevalence far lower than that of the Italian-born population [185–187]. Similarly, 1.8% of Albanian and 0% of Kurdish refugees in Greece had anti-HCV, again far lower than the Greek local population [188,189].

A new type of "short-term-treatment-seeking" immigration, involves young Eastern European IDUs specifically seeking free rehabilitation programs in EU countries [190]. This phenomenon might become a real problem (treatment failure hampers their return and frequently sends them to the street and eventually to prison), unless full cooperation between Official State Agencies is implemented.

Immigration from endemic areas also diversifies HCV genotype distribution. In a Paris district, in which 19% of the population are of African origin, seven different subtypes of HCV genotype 4 (10% of HCV infections) have been identified, six of them among immigrants who had acquired the infection likely acquired in their endemic home countries [155]. Similar findings have been reported from Southern France [154,157]. Unusual subtypes (1g, 2e 3k, 4a and 4k) were also detected in immigrant first-time blood donors in the Netherlands [152].

7. Facing the consequences of the changing epidemiology of HCV in Europe

Epidemiological changes of HCV infection in Europe have long been identified, but the consequences have yet to be adequately addressed. Fig. 5 summarizes the recommended strategies to face current challenges of the new epidemiological situation. New large-scale epidemiological studies, including accurate molecular methods to identify subtypes and recombinants, are required to estimate the current and future burden of the infection. Such studies, however, should not delay the immediate

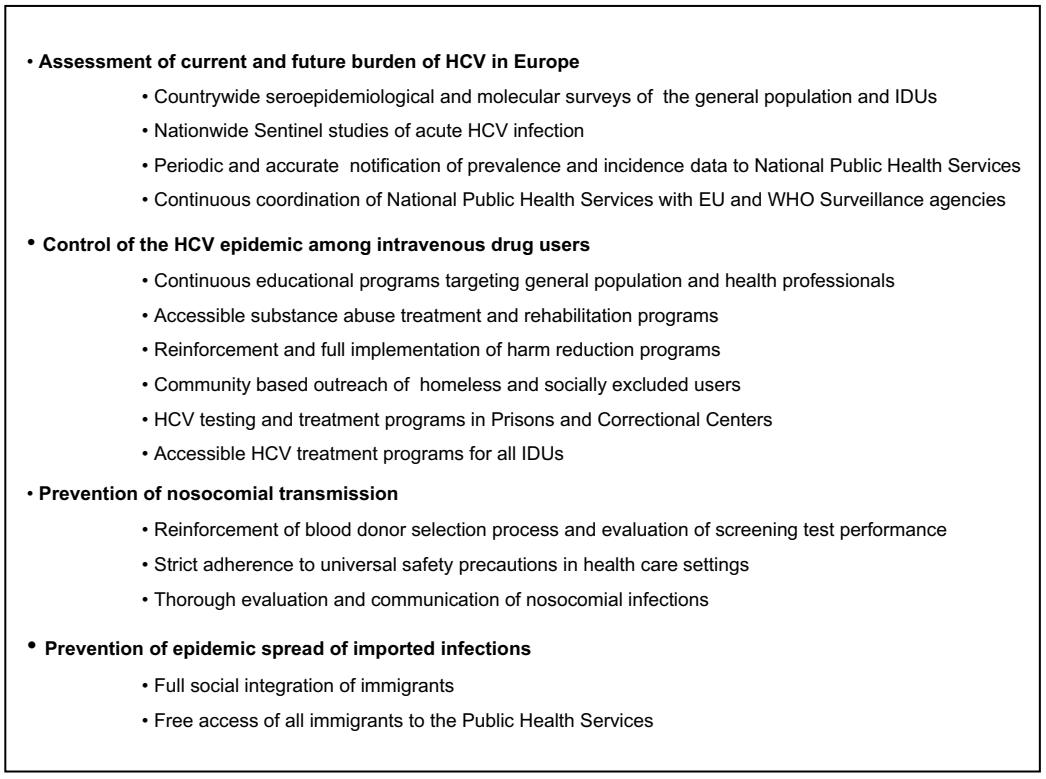

Fig. 5. Recommended strategies to face challenges of the current situation of the ongoing HCV epidemic in Europe.

measures (Fig. 5) that must be implemented to stop the uncontrolled IDU-associated epidemic, which will undoubtedly require a co-ordinated effort of supranational agencies, strong co-operation of health professionals from different fields and full commitment (both political and financial) from health authorities. Similarly, every effort should be made to promote social integration of immigrants and provide them free access to the Public Health services in their countries of adoption.

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