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Review Article

# Epidemiology of hepatitis C in Europe

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ABSTRACT

The advent of potent and safe direct-acting antivirals against the hepatitis C virus has the potential of fulfilling the dream of eliminating this infection and its impact on global public health. However, even if effective drugs are at hand, most patients remain unaware of their infection, which may be recognized only in late stages when dire complications have occurred. Europe is not spared by this scourge, with its estimated 19,000,000 persons infected, and knowledge of the epidemiology of HCV and its drivers is a critical tool in fighting this virus. A thorough review is provided on the extent of the HCV epidemic across Europe, with a discussion of the most important subgroups affected, and of the risk factors of infection, both traditional and new.



## 1. Introduction

The hepatitis C virus (HCV) is a major global pathogen, and its related public health burden is expected to increase further in the next few years [1,2]. According to some estimates, 3–4 million people are newly infected every year worldwide, and 350,000 patients die every year due to HCV-related disorders [3]. The toll of HCV infection is essentially due to its long term hepatic and extrahepatic consequences [4,5] The limited effectiveness of treatments available until a couple of years ago have led HCV-associated mortality to exceed that due to the human immunodeficiency virus (HIV) in developed countries, where potent drugs exist to manage HIV [6,7]. It must be added that HCV is widely under documented on death certificates [8] and therefore a true appreciation of the HCV-related health burden is lacking. In addition, the clinical impact of some extrahepatic disorders, leading to renal, cardiac and cerebrovascular outcomes associated with cryoglobulinemia and diabetes, has been emphasized only recently [4,5,9,10] and traditionally neglected in cost-effectiveness analyses. Safe and effective drugs are now available, although their cost will impose prioritization in their allocation. Thus, the next challenge will consist in identifying patients at risk of increased morbidity and mortality due to HCV, to link them to proper care, and to treat them. Through mathematical modelling, it has recently been shown that continuing to treat chronic hepatitis C patients with the current uptake rate will have a minor impact on the health burden by the year 2030, when the incidence of terminal stages of liver disease will reach its peak [2]. Thus, a better knowledge of HCV epidemiology and its movers may substantially contribute to an effective control of this troubling pandemic by focusing screening strategies on people at risk of disease progression, in order to get them into proper care and earlier treatment. The scope of this review article is to provide an update on the challenges regarding the epidemiology of HCV across Europe, and to foster the discussion about such potential strategies.

## 2. General epidemiology of HCV in Europe

A recent study [11], covering the geographical area of Europe as defined by the WHO (i.e. including the former USSR republics) 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 persons, a number to be adjusted in the future given the limited evidentiary support, especially for some countries in Central Europe and for the whole Eastern European bloc. The shortcomings of this and other studies reside in the fact that evidence is based on surveys often conducted in selected groups, or excluding high-risk populations such as prison inmates and groups of persons living in social exclusion. Furthermore, many studies are outdated and have failed to take into consideration the influence of some recent drivers such as migratory movements, including those regarding war refugees and illegal human trafficking. We will discuss some of these shortcomings below.

Even more patchy is the evidence concerning the disease burden, although recent studies have tried to fill the gap conducting

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intensive local surveys and expert interviews [12–14]. According to the study by Perz et al. [3], from the US Centers of Disease Control and Prevention, the attributable fractions of cirrhosis for HCV are 38% for Western and 34% for Eastern Europe [3], while those for hepatocellular carcinoma are, respectively, 44% and 15%. HCV-specific mortality is available for a few selected countries. For example, the mortality due to HCV in Spain is 11.25 per 100,000 [15] while in France there are 2.5 HCV-associated deaths per 100,000 inhabitants (95% had cirrhosis at the time of death) [16]. Concerning the disability-adjusted life years (DALYs) related to hepatitis C, the same Spanish study estimated that approximately 76,000 DALYs – calculated without applying social values – were attributed to HCV in 2006, although after the application of the discount rate and age-weighting, the burden of disease is almost halved. Nonetheless, this study underscored the fact that the overall burden of hepatitis C is the leading cause of DALYs among transmissible diseases, at least in Spain, although it is reasonable to assume similar conclusions for other major European countries. The mortality component, in the same study, represented more than 90% of the burden of hepatitis C. Overall, estimations via HCV-attributable fractions suggest that HCV causes more than 86,000 deaths and 1.2 million DALYs in the WHO European region [17]. Finally, about one-quarter of liver transplantations performed in 25 European countries in 2004 were attributable to HCV [17].

Although these figures are already compelling, recent modelization has estimated how these numbers will increase in the next decades [2]. The disease progression model took into account the historical number of HCV infections, the age and gender distribution, the extent and impact of the movers of the HCV viraemic pool (i.e. so-called inputs and outputs, encompassing acute infections progressing to chronicity, migration movements, treatment uptake succeeding into viral eradication and deaths), the progression rates (based on literature data) and the all-cause mortality data gathered from the Human Mortality Database [18] adjusted for incremental increases due to drug abuse and blood transfusion. This model was applied to several major European countries, including Austria, Belgium, the Czech Republic, Denmark, England, France, Germany, Portugal, Spain, Sweden and Switzerland [2] (Table 1). Accordingly, the number of decompensated cirrhosis cases of HCC and the liver-related mortality will increase by 55–110%, 10–140% and 1–130%, respectively, across the period 2013–2030, with only one exception represented by France, where these figures will decrease by 80%, 85% and 75%, due to the fact that the use of more potent antivirals will be implemented via an aggressive treatment uptake.

The diagnosis rate is clearly a major hurdle to implement strategies to reduce the future health burden of HCV. As shown recently [2], countries with a centralized registry, such as Austria, Denmark, France, Germany, Sweden and Switzerland, tend to boast the highest diagnosis rates (i.e. up to 80% for Sweden), while the lowest rates were reported for Portugal (33%). Virtually everywhere screening strategies have been dictated by identification of patients with a history of exposure via the traditional routes. However, screening strategies based on risk factors have traditionally failed to identify all patients at risk of infection, leaving a sizable proportion of patients unaware of their infection. The diagnosis rate varies across European countries between 31% in the Czech Republic and 81% for Sweden [2], indicating that strategies should be radically modified (see below).

## 3. Old and new drivers of the HCV epidemic: iatrogenic transmission of HCV

The relative impact of the different drivers of the HCV viraemic pool (Fig. 1) has changed over recent decades. A significant number of individuals acquired HCV in the 1970s and early 1980s, i.e.

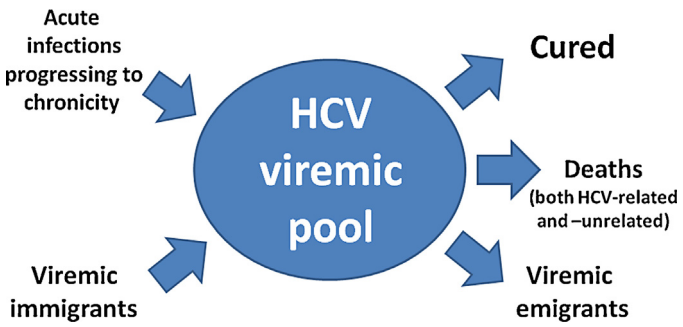


**Fig. 1.** Inputs and outputs of the hepatitis C viraemic pool in any given geographical area. *Abbreviations*: HCV, hepatitis C virus.

before screening assays were available and the improved awareness of blood borne pathogens – catalyzed, among others, by the AIDS scare – prompted safer medical practices. Across most of Europe, before the advent of screening assays, most infections were iatrogenic, i.e. due to transfusions with infected blood and its derivatives or to unsafe invasive medical and surgical procedures. Although before 1990 the risk of transmitting HCV via *blood transfusions* was significant (0.45% per unit transfused) [19], the introduction of screening assays reduced this risk to less than 1 per 1,000,000 units of blood [20], and the transmission of HCV via other blood products and even organ transplantation has been reduced to zero. Similarly, the prevalence of HCV in haemophiliacs has been traditionally very high [21], but after the introduction of recombinant clotting factors new cases of HCV in haemophiliacs have become exceptional [22]. On the other hand, HCV transmission has been consistently documented through use of blood-contaminated objects. A case–control study from Italy showed how the *use of non-disposable needles* within or outside the same family bore a significant risk of spreading HCV within close communities [23]. Iatrogenic transmission of HCV has since declined dramatically, and unsafe injections and medical procedures (such as wound sutures, surgical interventions and dental treatment) are still a scourge predominantly in resource-poor areas of the globe [9]. However, some small outbreaks are still reported also in Europe, due to breaches in standard safety procedures, suggesting insufficient awareness among health care providers, such as the case in a carefully documented series of patients having undergone sclerotherapy of varicose veins in France [24]. Similarly, an interesting case–control study on 450 HCV seropositive persons conducted in France [25] identified several unconventional risk factors for transmission of HCV and possibly other blood borne agents. Routes at risk of transmitting HCV included not only nosocomial admissions, but also digestive endoscopy, abortions, skin ulcer and wound cares, diathermy, injections, varicose vein sclerotherapy, acupuncture, practice of contact sports, beauty treatments and professional pedicure/manicure [25].

A strict adherence to standard precautions is obviously mandatory to prevent nosocomial HCV transmission, and this is the case for *digestive endoscopy* and *invasive radiology procedures*, as shown by studies conducted in Spain [26–28] and France [25,29] in recent years. Nevertheless, according to a large prospective cohort study carried out in a tertiary referral hospital in Turin, Italy [30], all 8260 persons undergoing digestive endoscopy remained negative for anti-HCV 6 months after the procedure, and even the 912 patients who had undergone endoscopy with the same instrument previously used on HCV-infected patients failed to seroconvert to anti-HCV, suggesting that proper hygiene and infection control practices may avoid transmission of HCV. Using dedicated endoscopy devices and rooms for patients with HCV may be an excessive measure, whereas experiments conducted on endoscopes intentionally contaminated with HCV and later disinfected

**Table 1**
Variation in the estimated number of decompensated cirrhosis cases, hepatocellular carcinoma and liver-related deaths during the period 2013–2030 in selected European countries.

| | Decompensated cirrhosis | | | HCC | | | Liver-related deaths | | |
|---|---|---|---|---|---|---|---|---|---|
| | 2013 | 2030 | % change | 2013 | 2030 | % change | 2013 | 2030 | % change |
| Austria | 200 | 180 | −10 | 110 | 150 | +35 | 100 | 130 | +30 |
| Belgium | 820 | 1400 | +70 | 300 | 640 | +110 | 290 | 570 | +95 |
| Czech Republic | 190 | 390 | +105 | 90 | 170 | +90 | 80 | 160 | +100 |
| Denmark | 230 | 480 | +110 | 90 | 210 | +140 | 80 | 180 | +130 |
| England | 860 | 1370 | +60 | 410 | 920 | +125 | 390 | 770 | +100 |
| France | 3650 | 760 | −80 | 1770 | 300 | −85 | 1570 | 380 | −75 |
| Germany | 2430 | 2200 | −10 | 1530 | 1640 | +10 | 1300 | 1430 | +10 |
| Portugal | 2410 | 4910 | +105 | 1150 | 2050 | +80 | 890 | 1700 | +90 |
| Spain | 4230 | 6710 | +60 | 2210 | 4500 | +105 | 1940 | 3750 | +95 |
| Sweden | 430 | 360 | +15 | 270 | 290 | +10 | 170 | 170 | = |
| Switzerland | 1140 | 1790 | +55 | 400 | 740 | +85 | 380 | 650 | +70 |

Adapted from Ref. [2].
*Abbreviations*: HCC, hepatocellular carcinoma.

showed that transmission of this virus can be reduced, if not eliminated, with the current mechanical cleaning–washing–disinfection procedures [31]. On the other hand, invasive radiological procedures may carry the risk if multidose vials of contrast media are improperly managed.

Transmission of HCV in *haemodialysis units* has become rare, and a recent cross-sectional survey conducted in France estimated the incidence of new HCV infections to be as low as 0.05% per year [32]. A Belgian prospective multicenter study showed a reduction from 1.4% to 0% in the annual incidence of HCV seroconversions, and this simply by reinforcing universal standard measures designed to prevent transmission of blood-borne pathogens, i.e. without any specific isolation measures [33]. The prevalence of anti-HCV in haemodialysis patients has decreased in most – but not all – European countries [34], although micro-outbreaks are still occasionally reported [35]. HCV infection is still the most common blood-borne viral infection in haemodialysis patients. Guidelines to reduce transmission have been issued [36], and although the isolation of anti-HCV positive patients is not warranted in all units, it should be considered where nosocomial transmission of HCV persists despite reinforcement and audit of hygiene precautions [37]. Use of multidose vials, sharing of trivial medical tools (including gloves) and carts, poor hand hygiene and a low ratio of nurses to patients may be risk factors of transmission of blood borne agents in haemodialysis units. In particular, the risk of inadvertently contaminating surfaces with blood by failing to immediately remove gloves after invasive procedures has been emphasized [38]. It is worth remembering that HCV environmental stability has been reassessed recently, and that HCV infectivity on inanimate surfaces is still detectable in the presence of serum for up to 5 days [39], whereas in a liquid environment it is detectable for up to 5 months at lower temperatures [40]. Different alcohols and commercially available antiseptics can reduce HCV infectivity to undetectable levels, provided that hand disinfectants are not diluted [40].

## 4. HCV in people who inject drugs

A formidable cause of transmission of HCV, widely spread throughout the globe, is represented by sharing the paraphernalia used by *people who inject drugs* (PWID). It has been estimated that up to 10,000,000 active drug users may be anti-HCV-positive worldwide [11]. This is of the highest concern, as drug dependence and disease burden are highest in young adults (mostly the third decade) [41].

If the incidence of HCV infections in Europe is estimated at 6.19 per 100,000 inhabitants per year [17], the majority of these new infections are indeed related to illicit drug use [2]. According to recent estimates [42] the number PWID in the WHO European Region is approximately 4.5 millions, among which about 2.0 million are HCV RNA-positive, i.e. 44% of the total. Restricting the area to the EU/EFTA region (i.e. the 27 EU member states plus Norway, Iceland, Liechtenstein and Switzerland), the number of PWID is about 1.2 million, among which 500,000 (or 43%) have HCV RNA. Indeed, HCV-infected PWID represent a substantial proportion of patients at risk of advanced liver diseases, and the major reservoir for the continuous spread of the epidemic. The modalities of transmission in this community are well known: the reuse of syringes and needles, the sharing of "cookers" (i.e. small containers to dissolve the drug, e.g. even a simple spoon), of cotton filters and of the water used to mix the drug, and even of swabs may transmit blood borne pathogens including HCV [43].

If the incidence of HCV in PWID was dramatically high in the early 1990s, the implementation of HIV prevention programs has reduced transmission rates in many countries. The window of infection from the moment PWID start injecting has been lengthening, suggesting the effectiveness of prevention strategies, including the access to sterile injection equipment [44], availability of safe injection facilities with on-site care and professional counselling on harm reduction practices, aimed at modifying injection risk practices and at facilitating medical and substance-abuse treatment. Counselling can also integrate PWID family members, if necessary. According to a study conducted in the setting of the Swiss HIV Cohort, the incidence rate in PWID decreased from 13.89 per 100 person-years in 1998 to a staggering low rate of 2.24 in 2011 [45], thanks to methadone substitution, needle exchange and heroin prescription programs. However, the data is not universally encouraging, and the rate of new infections may remain high, especially among new injectors and prison inmates. This is exemplified by a study carried out in London, where despite the existence of prevention programs, the HCV incidence rates remain as high as 41.8 cases per 100 person-years [46]. In Russia, which has the highest number (1.3 million) of anti-HCV-positive PWID [47] needle and syringe exchange programs are still poorly implemented, as in most Eastern European countries [48], incidence rates are likely to be even higher, although precise data is lacking.

The prevalence of anti-HCV among PWID varies among countries, although rates are constantly very high. The proportion ranges between 50% in Cyprus [49] to >80% in Germany [50], Italy [51] The Netherlands, Estonia, Lithuania and Portugal [47]. A study from St Petersburg [52] reported a prevalence of anti-HCV as high as 94.6% among PWID. Notable risk factors associated with an increased risk of being infected in the PWID community include older age, unemployment, a higher number of rehabilitation treatment episodes, current co-consumption of cocaine and a longer history of injecting drug use [50,51]. PWID are also at risk of infection with other blood borne pathogens. For example, the study by

Reimer et al. [50] analyzed the serological status for the hepatitis A virus (HAV), HBV and HCV in 1512 abusers admitted for opiate detoxification and concluded that coinfections were highly relevant in injecting drug users. Antibodies to HAV were present in 57.7%, to HBV in 53.0%, and to HCV in 75.0% of the persons. Lack of any hepatic marker was reported in only 11.2%, whereas at least one marker was positive in 24.7%, two markers were positive in 31.2%, and all markers were positive in as many as 32.9% of the total, and this even though HAV does not share the same risk factors as HBV or HCV transmission [50]. A most relevant coinfection is obviously represented by HIV. It is estimated that as many as 7 million persons are coinfected with HIV and HCV globally [53]. The prevalence of coinfection is quite variable, and it depends on the local prevalence of injection drug use, and the relative prevalence of both viruses: on average, up to one third of HCV-infected PWID are also coinfected with HIV. The coinfection with HIV is a major disease modifier in the natural history of chronic hepatitis C. According to a meta-analysis on 3567 individuals coinfected with HIV/HCV from 17 studies [54] the prevalence of cirrhosis after 20 and 30 years of HCV infection was 21% and 49%, with a rate ratio of cirrhosis more than twice the rate reported for monoinfected patients. This trend was only partially corrected by antiretroviral therapy.

Mortality in HCV-infected PWID is exceedingly high, but mostly not due to liver-related causes. In a seminal community-based linkage study from Australia, drug-related standardized mortality rates were dramatically high, especially in people between 15 and 24 years of age [55]. The generalization of these data is arduous, but a Swiss study showed that HCV-infected patients with a history of drug use had a standardized mortality ratio of 9.65 (6.90–13.51) [56]. Mortality in PWID is largely attributable to drug overdose, suicide, accidents, concomitant alcohol abuse, and coinfections.

It has been suggested that HCV-infected PWID should be treated aggressively, with antiviral administration being considered also as a preventive tool to avoid the spread of the infection within the PWID community. Scale-up of opiate substitution and needle/syringe exchange programs is however mandatory to optimize the control of the epidemic [57]. Drug price will certainly represent an issue given the scale of the problem [58]. In addition, control of coinfections and concomitant substance abuse must be implemented.

## 5. The new challenge: HCV in migrants

Arguably the most important input contributing to the HCV viraemic pool in many resource-rich countries is provided by *HCV-infected immigrants* coming from countries traditionally characterized by a high endemicity rate. Few studies have been performed on this sensitive topic, which, however, deserves thorough attention. The proportion of anti-HCV-positive persons among the total infected population in a given country can be as high as one quarter and one third of the total, such as in the case of The Netherlands and Germany, respectively [59]. In Germany, strong immigration flows from Turkey have contributed to the HCV pool: a report shows that the HCV prevalence among Turkish immigrants is comparable to that reported in their country of origin [60]. Furthermore, in Germany, immigration from Eastern Europe (mostly Poland and Russia) has also contributed to the estimated 23–37% of HCV-infected persons not of German nationality [61]. In Switzerland, detailed estimates based on figures provided by the Federal Office of Statistics [62,63] have shown that during the decade 2002–2011 no less than 655 viraemic infections were added annually to the HCV viraemic pool via the immigration/emigration balance, i.e. more than twice the input due to acute HCV infections progressing to chronicity (author's unpublished data). These data suggest that targeted screening programs – possibly extended to other infectious diseases such as hepatitis B – may help in limiting the future health burden due to migration.

## 6. What is the role of sex in HCV transmission?

*Heterosexual transmission* is not a significant driver of the HCV epidemic. A large US cross-sectional study on 500 monogamous, heterosexual, anti-HIV-negative cases and their partners (with an anti-HCV prevalence of 4%), followed for a median duration of sexual activity of 15 years (range 2–52 years), showed that only three couples at the end of follow-up had HCV RNA sequences compatible with interspousal transmission, with an incidence rate of 0.07% per year (i.e. 1 per 190,000 sexual contacts) [64]. This risk is lower than that estimated in the past by a study from Southern Italy [65]. Nonetheless, heterosexual transmission is unlikely to affect the spread of HCV. Despite this, HCV transmission has become a major problem in *HIV-positive homosexual men*. Here, the incidence of HCV has increased by about 20-fold during the past 15 years, from 0.23 to 4.09 per 100 person-years [45]. Risk factors predisposing to HCV acquisition include history of inconsistent condom use, past syphilis and unprotected anal intercourse with multiple partners. Reinfection after clearance is also possible. This community may also soon become the target of a specific treatment-as-prevention program, as advocated for PWID.

## 7. The HCV crisis in prisons

*Incarcerated persons* are characterized by high prevalence of blood borne and sexually transmitted pathogens. Although some data suggest that this phenomenon is to some extent declining [66–68], this population still bears a significant share of the HCV epidemic: the prevalence of HCV infection is indeed higher among prison inmates compared with the general population primarily because of the massive high risk behaviour, mostly sharing drug injection paraphernalia (see below). Despite the size of the problem, the number of large-scale, well-conducted studies is surprisingly low, as is the provision of specific care programs. In Europe, carefully conducted prevalence and incidence studies are scarce and concern only a few countries, while for the majority, especially the Eastern European countries, virtually no data is available. Official guidelines specifically aimed at managing viral hepatitis in inmates have been published only rarely [69].

A prison sentence obviously provides the opportunity to manage traditionally hard-to-reach patients. Thus, correctional facilities should be considered as important locations not only for applying screening strategies, but also for preventive and therapeutic interventions, and the very moment of incarceration seems to provide an ideal opportunity for testing and treating [70]. Indeed, a significant proportion of subjects may be identified with a previously unknown infection [71]. Unfortunately, testing uptake is disappointingly low [72,73]. Both personal and institutional barriers have been identified: prisoners' fears and lack of knowledge about HCV, lack of motivation and/or of awareness about the testing procedure, concerns about confidentiality, fear of stigma but also complex procedures for testing, inadequate pre- and post-test counselling, lack of pro-active approaches from the personnel, and lack of continuity of care after release from prison. These factors may account in part for the paucity of good quality studies on this sensitive topic. Some data focusing on the prevalence and incidence of the major blood borne pathogens and the risk factors associated with their acquisition is, however, available from a few countries. Intravenous drug use is obviously the most important factor for HCV infection and its spread whilst in prison. A cross-sectional survey carried out on inmates in six European prisons (France, Germany, Italy, The Netherlands, Scotland and Sweden)

[74] showed that 27% had injected drugs at least once and that half had injected whilst in prison. According to a meta-analysis [75], PWID were approximately 24 times more likely than non-PWID to be infected with HCV in European prisons. Two important cross-sectional studies from the Department of Community Health and General Practice at Trinity College, Dublin, Ireland, clearly pinpointed the fact that serving a prison term exposed inmates to infection due to the sharing of harmful behaviours. In the first study, the anti-HCV prevalence rate was the lowest (3%) among those who had never previously been in prison, and only 7% of these reported ever injecting drugs, while 40% of those previously in prison did so [76]. In the second study [77], where the anti-HCV prevalence rate was a worrying 37%, a fifth of PWID reported first injecting in prison, and 71% users reported sharing needles in prison. Similarly, in a large study from Spain [78], where the proportion of anti-HCV-positive inmates was even higher (48%), the variables associated with HCV infection by logistic regression analysis included the months spent in prison and a history of previous prison sentences. In a further nationwide study from England and Wales [79], 24% of adult prisoners reported having injected drugs, 30% of these reported having injected in prison, with three quarters admitting to having shared needles or syringes. Overall, these studies indicate the urgent need for preventive measures, such as harm reduction programs, to be implemented in prisons as from admission. The need is further stressed by the risk of contracting multiple infections with additional blood borne pathogens during prison stay, such as HBV and HIV. This risk is exemplified by two Spanish studies where monoinfections were very uncommon (overall: 13%) [80] and 40.5% of anti-HCV-positive inmates were co-infected with HIV while 1.5% had a triple virus co-infection (HBV + HCV + HIV) [67]. Interestingly, the latter study observed also that the prevalence of HCV has decreased in the Spanish prison population, probably as a result of an increase in immigrant prisoners who are not traditionally PWID.

The first prison-based syringe exchange program started in 1992 in Switzerland, and was then extended to Germany and Spain. According to a review of the problem [81], drug use decreased or remained stable over time, syringe sharing declined, and no new cases of HIV, hepatitis B or hepatitis C transmission were reported. There were no reports of program misuse, e.g. initiation of injection while in prison or use of needles as weapons, showing that such syringe exchange programs are feasible in prisons, and may reduce risk behaviour and the transmission of blood-borne infections without untoward consequences.

A major debate concerns the effectiveness of treating inmates with antivirals. If screening uptake is low, as seen above, and attrition rates are seemingly high, especially at the time inmates are referred to specialists upon discharge, the yield of patients eligible for treatment is very low, at 7/1000 inmates tested [82]. In one study, only 7% of HCV RNA positive inmates received treatment while in prison [72]. It was therefore suggested that a prison outreach clinic may provide the ideal setting to deliver effective therapy. Why are so many patients not treated? Many factors seem subjective and therefore modifiable, i.e. depending on patient education and adequate care [72]. Reasons encompass lack of awareness and motivation, fear of side effects, impending release or prison transfer, but also medical contraindications, such as psychiatric and neurological disorders [72]. The advent of well tolerated direct acting antivirals may obviously eliminate many residual barriers, once logistic issues are properly addressed. In fact, once all barriers are overcome, SVR rates can be high in this setting, probably due to elevated adherence rates [83], with the recurrence of intravenous drug consumption (in or out of prison) as the only predictive factor of treatment interruption [84], suggesting the need for integrated management of viral infections and dependence. Counselling is mandatory, as reinfection is frequent once SVR has been achieved. In an interesting study from Catalonia [85], 119 inmates (81% former PWID) who had achieved SVR were followed on average for 1.4 years: HCV reinfection occurred in nine former PWID, corresponding to an overall reinfection rate of 5.27 cases per 100 person-years. Active drug use and engaging in more than one risk behaviour after treatment predicted reinfection.

## 8. Mother-to-infant transmission of HCV

*Mother-to-infant transmission of HCV* is the first cause of HCV infection among children in developed countries, including Europe. The average risk is, however, low, i.e. about 4% per birth, with about one third of transmissions occurring in utero [86]. Factors predisposing to transmission are a high maternal viral load – although no threshold has been set –, maternal drug use and an untreated HIV infection. A systematic review of 18 observational studies on 3264 participants showed how no intervention could reduce the risk for mother-to-infant transmission and clearly stated that breast-feeding can be safely carried out [86]. With the advent of safe, well tolerated and highly efficacious direct acting antivirals, more and more mothers may opt for a pre-emptive treatment to eradicate HCV before a planned pregnancy. Therefore, the indication to screen before pregnancy may soon become the subject of debate.

## 9. Conclusions

The arrival of potent antivirals, administered in short courses of treatment, without major side effects or contraindications has opened a new era in the management of HCV worldwide. The next greatest challenge will be the identification of patients who are unaware of their infection before serious liver-related or extrahepatic complications develop. This confers a new role on full-scale epidemiological work: the number of diagnosed HCV infections is still too low in many countries, and risk-based screening strategies have traditionally failed to identify all infected patients. Even more importantly, continuing to treat with the current uptake, disparagingly low in some countries, will have little impact on the HCV-related health burden in the next decades. Models have estimated that the number to be treated annually with potent antivirals should be multiplied by a factor of 4 in order to significantly reduce HCV-related mortality by the year 2030 [87]. Thus, more effective screening strategies should be adopted, as was the case recently for the US, with the proposal of a birth cohort screening policy [88]. The necessity to adapt this approach to the realities of each single European country, where the patients' age distribution may vary, has been discussed recently [14], and is beyond the scope of this short review. However, birth cohort screening seems cost-effective [89], provided that patients are then managed accordingly. We may be on the brink of an effective solution for the HCV epidemic.

### Conflict of interest

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