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Securing wider EU commitment to the elimination of hepatitis C virus

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REVIEW

Securing wider EU commitment to the elimination of hepatitis C virus

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Abbreviations: CDA, Centre for Disease Analysis; C-EHRN, Correlation European Harm Reduction Network; CoC, cascade of care; DAAs, direct-acting antiviral agents; EASL, European Association for the Study of the Liver; ECDC, European Centre for Disease Prevention and Control; EEA, European Economic Area; ELPA, European Liver Patients' Association; EMCDDA, European Monitoring Centre for Drugs and Drug Addiction; EU, European Union; GPs, general practitioners; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HepBCPPA, Hepatitis B and C Public Policy Association; HIV, human immunodeficiency virus; HMOs, health maintenance organizations; MEP, Member of the European Parliament; MoC, models of care; MOP, mobile outreach programmes; MSM, men who have sex with men; NHS, national health system; NSP, needle and syringe programmes; OST, opiod substitution programmes; PoC, point of care; PWID, people who inject drugs; SVRs, Sustained Virological response; TBC, tuberculosis; WHO, World Health Organization.

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Abstract

In 2016, the Hepatitis B and C Public Policy Association (HepBCPPA), gathered all the main stakeholders in the field of hepatitis C virus (HCV) to launch the now landmark HCV Elimination Manifesto, calling for the elimination of HCV in the EU by 2030. Since then, many European countries have made progress towards HCV elimination. Multiple programmes—from the municipality level to the EU level—were launched, resulting in an overall decrease in viremic HCV infections and liver-related mortality. However, as of 2021, most countries are not on track to reach the 2030 HCV elimination targets set by the WHO. Moreover, the COVID-19 pandemic has resulted in a decrease in HCV diagnoses and fewer direct-acting antiviral treatment initiations in 2020. Diagnostic and therapeutic tools to easily diagnose and treat chronic HCV infection are now well established. Treating all patients with chronic HCV infection is more cost-saving than treating and caring for patients with liver-related complications, decompensated cirrhosis or hepatocellular carcinoma. It is more important than ever to reinforce and scale-up action towards HCV elimination. Yet, efforts urgently need the dedicated commitment of policymakers at all governmental and policy levels. Therefore, the third EU Policy Summit, held in March 2021, featured EU parliamentarians and other key decision makers to promote dialogue and take strides towards securing wider EU commitment to advance and achieve HCV elimination by 2030. We have summarized the key action points and reported the 'Call-to-Action' statement supported by all the major relevant European associations in the field.

KEYWORDS
epidemiology, health policy, hepatitis, hepatitis C, prevention

1 | INTRODUCTION

In 2016, the Hepatitis B and C Public Policy Association (HepBCPPA), held the first European Union (EU) hepatitis C virus (HCV) Policy Summit. It was the first meeting that gathered all the main stakeholders of the EU in the field of HCV and culminated in the presentation of the HCV Elimination Manifesto (Box 1), which aligns with the World Health Organization's (WHO) goal of eliminating HCV as a public health threat by 2030. The summit provided a starting point for the EU's wider commitment to implementing action towards achieving the HCV elimination targets by 2030.[1] In June 2018, the second EU HCV Policy Summit was held with a particular focus on securing sustainable funding for HCV elimination strategies, given that HCV treatment costs represent

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a serious challenge for the health budget of countries. During this summit, it was underlined that HCV elimination is not only feasible and cost-effective but is even cost-saving in the long term for countries' health systems.[2]

On 24 March 2021, the HepBCPPA organized its third EU Policy Summit entitled 'Securing Wider EU Commitment to the Elimination of HCV'.

Key points

- Hepatitis C virus (HCV) infection remains a major health threat in the European Union.
- Diagnostic and therapeutic tools to easily diagnose and treat chronic HCV infection are well established and elimination of the disease is possible.
- Most European countries are not on track to reach the 2030 HCV elimination targets set by the World Health Organization and the COVID-19 pandemic has resulted in a decrease in HCV diagnosis and antiviral treatments.
- Wider EU commitment is needed to achieve HCV Elimination.

2 | OVERVIEW AND EPIDEMIOLOGY

Although HCV infection is curable a disease, it still remains a major global health threat.[3,4] Globally, an estimated 58 million people are living with chronic HCV in 2021.[5] The ECDC estimates that there are approximately 3 900 000 people living with chronic HCV infection in the EU, the European Economic Area (EEA) and the United Kingdom (UK) in 2020.[6] In the EU, modelling data suggest that newly diagnosed HCV cases peaked in 2016 with approximately 100 000 newly diagnosed cases, whilst the number of treated patients peaked in 2017 with approximately 150 000 people initiating HCV treatment and over 144 000 successfully achieving sustained virological responses (SVRs).[7,8] Overall, diagnosis rates continue to be high in many western European countries, but according to the Polaris Observatory, patients with diagnosed HCV infection often get lost in the cascade of care (CoC) and never reach antiviral treatment initiation and subsequent HCV infection cure (Figure 1).[7] In 2019, the ECDC established a hepatitis monitoring system for the EU, which gathers data from existing sources or which are reported directly to the ECDC by national focal points.[9] As of 2019, only an estimated 14% of all diagnosed patients in the EU were being treated, accounting for an estimated 6% of all reported infections (including undiagnosed people), leaving over 70% of all cases unlinked to appropriate antiviral treatment since 2015.[8] Importantly, the COVID-19 pandemic has led to a drastic decrease in the number of diagnosed/reported cases and treatment rates.[10] Despite this, progress has continued to be made since the availability of direct-acting antiviral agents (DAAs) towards HCV elimination, especially amongst high-risk groups such as prisoners, migrants, people who inject drugs (PWID) and men who have sex with men (MSM). Targeted screening and treatment of these key populations has led to an overall reduction of HCV prevalence in them and hence in the wider public. Recently, a number of alternative approaches to reach these high-risk groups have been proposed and successfully conducted,[11] and whilst these programmes have shown success, their continuation amongst high-risk populations is important, since HCV prevalence might increase as soon as treatment and/or harm reduction programmes end.[12] Furthermore, new data suggest that there are still risk groups such as people with mental health problems that have not been adequately addressed and reached in recent years. Indeed there are reports of a 5- to 10-fold higher HCV prevalence amongst these people compared to the general population.[13,14] Whilst targeting high-risk populations is crucial to decreasing transmission rates and hence the overall prevalence of viremic HCV infections, there are still many individuals in the general population who may be unaware of their HCV infection. Therefore, national screening programmes have been proposed to identify people living with HCV but are

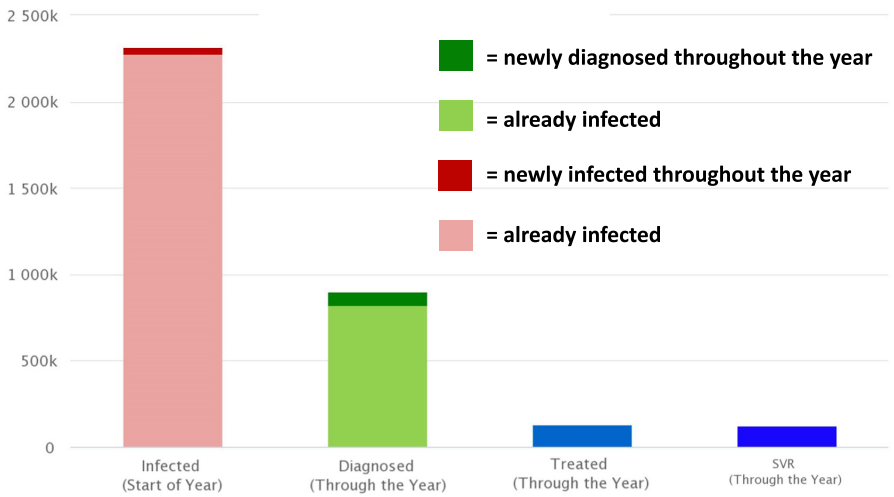

FIGURE 1 Cascade of care in 2019. Many patients did not receive antiviral treatment, despite being diagnosed with chronic hepatitis C virus. Adapted from Ref. [7].

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BOX 1 Elimination manifesto

Hepatitis C Elimination in Europe.

"Our vision for a Hepatitis C-free Europe".

We, the signatories of this declaration, gathered in Brussels on the occasion of the first EU HCV Policy Summit, on 17 February 2016, are committed to the elimination of hepatitis C in Europe.

➢ Hepatitis C is a life-threatening disease; it affects millions of people across Europe and has significant morbidity and premature death burden (the WHO estimates that there are 14 million people affected by hepatitis C across WHO European Region and various accounts report some 6 million living in the EU alone).

➢ Today, scientific breakthroughs give us the unique opportunity to eliminate hepatitis C in Europe, averting a significant toll in terms of deaths and societal and economic costs;

➢ The specific challenges of hepatitis C require holistic, people-centred, health systemwide approaches to disease awareness, prevention and integrated care, with all stakeholders combining their diverse skills and resources in a unified response.

We share the vision that eliminating hepatitis C in Europe by 2030 (in line with the goals of the draft WHO Global Health Sector Strategy 2016–2021, November 2015—link) will require us to:

1. Make hepatitis C and its elimination in Europe an explicit and adequately resourced public health priority, to be pursued using appropriate means at all levels—through collaboration between individual citizens, civil society organizations, researchers, the private sector, local and national governments, EU institutions—including the Commission, ECDC, EMCDDA, the WHO Regional Office for Europe and other relevant regional bodies;
2. Ensure that patients, civil society groups and other relevant stakeholders are directly involved in developing and implementing hepatitis C elimination strategies, with existing best practice examples and guidelines serving as the basis for people-centred health system-based strategies that emphasize tailored implementation at the local level;
3. Make the development of integrated care pathways a core component of hepatitis C elimination strategies, taking into account the specific health system barriers and other challenges related to the management of hepatitis C infection;
4. Pay particular attention to the links between hepatitis C and social marginalization, and for all hepatitis C elimination-related activities to be consistent with fundamental human rights principles including non-discrimination, equality, participation and the right to health;
5. Strengthen efforts to harmonize and improve the surveillance of hepatitis C across the EU, to inform and evaluate hepatitis C elimination strategies;
6. Introduce a European Hepatitis Awareness Week (the week of World Hepatitis Day) to hold intensive, coordinated awareness-raising and educational activities across Europe;
7. Review progress on achieving the objectives and goals set out in this manifesto on a regular basis and promote the manifesto at all relevant opportunities.

To Note:

In developing this Manifesto, the following documents were taken into consideration:

- World Hepatitis Summit, 2–4 September 2015, Glasgow—link.
- Glasgow Declaration on Viral Hepatitis, September 2015—link.
- World Health Assembly, Resolution 67.6 on Hepatitis, 24 May 2014—link.
- WHO, Prevention and Control of Viral Hepatitis Infection: Framework for Global Action, 2012—link.
- World Health Assembly, Resolution 63.18 on Viral Hepatitis, 21 May 2010—link.
- Hepatitis B and C Public Policy Association, High-Level Meeting "Economic crisis and healthcare –ensuring access to public health services: the case of hepatitis B and C", 3–4 June 2014—link.
- Hepatitis B and C Public Policy Association, Summit Conference on Hepatitis B and C in the Mediterranean and Balkan Countries, 5–7 September 2012—link.
- Hepatitis B and C Public Policy Association, Summit Conference on Viral Hepatitis, 14–15 October 2010, Brussels—link.

unaware of their infection status. Finding new undiagnosed cases without national, population-based programmes, has become increasingly challenging. Thus, many patients will be diagnosed late, leading to more advanced liver disease at presentation and hence unnecessarily high hepatocellular carcinoma (HCC) incidence rates in the long term (Table 1).[15-17]

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3 | REVISITING THE ELIMINATION MANIFESTO—ARE WE THERE YET?

Elimination of HCV by 2030 remains the ultimate goal and significant progress has been made in recent years. For example, in all European countries, blood screening to prevent blood transfusion-linked HCV infections is mandatory and overall HCV prevalence is declining. Most countries have established national strategies and/or are working with high-risk groups to prevent new HCV infections, resulting in a decrease in the overall incidence of viremic HCV infections and liver-related mortality and the incidence of decompensated cirrhosis/HCC (Figure 2).[8,18] In times of highly effective pangenotypic DAAs, a single treatment course achieves SVR in >95% of cases and effective treatments are now available for re-treatment.[19] Whilst treatment costs have decreased over recent years, treatment rates have not increased as required. Globally, 80% of all countries are still not on track to achieve the 2030 viral hepatitis elimination targets set by the WHO.

TABLE 1 Key challenges in the fight against HCV.

Key challenges
1. Increase screening and treatment rates
2. Secure programmes for risk populations, i.e. PWID, prisoners, migrants, etc.
3. Secure sustainable funding for HCV treatment
4. Simplify diagnostic and treatment algorithms
5. Secure political will to support anti-HCV programmes

Abbreviations: HCV, hepatitis C virus; PWID, people who inject drugs.

In fact, 67% of countries are off-track by at least 20 years.[20] Moreover, only 16 European countries have reported sufficient data to allow them to make reliable estimates on the proportion of patients living with HCV.[9,21] In addition to the lack of epidemiological data in Europe, some countries still have not established national HCV policies or guidelines for treatment, prevention or harm reduction.[21,22] Since many national plans do not yet include wide-scale screening to identify undiagnosed HCV cases in the general population, HCV treatment rates have been declining over the past few years and some countries do not have the number of patients to treat that current resources would permit.[8] As of 2021, treatment and diagnostic rates remain relatively low in most countries and thus only France, Iceland and Spain are expected to meet the WHO elimination targets, which call for a significant increase in HCV treatment and diagnosis rates by 2030 compared to 2015. Thus, countries with comparably low HCV incidence rates such as Germany, the Netherlands and Austria struggle to reach the elimination goal and because of this a shift from relative to absolute targets was proposed by the Center for Disease Analysis (CDA) and their collaborators,[23] not to stop viral hepatitis programmes, but to recognize the low endemicity of HCV in some countries.[4]

In a recent study by the EMCDDA, in 8 out of 14 countries anti-HCV is present in over 50% of PWID and they remain the main source of new HCV cases.[24,25] Other high-risk groups such as prisoners and migrants have also been targeted in recent years-HCV prevalence amongst prisoners ranges between 4.3% and 6.7% and screening for HCV in this group is conducted in 36%–70% of countries. In 2015, a study in France indicated that only up to 46% of viremic inmates receive antiviral treatment.[26] More proactive interventions for

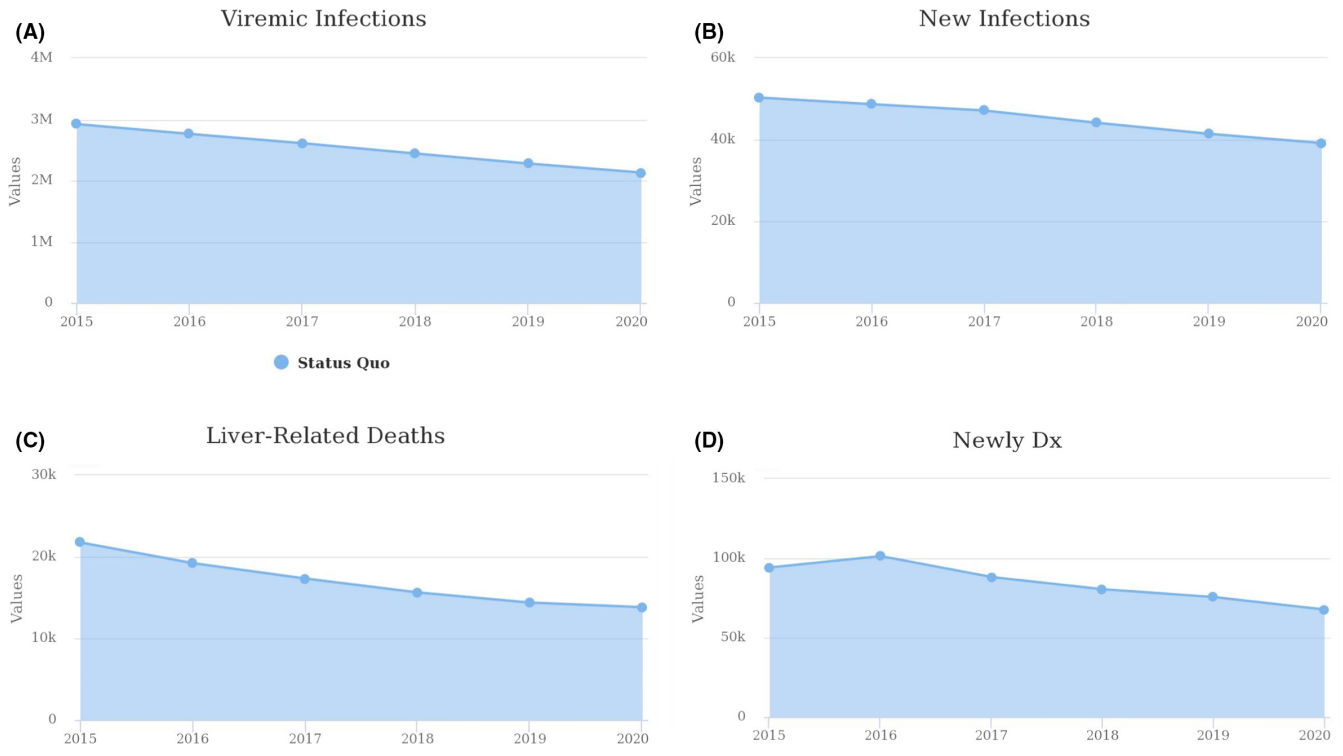

FIGURE 2 Number of viremic infections (A), new hepatitis C virus infections (B), liver related-deaths (C) and new diagnosed hepatocellular carcinoma (D). Adapted from Ref. [7]

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screening and treatment are needed to improve care in this population. Migrant populations also remain of concern, since some studies report high prevalences of 8% for hepatitis B virus (HBV) and 2% for HCV in different migrant populations.[26-28]

Despite the progress that has been made in many parts of the world, HCV elimination remains one of the most important public health challenges, especially given that the COVID-19 pandemic has led to a dramatic decrease in HCV treatment rates, and the potential for a significant increase in HCV-related morbidity, mortality and healthcare costs over the long-term.[10] Therefore, wider EU commitment by policymakers to the elimination of HCV is thus urgently needed.

4 | COVID-19 AND HEPATITIS C VIRUS

4.1 | COVID-19, liver disease and impact on screening and treatment of hepatitis C virus

Abnormal liver function has been observed in over 70% of all hospitalized patients with COVID-19 infection, and severe pneumonia is more frequently observed in those with abnormal liver tests at admission.[29,30] It has been reported that patients with COVID-19 illness and cirrhosis have a greater risk of further clinical deterioration and 30-day-mortality of over 30% as compared to those without liver complications.[31,32] In addition, severe infection can lead to chronic cholangiopathies since cases of secondary sclerosing cholangitis have been reported.[31] However, chronic liver disease per se in the absence of cirrhosis does not appear to be associated with higher mortality in COVID-19-infected patients (Table 2).[33,34]

TABLE 2 COVID-19 and the liver.

COVID-19 and the liver
1. Abnormal liver tests are present in 76.3% of all patients
2. Liver disease per se does not lead to a higher mortality
3. Presence of liver cirrhosis is associated with a higher mortality
4. Severe COVID-19 might lead to secondary sclerosing cholangitis

The COVID-19 pandemic has led to a drastic decrease in HCV screening in 2020, especially in ambulatory clinics, and in parallel with the substantial decrease in the total activity and number of services offered within hepatology units.[35] The pandemic has also resulted in a reduction in HCV treatment rates in 2020, compared to 2019 (Figure 3).[8] The number of patients starting DAA therapy in some European countries such as Italy and Germany fell rapidly in April 2020 with the first lockdown and slowly increased again during 2021.[35,36] EU-wide delays in HCV screening and treatment may be associated with substantially higher morbidity and mortality of European HCV patients in the future. One study estimated that the potential effects of a 1-year hiatus in HCV elimination programmes could be more than 40000 additional HCC cases and over 70000 more liver-related deaths globally. Given that any delay in treatment can result in an increased rate of de-novo HCC and cirrhosis, even high-middle-income countries can be expected to suffer severe health-related and economic consequences as a result of a year without HCV treatment.[10] One study has already reported a potential delay in HCC diagnosis because of reduced HCC screening.[36] It is therefore more crucial than ever to reinforce and sustain HCV programmes if the WHO elimination goal is to be achieved.

4.2 | Opportunities—from one pandemic to another

Modern diagnostics, telemedicine and other IT tools offer a number of new opportunities. They can decrease the amount of needed visits along the CoC in order to ensure better linkage to care and subsequent treatment rates, given that new diagnostic tests allow for easier and quicker HCV-testing and pangenotypic regimens which promise high SVR rates in most patients, even without continuous monitoring.[16,37,38,39] Screening and treatment of patients can be conducted by non-specialists, such as general practitioners (GPs) and prison doctors. Moving forward, diagnosis and treatment initiation could be done on the same day, thus creating potential 'one-stop-shops', that would be especially attractive to some high-risk groups.[11] Furthermore, decentralization of testing and treatment initiation could be further

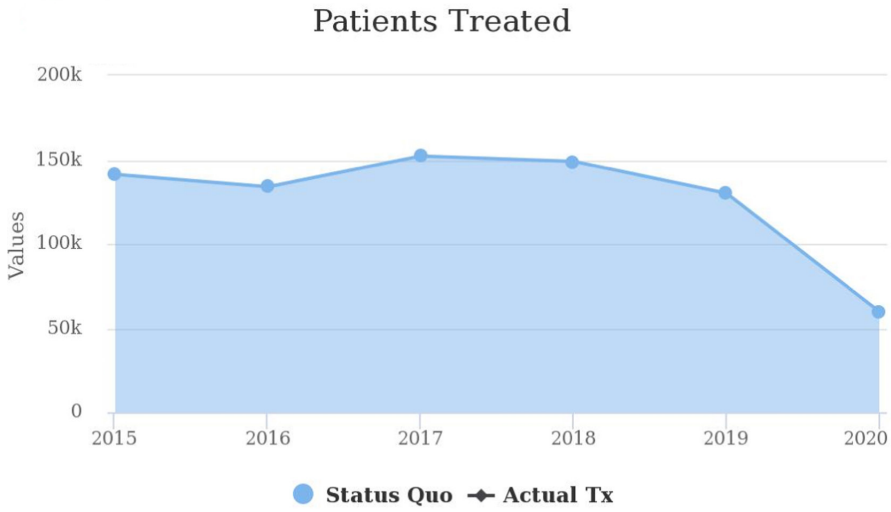

FIGURE 3 Patients were treated for chronic hepatitis C virus between 2015 and 2020. The COVID-19 pandemic led to a substantial decrease in treatment numbers. Adapted from Ref. [7]

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supported using mobile units, which are already used to target risk groups and to reach marginalized patients, which could be an approach for populations, who often have difficulty accessing formal health services such as homeless people and PWID.

It is crucial to emphasize that besides HCV, PWID are also at increased risk for COVID-19 infection. A seroprevalence study conducted in Zurich, at the beginning of the pandemic reported a prevalence of 9.8% of Sars-CoV-2 antibodies amongst PWID, which was significantly higher than in the general population (3.4%, August 2020). In addition, PWID are also at high risk of severe COVID-19 because of the high prevalence of comorbidities such as *chronic obstructive pulmonary disease*, cardiovascular diseases, or human immunodeficiency virus (HIV) infection.[40] Therefore, expanded harm reduction actions have been proposed, including the provision of extended take-home dosages for OST, home delivery of opioid-agonist treatment or increased supervised consumption rooms.[40]

Importantly, the COVID-19 pandemic might be an opportunity to increase awareness of viral infections in general and to promote decentralization or population-level screening. In Italy, a combined programme screening for HCV and COVID-19 infection was conducted in an urban setting in the town of Casola where the entire population (>6 years old) was invited via social media and widespread announcements throughout the area to participate. Out of 2740 individuals (77% of the eligible population), 41 (1.5%) were found to be anti-HCV positive and five (0.18%) were viremic, of which two patients were newly diagnosed with chronic HCV infection.[41,42] A pivotal screening programme targeting subjects born between 1969 and 1989 has been conducted in Lombardy, Northern Italy, where point-of-care testing was offered for free concomitantly to COVID-19 vaccination. Amongst 7219 subjects born between 1969 and 1989 for whom HCV screening is thought to be cost-effective, only 7 (0.1%) subjects tested anti-HCV positive and 3 (0.04%) were HCV-RNA positive by standard confirmation tests, suggesting to move the bar of HCV screening beyond the age of 62.[43] Thus, the COVID-19 pandemic could also help to facilitate HCV screening efforts and micro-elimination activities.[41,42,44,45,46] Furthermore, during the pandemic, many laboratories set up fully integrated, automated sample-to-result molecular analyzers that could also be used for large-scale HBV/HCV testing. Innovations around molecular COVID-19 detection point of care (PoC) testing can easily be converted and transferred to HCV diagnostics.[47,48] However, this would need dedicated funding, political will and, importantly, immediate action if it is to become useful in the way described.

5 | SPECIFIC HEALTH SYSTEM BARRIERS, INTEGRATED CARE PATHWAYS AND CHALLENGES

Even though many patients are diagnosed with HCV, some never find their way to effective treatment and are lost in the CoC, even in the general population.[3] Diagnosis of HCV is typically made through GPs, whilst DAA treatment is mostly initiated by specialists. This may be because of the relatively high cost of the treatment or the fact that GPs are not adequately trained to treat these patients.[49] However, GPs must be seen as a valuable resource to extend screening and treatment capacities,[13,50] especially given that pangenotypic regimens have simplified HCV treatment in recent years and the fact that in most cases genotyping is not necessary.[15] Of note, one study suggested that financial incentives can improve screening rates for GPs.[50] In EU countries another approach might be the general screening of the population. This approach proved to be highly effective in Egypt and analyses revealed that universal screening would be highly cost-effective.[51] This approach was proposed in France but was ultimately rejected by health authorities.[13] It has been suggested to screen only age groups with a comparably high prevalence of HCV, i.e., the generation of 'baby boomers'.[13,52,53,54,55] A calculation for the United States (US) estimated that by screening every adult born between 1945 and 1970, 74% of all HCV cases could be identified. However, screening baby boomers may not be effective in every country and strategies should be adapted to local epidemiology and culture. Nonetheless, analyses suggest that universal screening in any population with HCV prevalence >0.1% is cost-effective.[56] Yet, A more decentralized approach to HCV screening and treatment could also facilitate HCV management and facilitate a more integrated care pathway in both the general population and high-risk populations.[11,50]

People at increased risk of HCV infection, such as PWID, remain the most frequent source of new infections in European countries.[24] PWID experience social exclusion and stigmatization and often suffer from psychological vulnerabilities or concomitant psychiatric illnesses.[57] Different approaches to the prevention of stigmatization and discrimination and even criminalization have been suggested by EASL, ELPA and PWID organizations[58] together with harm reduction programmes, education on safe sex and improved access to care. Harm reduction services such as needle and syringe programmes (NSP) or opioid substitution programmes (OST) which also improve access to healthcare, testing services and DAA treatments at the community level, have been associated with a decrease in HCV prevalence and incidence. Preventive interventions like OST or NSP have been shown to be cost-saving and help to bring DAA treatment closer to the people in need and are essential in order to achieve the WHO elimination goal.[24,59,60] In this context, country-level data indicate that only Austria, the Netherlands and Norway have a high NSP and OST coverage and only five EU countries report >50% of PWID entering OST being tested for HCV in the past year.[9] Scaling up of harm reduction and screening interventions thus remains a crucial priority for HCV elimination strategies and is also associated with beneficial effects for other infectious diseases such as HIV.[61,62] Yet, targeting this particular group can nevertheless be difficult since PWID often do not attend conventional drug addiction treatment centres or other health and social services and are therefore considered difficult to reach and treat. Both, diagnosis of HCV and linkage to treatment are often not achieved. Hence, promoting HCV testing and treating every HCV patient at the earliest opportunity is crucial. Different models of care (MoC) have been

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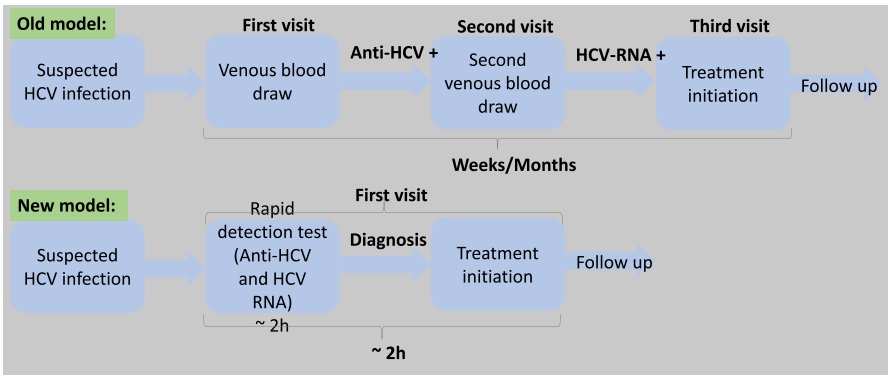

FIGURE 4 Different models of care—older models are based on repeated visits and repeated testing. New testing methods could therefore facilitate care and lead to fewer necessary visits. Adapted from Ref. [7]

suggested, reducing the number of necessary visits to confirm infection and starting treatment immediately may improve linkage to care.[63] Given new technologies, same-day diagnosis of viremic HCV is possible,[11] resulting in the reduction of necessary visits between diagnosis and SVR (Figure 4).

The EMCDDA Hepatitis C initiative supports EU member states in improving their national harm reduction practices by providing a comprehensive toolbox for national decision makers and professionals working in the field. In this regard, it has to be emphasized that an integrated approach that consists of prevention and harm reduction at different levels promises to be most effective. A potential solution for reaching PWID could be the implementation of mobile care such as the one created in Denmark, where a mobile unit visits the main train station in Copenhagen, Denmark's largest open drug scene. The project was peer-led and on-site nurses were present in the van to manage the process and operate the mobile diagnostic GeneXpert© machine of the mobile unit. Test results were made available approximately 1 h after the patient visited the van and, in case of a positive test, the hospital was contacted to provide rapid linkage to care.[39] In addition, other infections such as HIV or hepatitis B could also be targeted using this approach, further decreasing the overall morbidity in PWID.

For other high-risk populations such as prisoners, the ECDC recommends offering HCV testing to all people who are incarcerated. Testing both at admission and also during the prison stay is considered important.[64] In the region of Catalonia, Spain, systematic HCV screening amongst people who are incarcerated upon admission was introduced in 2016. In the case of HCV, patients were linked to a treatment centre and could also be linked to community specialists upon release in order to ensure continuity of care and decrease the rate of lost-to-follow-up post-release. By 2020, the prevalence of viremic HCV was reduced from 4.3% to 1.1% in this group.[65]

For migrants, community-based testing may increase awareness, efficacy of screening programmes and linkage to health services in the long term. In Catalonia, as a part of the HCV elimination programme 'Microhepcero', a pilot programme with rapid HCV testing, was launched in the Pakistani community which accounts for approximately 5.3% of the Catalan population and showed high acceptability. The community intervention was done in collaboration with immigration services and included HCV screening and opportunistic screening for HBV and HIV combined with educational workshops aimed at facilitation of access to the standard healthcare pathways and treatment of the respective viral infections.[65] Community interventions could, therefore, be a valuable tool for further micro-elimination strategies in migrant communities. There are also strategies for arriving migrants: One study investigated over 2600 migrants who arrived in western Sicily from Africa regarding HBV and HCV infection. Ongoing HBV infection was present in over 9% of this population, whilst over 2% had anti-HCV antibodies.[29-31] These findings imply that early screening is feasible and highly effective. Overall, the need for different approaches needed with PWID, migrants or prisoners emphasizes the fact that distinct elimination strategies may be required for different populations. In general, integrated care pathways need to be promoted and must be seen as a key element of effective hepatitis elimination plans.

In summary, different strategies to promote HCV elimination have been proposed. Different tools to target high-risk groups have been established and are available but political action is needed to ensure funding and implementation.

6 | PROGRESS IN THE FIGHT AGAINST HEPATITIS C VIRUS: FROM NATIONAL ELIMINATION PLANS TO BEST PRACTICE CASE STUDIES

6.1 | Plans and progress in the European Union and beyond

Since the first launch of the HCV Elimination Manifesto and the introduction of the WHO HCV elimination targets, many countries have developed strategies to scale up HCV prevention, screening and treatment. An important milestone has already been reached and in 2018 Iceland met the WHO elimination goal of treating 80% of all HCV cases.[66] In addition, other countries and municipalities have also made considerable progress towards HCV elimination:

6.1.1 | England

It is estimated that 89 000 people are living with chronic HCV in England. Since 2015, the number of annually treated patients steadily increased from 6031 patients to 12 229 patients in 2019/2020,

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resulting in 51 013 treated patients between 2015 and 2020. Treatment of every patient with DAAs has been possible because of different strategic procurements and close partnerships with the industry. Thus, HCV-related cancer and liver cancer mortality were reduced by 20% between 2015 and 2018. Furthermore, different pilot projects to increase screening capacities have been introduced, e.g. screening for HCV in selected emergency departments. Unfortunately, HCV infections because of intravenous drug abuse did not decline in the last years, whilst the estimated rates of infection in this setting rose from 14/100 person-years in 2011 to 17/100 person-years in 2018 amongst PWID, indicating that there is still some work to be done. However, 64% of the surveyed PWID reported adequate needle/syringe provision in 2018 and 53% were aware of their current HCV infection.[67] Nonetheless, recent data report a 35% decline of HCV-related mortality from 2015 to 2020, exceeding the WHO interim elimination target of 10% by far.[68]

6.1.2 | Italy

Direct-acting antiviral agent treatment rates have been continuously increasing in the last years as a part of the national Italian HCV elimination plan. The health policy changed from prioritized access to antiviral treatment in 2015 to universal access to DAA in 2017. This was made possible because of the implementation of dedicated funds for DAAs that granted treatment to every patient. Thus, Italy was on track to reach the 2030 elimination goal. However, the pool of diagnosed patients was calculated to run out in 2025. Based on this calculation, Italy has fallen behind the WHO target. Moreover, the fund to cover the costs of DAA treatment expired in April 2020. Thus, covering the future costs of antiviral treatment could pose a challenge. In addition, the COVID-19 pandemic has resulted in a drastic decrease in DAA treatments in outpatient units. Still, around 280 000 HCV patients with mild fibrosis are estimated to be asymptomatic and 100 000 patients in Italy with advanced fibrosis are awaiting diagnosis and treatment.[69] HCV treatment in Italy will be cost-saving. Treatment costs could be recovered in approximately 5.5 years. Graduated birth cohort screening in birth cohorts 1968–1987 beginning in 2020 to identify young populations at risk for transmitting HCV, expanding to the 1948–1967 birth cohort beginning in 2023 to identify older populations before their disease advances have both clinical and economic benefits to the population and could sustain Italy's momentum towards achieving the HCV elimination goals.[70] Recently, 71.5 million euros were approved for a free-of-charge universal HCV screening for PWID, prisoners and, general population birth cohorts from 1969 to 1989.[71] Hence, specific integrated pathways are financed with a high focus on GPs, PoC diagnostic and simplified HCV testing.

6.1.3 | Israel

Israel reports a high overall HCV prevalence of 1.5%–6.50.1–5%, with the highest HCV prevalence amongst PWID and people who emigrated from the former Soviet Union. Of all potentially-infected patients, an estimated 70% still await screening and antiviral treatment. On 17 February 2021, the national programme for HCV elimination was launched. The programme focuses on a dedicated screening strategy without stigma, removal of barriers (screening and treatment), ongoing monitoring (national registry) and support to health maintenance organizations (HMOs) and patients, and increasing public and healthcare professionals' awareness. One very important feature is the recent adoption of the globally established clinical guideline, significantly reducing the necessary performed diagnostic steps before HCV treatment, resulting in an overall simplification in the screening process prior to and treatment initiation algorithm.[72] Furthermore, every patient is to be included in a national registry to monitor the clinical workup and treatment and progress. Upcoming challenges will be the collaboration with the GPs and HMOs, securing screening test funding and patient identification and invitation for screening testing via electronic medical records systems. Nonetheless, complete national coverage of the national programme is assured and treatment costs will be fully covered, for all severity levels and genotypes.

6.1.4 | Romania

In 2000, HCV was the most prevalent infectious disease in the country, resulting in a high burden of end-stage liver disease and HCC in 2010. Still, the HCV burden is considered high in Romania. In 2016, the WHO target was defined and with help of EU funding, a national plan was established to support vulnerable groups and to screen for the most common sources of morbidity and mortality, including infectious diseases like tuberculosis, HBV or HCV infections in the general population. In 2018, the first national plan to control viral hepatitis was approved, and subsequently, population-based screening was first conducted in 2019, starting with the poorest and most prevalent regions. As of 2021, the plan to offer screening and treatment for everybody, including those who are uninsured, is underway and further screening is expected to start by the end of 2021.[73] Furthermore, there are plans to train over 8000 health professionals and diagnose 75% of the patients with cirrhosis and screen 50% of the high-risk population by 2023. Currently, Romania continues to work towards the WHO elimination goal and tries to adapt its CoC to the COVID-19 situation.

6.1.5 | Egypt

Egypt was long considered the country with the world's highest HCV prevalence (~15%). This was because of poorly implemented schistosomiasis treatment campaigns between 1950 and 1980 that led to a high burden of chronic HCV infections amongst the general population. In 2006, the national committee for control of viral hepatitis was established to start the fight against the HCV epidemic. With the emergence of DAAs, patients with advanced fibrosis and cirrhosis

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were treated from 2014 to 2016 until generic DAAs became available and treatment for everybody could be achieved. Over 600000 patients were treated in 2016, leaving no more people on waiting lists. Since then targeted screening for HCV in Egypt was introduced to further facilitate screening, including for families of HCV patients, healthcare providers, prisoners, students and patients admitted to the hospital, resulting in 250000 new diagnosed HCV patients per year. The next step was a nation-wide screening ("screening for all"), which was one of the largest screening campaigns in history. Over 5000 teams screened 49.6 million people over 7 months, leading to 2.2 million newly diagnosed HCV cases.[51,74] Throughout the national HCV programmes, over 4 million people were treated. This, however, was only made possible as a result of a strong political will and the realization that major economic gains would be made by avoiding chronic HCV infection—over 100000$ for an untreated patient versus 131$ for identifying and treating a patient. Now, it is important to continue the work and to shift the focus to the prevention of new HCV cases and micro-elimination attempts (i.e. for PWID) to maintain this success. The results from Egypt show how decisions from policymakers can impact the cure rates of HCV in a whole country and could also serve as a role model for countries in Europe.

6.2 | Towards an HCV-free future—best practice case studies in municipalities

Whilst the aforementioned national elimination plans are all very important, tailored approaches are needed to achieve HCV micro-elimination on the level of communities and municipalities. There are several examples of best practices to guide this:

6.2.1 | Athens and Thessaloniki, Greece

People who inject drugs are a key population because of their high HCV prevalence. To reach this particular hard-to-reach population, a community-based, peer-driven programme was set up in Athens and Thessaloniki (i.e., Aristotle HCV–HIV and Alexandros). Peer-driven chain referral was used in multiple recruitment rounds and monetary incentives were offered to recruit patients and to achieve high coverage of the PWID network. All necessary procedures were performed on-site at a single visit (FibroScan, blood sampling, etc.) and a network of clinicians was set up to support the study site. HCV viremic individuals were then registered in the national chronic HCV registry for treatment approval. To assure HCV treatment, follow-up of patients was conducted at the respective study sites, and counselling and monetary incentives were offered. In Athens, the programme was conducted between April 2018 and March 2020, and over 1600 individuals participated, covering 82% of the high-risk population. Of all participants, 76% tested anti-HCV positive and it was found that 77% of PWID were not linked to opioid substitution therapy programmes. To date, 395 patients with chronic HCV have been identified and 159 patients have successfully started DAA treatment. In Thessaloniki the programme continued despite the ongoing COVID-19 pandemic and the lockdowns imposed in the country; as of March 2021, 981 people have participated, of whom 62% were anti-HCV positive. Importantly, the programme allowed early identification of an HIV outbreak in Thessaloniki, further underlining the importance of decentralized testing.[75,76] Furthermore, on 16 March 2020, the City of Athens, in cooperation with different non-governmental organizations, approved an emergency plan against COVID-19 for PWID and marginalized groups without shelter. The city offered temporary accommodation in hostels and worked in co-operation with organizations in the harm reduction field, performing rapid HCV tests or connecting people with street workers. Thus, the impact of the COVID-19 pandemic on the marginalized parts of society could be restricted thanks to rapid political action.

6.2.2 | Lisbon, Portugal

Many PWID do not attend conventional drug addiction treatment centres or other health/social services. As a result, mobile outreach programmes (MOPs) in the form of dedicated user-centred mobile vans were introduced in a decentralized, multimodal approach to target this high-risk community. The MOPs' main features are: easy accessibility (the unit visits different locations close to the local drug scenes) 365 days a year, prompt response to any request and simplified admission procedures. Subsequently, MOPs provide screening for infectious diseases, administration or monitoring of medication, referral to healthcare and social services and offer the connection to other harm reduction programmes such as the methadone programme or NSP. Of note, by 2019, all steps in the HCV CoC can be provided by the MOP, resulting in high treatment adherence of the respective population (81%) compared to only referral to GPs (45%) or specialized services (10%). Unfortunately, the COVID-19 pandemic led to a drastic decrease in the MOPs' utility. Therefore, a multimedia van was recently introduced, providing online meetings with hepatologists. Thus, care can be assured even in times of an ongoing pandemic.[57]

6.2.3 | Catalonia, Spain

In order to work towards the elimination and prevention of HCV, the plan for prevention and control of HCV in Catalonia was created, targeting migrants and prisoners in tailored MoC. In addition, in 2020 a protocol for drug users for increasing the detection of hidden infection and improvement of access to treatment was established and is based on two key ideas: diagnosis of viremia and immediate treatment, if possible, on site, ideally in drug-addiction units or harm reduction centres. From over 700 users, 50% accepted to be screened for HCV, of whom 54.2% were viremic. Overall, treatment was initiated in 70% of which 73% reached SVR, indicating that decentralized screening and treatment can be conducted and leads to an acceptable SVR rate.

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6.2.4 | Tayside, Scotland

In Scotland, the national HCV strategy promotes the delivery of HCV treatment in community settings, since tertiary-care-based models reached a ceiling in terms of antiviral treatment capacities. The NHS tested the feasibility of a rapid scale-up of HCV care with DAA treatment in PWID in Tayside with the aim of reducing HCV prevalence amongst this group from around 30% to <10% by intensified testing and treatment in multiple community settings.[77] The scale-up intervention was associated with a 2.7-fold rise in DAA treatments in the Tayside region between 2013 and 2018, compared to a 2.1-fold increase in the rest of Scotland, leading to an overall decline of HCV prevalence amongst PWID of 29% (vs. 9% decline in the rest of Scotland).[78] Since 2018, treatment rates were further scaled-up, demonstrating that a major, rapid scale up of antiviral treatment is feasible in a PWID population. Unfortunately, HCV re-infection rates also increased with the scale-up of DAAs in community drug services, implicating the need for continued harm-reduction services and screening for re-infection amongst high-risk populations.[59,79]

7 | THE IMPORTANT ROLE OF THE EU AND POLICYMAKERS

The EU Commission presented a proposal to expand the legal mandate of the ECDC to reinforce surveillance, improve data reporting and fill information gaps throughout Europe. Furthermore, the EU has already funded some projects to improve HBV and HCV care, e.g. the HA-REACT Joint Action and HepCare Europe. HA-REACT Joint action was funded by the EU Health programme with a budget of 3.75 million euros and addressed the existing gaps in the prevention of HIV and other co-infections amongst PWID. HepCare Europe introduced integrated MoC for HCV for at-risk populations and tested more than 2600 people in Romania, Ireland and the UK, of whom over 1000 (41.8%) individuals were infected with HCV of which over 650 (60.5%) were linked to care. Over 500 healthcare professionals and 29 peers were trained for peer support.[21] In Ireland, intensified screening was conducted in communities, a specialist nurse intervention was developed for GPs and primary care centres to provide support for a large number of GPs to deal with HCV patients, peer support was offered to patients needing further support and education was provided to patients, peer workers and healthcare professionals.[80] Of note, a cost-effectiveness analysis revealed the cost-effectiveness of peer support interventions and nurse interventions.

Tools to eliminate HCV have been established, but as a result of the COVID-19 pandemic, screening and treatment rates have been scaled down in most regions. The ongoing HCV pandemic has been responsible for over 40 000 annual deaths to date.[81] Meanwhile, the EU is now facing the highest availability of high purity and potency drugs ever seen in the region.[24] Thus, it is now more important than ever to reinforce HCV-related programmes that promote prevention, screening, diagnosis and linkage to care in all countries. It is crucial to remove health-care barriers for PWID, fight stigmatization, promote decriminalization of minor, non-violent drug offences, respect human rights and consider the continuously growing body of evidence. All projects need support from policymakers from all EU countries. The importance of policymakers and their decisions was already demonstrated in recent years: The City of Athens showed that rapid reaction from policymakers to pandemics like COVID-19 can facilitate the overall care of HCV patients, and Egypt demonstrated how to translate political will into action with country-wide programmes that ultimately led to a substantial decrease of the HCV burden.[76,81] On the other hand, Italy, once on track to achieve the elimination goal by 2030, lost some of its DAA funding and could now fail to achieve the WHO target, underlining the importance of continuous governmental support.[82] HCV medication is still very expensive in some countries and thus EU wide procurement collaborations might effectively decrease the cost of DAA. Furthermore, national HCV guidelines, including integrated care pathways need to be established in cooperation with key stakeholders for every EU country and good practices have to become the standard of care. Multiple examples of successful micro-elimination attempts in target populations indicate the feasibility and cost-effectiveness of these strategies. Ultimately, achieving the elimination goal will lead to a substantial decrease in direct and indirect health-related costs, and decrease the burden of future HCC development and it will therefore go hand in hand with other EU-funded projects like Europe's Beating Cancer Plan. Moreover, it will have a positive impact on containing other diseases like HBV or HIV, since the screening of both infections can be conducted together. Importantly, the EU health budget for the next years is approximately 12 times bigger than the previous years.[83] The new established EU Health programme must ensure that HCV elimination is adequately funded and addressed soon to achieve the WHO 2030 elimination goal. All stakeholders need to work together to achieve this ultimate goal: HCV elimination.

8 | CALL TO ACTION

In 2016, the Elimination Manifesto was launched to provide a starting point for EU-wide action to ensure that HCV elimination was made an explicit public health priority and to achieve the cooperation of all key stakeholders in the field of HCV to develop and implement HCV elimination strategies. This was followed by a Call to Action in 2018, to promote comprehensive, costed HCV elimination strategies, calculation of the respective country-based HCV-related economic burden and innovative financing mechanisms. Healthcare systems are experiencing increasing pressure and although HCV elimination results in high ad hoc costs, non-action will result in an even higher economic burden. The present Call to Action is endorsed by 17 organizations and again addresses all key stakeholders in Europe and beyond, especially politicians and decisionmakers, from small municipalities to the EU level. HCV elimination is feasible,

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cost-effective, ethical and achievable; however, greater political will and renewed action are urgently needed (Appendix A).

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CONFLICT OF INTEREST

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APPENDIX A

A.1 | CALL TO ACTION FOR A EUROPE FREE OF HEPATITIS C

We, the signatories of this Call to Action, launched at the third EU HCV Virtual Policy Summit (*Securing Wider EU Commitment to the Elimination of HCV*) on 24 March 2021, call on policymakers to commit to the elimination of hepatitis C throughout Europe. We, in turn, commit to reviewing progress on achieving the goals set out in this Call to Action on a regular basis and promoting it to key stakeholders at all relevant opportunities.

A.2 | INTRODUCTION

Despite the progress that has been made since the publication of the first European Union (EU) HCV Elimination Manifesto (*Our vision for a Hepatitis C-free Europe*) in 2016,[84] hepatitis C remains a major public health challenge in Europe:

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- In 2016, the World Health Organization (WHO) estimated that more than 7 million lives would be saved worldwide by 2030 if hepatitis elimination targets were reached.[85]
- A key step in addressing the problem is improving diagnosis rates. However, according to recent European Centre for Disease Prevention and Control (ECDC) data, three out of four people with hepatitis C infection across the European Union and European Economic Area (EU/EEA) and the United Kingdom have not been diagnosed—far below the 2020 target of the WHO European Action Plan of diagnosing 50% of people with chronic hepatitis C.[86]
- In the WHO European region (which consists of 53 countries), 33 countries now have viral hepatitis action plans; and a further 17 countries are developing plans.[87]

Hepatitis C has substantial morbidity and premature death burden, particularly in marginalized groups:

- In the European Union (EU) more people die each year from hepatitis C than from AIDS.[88]
- In the WHO European Region, an estimated 14 million people are infected with hepatitis C[89] and the European Centre for Disease Control estimates that there are 3.9 million chronic hepatitis C cases in European Union member states.[90]
- New infections are still occurring, with an estimated hepatitis C incidence of 8.7 per 100 000 in the Member States of the EU.[91]
- People who inject drugs are particularly vulnerable to hepatitis C[89] and unsafe injecting drug use is one of the main drivers of the epidemic.[92]
- Hepatitis C is often asymptomatic and, left untreated, chronic hepatitis is a major cause of cirrhosis and liver cancer.[89]

Europe's Beating Cancer Plan commits the European Commission to help 'ensure access to … treatments to prevent liver … cancers associated with the hepatitis C virus'.[93]

In the current context of strained healthcare systems and shifting priorities, particularly as a result of the COVID-19 pandemic, it is essential to ensure that the importance of eliminating hepatitis C is not forgotten.

Initial data confirm that the pandemic has had a considerable impact on testing for infectious diseases including hepatitis C in the WHO European Region.[94] For example, in a survey of 34 countries in the region, it was found that almost all reported a reduction in testing during the first months of the COVID-19 pandemic (March to May 2020), with more than 65% reporting severe disruptions in hepatitis C testing.

For chronic infections such as viral hepatitis, delayed diagnosis and treatment may result in further long-term consequences for individual patients and even a stalling of progress achieved to date in controlling these infections in the WHO European Region.[94] It is vital that testing, linkage to care, and treatment must continue, and quickly be scaled up. In fact, the current pandemic should underline the need for widespread and effective public health responses, and synergies such as viral hepatitis testing linked to COVID-19 vaccination should be explored.

In the midst of the health system challenges resulting from the COVID-19 pandemic, renewed political action is needed to address the growing hepatitis C public health threat and re-focus on achieving the WHO viral hepatitis elimination targets.

A.3 | ACTION POINTS

We share the vision that eliminating hepatitis C in Europe by 2030 will require policymakers to:

1. Ensure that data on the impact of the COVID-19 pandemic on efforts to eliminate hepatitis C is collected and analysed and that the findings are published in an official report: Relevant agencies such as the ECDC, EMCDDA and the WHO Regional Office for Europe should collaborate on regularly collecting assessing and publishing data from all Member States. The official report should include recommendations and a roadmap for getting elimination efforts back on track.
2. Make hepatitis C elimination in Europe an explicit and adequately resourced public health priority: Hepatitis C elimination should be pursued using appropriate means at all levels—through collaboration between individual citizens, civil society organizations, healthcare professionals, medical associations, researchers, the private sector, local and national government and European Union institutions—including the European Commission, ECDC, EMCDDA and the WHO Regional Office for Europe. The new EU public health programme, EU4Health, must ensure that hepatitis C elimination is advanced through the adequate funding of projects which promote prevention, diagnosis and linkage to care in all countries.
3. Ensure every country has a published national viral hepatitis elimination action plan or strategy, and that key stakeholders are involved in developing and implementing these plans: Where national viral hepatitis elimination plans/strategies do not exist, developing and publishing a plan should be prioritized. Every country should ensure that patients, civil society groups and other relevant stakeholders—including at-risk groups—are directly involved in developing and implementing such plans. Surveillance and tracking of HCV cases and mortality, as well as agreed markers to monitor implementation, should be in place. Existing best practice examples and guidelines should serve as the basis for people-centred, health system-based strategies that emphasize tailored implementation at the local level.
4. Ensure integrated care pathways are included in national plans/strategies: Make the development of integrated care pathways a core component of viral hepatitis elimination plans/strategies, taking into account the specific health system barriers and other challenges related to the management of viral hepatitis infection, such as community-based care, for example, harm reduction services, which may not be linked to the national health system. Implementation of integrated care pathways should embed monitoring of their effectiveness over time.

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5. Support efforts to reduce the impact of hepatitis C on rates of liver disease and liver cancer through access to testing, treatment, screening and improved follow up: In line with *Europe's Beating Cancer Plan*,[93] support efforts to improve access to hepatitis C treatments to prevent liver cancer attributed to hepatitis C. Promote long-term follow-up/screening programmes for hepatitis C patients to reduce the risk of liver disease and liver cancer.
6. Remove barriers to people who inject drugs (PWID) accessing care, including decriminalization: Political resistance to harm reduction services is a major barrier to appropriate access to hepatitis C prevention services for PWID, as are laws and policies which criminalize drug use, drug possession and drug users.[95] In line with community statements and the European Association for the Study of the Liver's (EASL) policy statement,[95] we, therefore, call for the decriminalization of minor, non-violent drug offences and call for political support for harm reduction services in all European countries.
7. Address stigma and discrimination, and protect human rights, particularly of marginalized communities at risk for hepatitis C: All hepatitis C elimination-related strategies must be consistent with fundamental human rights principles including non-discrimination, equality, participation and the right to health. Stigma about hepatitis affects people accessing testing or treatment and can cause fear of disclosure, all of which hinder elimination efforts. Even once hepatitis C is cured, stigma and discrimination can persist and have real consequences for the individuals affected. The links between hepatitis C and social marginalization are well established, and particular care and attention should be focused on addressing stigma and discrimination in these populations.
8. Pursue micro-elimination strategies to maximize impact on reducing the incidence of hepatitis C: Micro-elimination strategies pragmatically target hepatitis C prevention and treatment to achieve the WHO targets in specific at-risk sub-populations (e.g., people living with HIV, people who inject drugs, people with haemophilia, people with liver disease), settings (e.g. hospitals, prisons, addiction centres), generational cohorts or geographic areas (e.g. a city or region).[96] This approach maximizes the impact of limited resources and allows countries to work towards the elimination of hepatitis C in a phased manner.
9. Support the introduction of the standardized continuum of care (CoC) monitoring in every European country: Strengthen efforts to harmonize and improve the surveillance of hepatitis C across the European Union to inform and evaluate hepatitis C elimination strategies, by asking every country to publish a continuum of care starting with prevalence estimates, and continuing through numbers diagnosed, linked to care, had treatment initiated and achieved sustained virologic response.

Endorsed by:

ACHIEVE Coalition.

AEHVE, Spanish Alliance for the elimination of viral hepatitis.

Correlation European Harm Reduction Network.

EASL, European Association for the Study of the Liver.

EATG, European AIDS Treatment Group.

ELPA, European Liver Patients' Association.

Hepatitis B&C Public Policy Association.

Fast-track Cities.

IAPAC—International Association of Providers of AIDS Care.

ICMHD—International Centre for Migration, Health and Development.

ILF EASL International Liver Foundation.

ISGlobal.

LPI—Liver Patients International.

UEG—United European Gastroenterology.

UNITE—Global Parliamentarians Network to End Infectious Diseases.

VHPB—Viral Hepatitis Prevention Board.

World Hepatitis Alliance.

To Note:

In developing this Call to Action, the following documents were taken into consideration:

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