

Hepatitis C

Setting Standards in a Journey towards
the Eradication of Infection and Disease
as a Serious Health Issue in the EU

Proposal for Consideration from Professors David Goldberg and Sharon Hutchinson



Authorship

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Professor Goldberg has undertaken consultancy work for MSD, Janssen and Roche – providing guidance on epidemiological and public health issues relating to HCV.

Glossary

BBV:	Bloodborne Viruses
EASL:	European Association for the Study of the Liver
ECDC:	European Centre for Disease Control
ELPA:	European Liver Patients Association
EMCDDA:	European Monitoring Centre for Drug Dependence & Addiction
HBV:	Hepatitis B Virus
HCC:	Hepatocellular Carcinoma
HCV:	Hepatitis C Virus
OST:	Opiate Substitution Therapy
PWID:	People Who Inject(ed) Drugs
VHPB:	Viral Hepatitis Prevention Board
WHO:	World Health Organisation

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Introduction

This report is aimed at everyone who is involved in drawing up policy to improve the delivery of services for Hepatitis C prevention, diagnosis and treatment. It is also relevant to all other individuals with a role in Hepatitis C service provision, service use and research.

Today, some six million people in the EU are estimated to be chronically infected with the Hepatitis C virus – a condition which, over time, can lead to life threatening illness and, ultimately, death. Yet HCV, an infection transmitted mainly through injecting drug use and sub-optimal infection control associated with healthcare procedures², is, as a consequence of major recent therapeutic advances, curable in the majority of instances³.

The acquisition of HCV infection among people in the EU is both current and historic, dating back many decades⁴. However, the understanding of its impact on health and the development of therapies and other interventions to counter this impact are recent phenomena. Accordingly, Hepatitis C infection is regarded as an emerging infectious disease problem and, as a result of this, the response to the challenge has been an evolving one⁵. In such circumstances, as observed with HIV and other emerging issues, “a helping hand” from national and international bodies in the early years is vital if the resources and infrastructure required to tackle the problem are to be put in place.

Within the EU, islands of good practice in terms of intervention provision, uptake and impact are evident; however, in most, if not all, countries, major challenges in delivering high quality, effective services for those infected with, and at risk of acquiring, HCV exist. European and Global agencies have worked hard to raise the profile of an infection which, due to its insidious nature, often smoulders away in people until, when finally noticed, it is too late.

As a consequence of the achievements of researchers, clinical practitioners, the pharmaceutical industry and others over the last 20 years, HCV guidelines, recommendations, strategies and policies, applicable to either the EU region as a whole or specific Member States, are no longer in short supply. While these are crucial for a consensus about what the problem is and how to manage it, they do not necessarily translate into action. Initiatives which translate evidence and strategy into Hepatitis C Action are few and far between in the EU.

In light of this and the prospect of Highly Effective Interferon- free Antiviral Therapy (HEIFAT) and the potential to make serious progress towards the eradication of infection and disease as a serious health issue, the author who led the team which generated and implemented Scotland’s Hepatitis C Action Plan – a now well-acknowledged paradigm – summarises the current state of play and makes recommendations on how the standard of service provision across the EU might be improved and made more consistent.

Summary of Principle Recommendation

Standards that raise the bar of Hepatitis C –related care and service provision across the EU should be developed. Such standards should adopt a holistic approach encompassing prevention, diagnosis, treatment/care, monitoring/surveillance and planning/coordination. For consistency they should align with existing/new guidelines.

Section 1: Background

HCV in the EU – identifying the causes, prevalence and demographic spread

Six million people have a chronic HCV infection in the EU, with prevalence ranging from 0.4 to 4.0% of the population. Injecting drug use and sub-optimal infection control have been the main means of transmission. Men are twice as likely to be diagnosed with HCV and an appreciable proportion of people diagnosed are migrants.

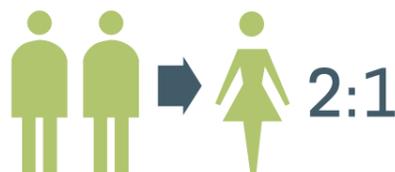
What is HCV?

- A RNA virus, discovered in 1989.
- Infrequently causes an acute symptomatic illness^{6,7}.
- Becomes chronic in approximately three-quarters of individuals^{8,9,10}.



How is it detected?

HCV is detected through the testing of blood for HCV Antibody (ever infected) and HCV RNA (current infection)¹¹.



Among people diagnosed HCV antibody positive in 2010, the male to female ratio was 2:1; approximately half were aged between 25 and 44¹⁵.

About one-half to three-quarters of infected people have genotype 1 virus, 0-10% have genotype 4 virus and the remainder have genotype 2 or 3¹⁶.

About a quarter of a million infected people are migrants¹⁷.

How many people are affected?

An estimated six million people have a chronic HCV infection¹².

6 MILLION PEOPLE HAVE A CHRONIC HCV INFECTION



However, the accuracy of this estimate is uncertain: countries' difficulties in accessing, for epidemiological investigation, vulnerable populations which are more likely to be infected compromise the robustness of this figure.

For many countries, data on the overall prevalence of chronic infection do not exist. However, for countries where data are available, prevalence ranges between 0.4 and 4.0% of the population. Generally, rates are lower in northern and western Europe and higher in southern and eastern Europe^{13,14}.

PREVALENCE OF CHRONIC HCV RANGES BETWEEN

0.4% & 4%

OF THE POPULATION

See annex 1 for estimates of country-specific HCV Ab positive results.

How do you treat HCV?

HCV is eradicated in approximately 80% (genotypes 2 and 3) and 60% (genotype 4) of instances following pegylated Interferon and Ribavirin therapy, and 70% (genotype 1) of instances following the addition of first generation protease inhibitors^{18,19,20}. The introduction of more potent Direct Acting Antiviral Agents will increase these rates appreciably^{17,22(b)}.

How is HCV transmitted?

HCV is principally transmitted by contaminated blood being inoculated into human tissue^{21,22,23,24}. Occasionally, infection is transmitted from an infected mother to her child in-utero or at birth²⁵. Infection is rarely transmitted through sexual intercourse though transmission among HIV infected men who have sex with men is more common^{27,28}.



Generally, in northern and western countries, injecting drug use has been the principal means of HCV transmission since the 1970s.

However, in recent years, the rate of transmission among this population has either stabilised or has declined^{29,30}.



Generally, in southern and eastern countries, sub-optimal infection control measures (including inadequately sterilised needles and glass syringes) are considered to be responsible for the bulk of

transmissions occurring among, now older, individuals during the mid-latter part of the 20th century. However, injecting drug use is responsible for the majority of new infections, principally among younger people; in recent years, the rate of transmission among such individuals has either stabilised or increased^{31,32}.

An increasing rate of HCV transmission among PWID (People Who Inject Drugs) in southern and eastern European countries correlates with outbreaks of HIV among this population group in Greece, Estonia and Romania^{33,34}.

Among PWID in southern and eastern Europe, in particular, more frequent injecting (and thus more frequent sharing of injection equipment) have been reported in the context of the increasing use of injectable amphetamines (including Legal Highs)³⁵.

What are its effects?

- HCV leads to cirrhosis in 8-16% of individuals within 20 years of infection acquisition³⁶. Longer infection durations, excessive alcohol consumption and HIV co-infection correlate with liver disease severity^{37,38,39}.
- HCV can cause very serious illness and death from liver failure or cancer^{40,41,42,43,44,45,46,47,48}.
- HCV probably has both direct and indirect (through the inflammatory and fibrotic process) carcinogenic effects^{49,50}.
- Increasingly, HCV is shown to be associated with the development of non-liver-related disease (neurological, cardiovascular, renal etc)^{51,52,53}.
- HCV is associated with reduced quality of life, even in those with mild liver disease^{54,55}.
- HCV is associated with reduced work productivity^{56,57,58}.

HCV-related disease in the EU: assessing the extent and drawing comparisons with the US.

- At an EU level, comparative and overall data on HCV disease outcomes do not exist at present⁵⁹.
- Data from the UK, however, are insightful; between 1998 and 2010, hospitalisations and deaths from HCV-related liver failure or hepatocellular carcinoma increased from 600 to 2000 and from 100 to 300, respectively. Modelling work, estimating the future burden of disease to 2020, indicates that this trend will continue⁶⁰. In Scotland, the number of people dying with HCV infection exceeds the number dying with HIV infection; this observation also applies to the US^{61,62}. Note that some HCV-related liver failure and hepatocellular carcinoma cases will have had co-morbidities (including excessive alcohol consumption) which may have contributed to their liver disease.
- The UK trends, as above, are also evident in Australia and the US.
- A recent assessment by the Centres for Disease Control and Prevention on HCV-associated morbidity and mortality in the US is particularly informative; the key points are as follows⁶³.
 - “An estimated 2.7-3.9 (1.0-1.5%) million people are living with HCV in the US (population 313 million); this compares with an estimated 5.9 million (1.2%) in the EU (population 502 million).”
 - “HCC and cirrhosis have been increasing among persons infected with HCV and these outcomes are projected to increase substantially in the coming decade.”
 - “HCC is the fastest growing cause of cancer-related mortality and infection with HCV accounts for approximately 50% of incident (i.e. new cases of) HCC.”
- Modelling studies project that during the next 40-50 years, 1.76 million persons with untreated HCV infection will develop cirrhosis, with a peak prevalence of 1 million cases occurring from the mid-2020s through to the mid-2030s; approximately 400,000 will develop HCC. Of persons with Hepatitis C who do not receive the treatment and care they need, approximately 1 million will die from HCV-related complications.”
- The EU, of course, is not the US; accordingly, caution needs to be adopted when comparing the two. Nevertheless, i) similar prevalences of infection in these two world regions, ii) the consistency of the UK morbidity and mortality trend observations with those evident in the US and, iii) the fact that almost all EU countries and the US witnessed increasing numbers of HCV infections among PWID (in line with the growth of injecting drug use) during the latter third of the 20th Century, means that the pattern of current and likely future burden of disease and death in the EU, in the context of low treatment levels, might be similar to that for the US.
- Various European and North American models have demonstrated the potential impact of antiviral therapy on future morbidity/mortality^{64, 65}. All draw the same conclusion – that the more people diagnosed, assessed for therapy and then administered it, the less the future burden of HCV-related disease and death. This trend is only attenuated in countries i) with more mature epidemics resulting in a larger proportion of infected people having already progressed to an advanced stage of disease, ii) where excessive alcohol consumption (Europe has the highest!), compromising the impact of HCV “cure”, is common and iii) a sizeable proportion of the HCV infected population is co-infected with HIV.

Patient Associations – a crucial role, a powerful voice

The importance of national, European and global-level patient associations for improving services for those at risk of acquiring, and already infected with, HCV should not be underestimated. They have a pivotal role in stimulating political interest. Robust data, effective therapies and public health/clinical champions are vital but without the patient perspective (the human face), civil servants, politicians and governments are less likely to respond effectively. In Scotland, for example, it was this potent combination of forces, working in synergy, which led to its Government providing industrial-scale investment to tackle the country's Hepatitis C problem⁶⁶.

Case Study 1: Hepatitis C Action Plan, Scotland.

In Scotland the investment of £43 million in its Hepatitis C Action Plan (2008-2011) would not have been realised without the critical advocacy and awareness-raising activities of the UK Hepatitis C Resource Centre and the UK Hepatitis C Trust (see full case study on page 11)⁶⁷.

Case study 2: The European Liver Patients Association.

The European Liver Patients Association (ELPA), formed in 2004, has 30 members from 24 countries. It functions as a network, allowing individual associations to support each other, and is a powerful voice for patients at European level. It has been instrumental in promoting the Eurohep Index⁶⁸ – a series of key indicators against which countries' performance in providing interventions to prevent Hepatitis B & C infections and related disease can be gauged. With Hepatitis C being one of its priority liver conditions, ELPA's role has, and will continue to be, integral to Hepatitis C action at an EU level.

Case study 3: World Hepatitis Alliance (WHA).

At a global level, the World Hepatitis Alliance (WHA), formed in 2007. The Alliance supports local and regional patient organisations, including ELPA, in their efforts to improve Hepatitis B and C services. The ultimate aim of the WHA is the eradication of these infections. WHA works closely with the World Health Organisation (Global Programme on Hepatitis) and functions very successfully by engaging with governments to promote the development of country-specific strategies, including awareness-raising campaigns that prevent infection and associated disease. One of its considerable achievements to date has been its advocacy role around both the establishment of the WHO's World Hepatitis Day (July 28) and the recognition of this day by 193 member states. A further achievement was its advocacy in securing the first ever WHO resolution on Hepatitis. Together with the WHO it was involved in the collection of information on country-specific interventions targeted at Hepatitis B and C infection and related disease prevention (Ref: Global Policy Report on the Prevention and Control of Viral Hepatitis in WHO member states; WHO, 2013).

International Organisations and Key Initiatives

International organisations and key initiatives are at the foundations for promoting Hepatitis service improvement and good practice.

Over the last 10 years, a considerable number of key initiatives at European/World level that recognise the importance of viral Hepatitis (B & C), have been launched.

These include:

1.

The establishment of the **European Liver Patients Association** (2004) and the **World Hepatitis Alliance** (2007) - an umbrella organisation for Hepatitis self-help groups worldwide.

2.

A **Resolution on Hepatitis by the World Health Assembly** (2010). Supported by 193 Member Countries, the Resolution states the need for global co-ordinated action, backed by dedicated resources, to tackle viral Hepatitis⁶⁹.

3.

The establishment of a **Global Programme on Hepatitis by the World Health Organisation (2012)**⁷⁰.

4.

The establishment of a **work programme on Hepatitis B & C Monitoring, Prevention and Diagnosis** by the European Centre for Disease Control (ECDC) in collaboration with the European Monitoring Centre for Drug Dependence and Addiction (EMCDDA)^{71,72,73,74}.

5.

The development of **Clinical Guidelines for the management of Hepatitis B (2012) and C (2011, currently being reviewed)** infections by the European Association for the Study of the Liver (EASL)⁷⁵.

6.

The formation of the **Hepatitis B & C Public Policy Association** – a network of experts who, through international meetings and policy statements (calls for action), raise awareness about, and provide direction in managing, these infections (2009)^{76,77}.

7.

The **Viral Hepatitis Prevention Board**, a network of experts who promote the sharing of best practice in preventing Hepatitis infection/disease in Europe, has made Hepatitis C a priority in recent years.



Relevant EU policy

Improving standards of Hepatitis C service provision across the EU needs to reflect the overarching EU approach towards improving health and the citizen's right to access and treatment.

1.

EU's White Paper: "Together for Health – a Strategic Approach for the EU 2008-2013"

Specific elements of the EU's White Paper "Together for Health – a Strategic Approach for the EU 2008-2013"⁷⁸ provide context for standard setting to tackle Hepatitis C (Annex 3) .

2.

Europe 2020 Vision for Growth

Such standard setting for the EU is also consistent with one of the five principal aims of the EU's Europe 2020 Vision for Growth: reducing social exclusion. Arguably, PWID (People Who Inject(ed) Drugs) – the dominant group affected by Hepatitis C – are one of the most socially excluded groups of all.

3.

EU Roundtable meetings on an Integrated Approach to Alcohol Related Harm

In the context of excessive alcohol consumption being one of the most important co-factors for the acceleration of liver disease among HCV infected individuals, the recent (2011-12) EU Roundtable meetings on an Integrated Approach to Alcohol Related Harm, emphasised both the extent of the challenge and the EU commitment to addressing it.

4.

The European Commission also aims to increase by two the average number of healthy life years in the EU by 2020 by "i) improving the health status and quality of European cities and, ii) supporting the long-term sustainability and efficiency of health and social care systems⁷⁹".



*"Health is central in people's lives and needs to be supported by effective policies and actions in Member States, at EC level, and at global level".**

*EU white paper - "Together for Health - a strategic approach for the EU 2008-2013"

Section 2: Improving Standards of Hepatitis C Service Provision across the EU: Making the Case

Making the Case: Aim

To strive towards the eradication of HCV infection and disease within the EU by improving services for those already infected and at risk of contracting the virus.

Making the Case: Audience

For an audience including politicians and other policy-makers, the generation of:

- i) A summary of the evidence base and the key issues/challenges relating to the EU's Hepatitis C problem and;
- ii) Proposed tangible actions to address these issues/challenges.



"Values relating to improving health must include reducing inequities in health. Although many Europeans enjoy a longer and healthier life than previous generations, major inequities in health exist between and within Member States..... The commission will propose actions aimed at reducing inequities including targeted health prevention and best practice exchange".

Making the Case: Methods

Principles

The author set out to make the case for standard raising which would be SMART:

SPECIFIC

Proposals which are not ephemeral and thus open to multiple interpretation.

MEASURABLE

Proposals for which it should be possible to measure progress.

ATTAINABLE

Proposals which could realistically be achieved – i.e. not pie in the sky aspirational ones.

RELEVANT

Proposals backed up by hard evidence highlighting issues needing to be addressed by action.

TIMELY

Proposals which can commence now/soon and be completed within a realistic and acceptable period.

Challenge for the EU

EU Member States are diverse in terms of size, geography, GDP, culture, and HCV epidemiology. To accommodate this diversity and be affective, focusing on a few high-level tangible goals was agreed to be crucial.

Design

- Five key dimensions were identified – Prevention, Diagnosis, Treatment/care, Monitoring and Planning/Co-ordination.



- For each dimension, an extensive search of the evidence-base was undertaken.
- Based on the evidence, key issues applicable to EU Member States, were identified.
- Proposals addressing these issues were then generated.

The Evidence Base

Scope

The focus was on high-level evidence on interventions to prevent HCV infection and disease among EU populations.

Generally, references to specific countries were avoided to ensure that the analysis remained clear and top-line; such detail, however, can be accessed easily via the referenced literature.

Approach

1. Examination of the titles of the recent (January 2010-March 2013) English written peer-reviewed articles on Hepatitis C (circa 13000) followed by an assessment of the most relevant; this comprehensive search was restricted to this period because of i) the large volume of published research, recently undertaken, and ii) the rapidly developing landscape of HCV knowledge.
2. The selection of other peer-reviewed articles, published pre-2010, considered by the author to be relevant.
3. Examination of HCV-specific or related reports published by European agencies.

Consultation

The report was shaped through consultation with a small group of individuals with public health, clinical, epidemiological and behavioural expertise relating to Hepatitis C.

Education and awareness raising - a crucial component.

All proposals relating to preventing, diagnosing and treating infection should take into account HCV education and awareness-raising.

- The evidence-base surrounding education and awareness-raising among the general population, those at high risk of acquiring HCV, those infected with HCV and those providing HCV services, is very limited; this reflects the difficulty in assessing the impact of such initiatives in improving knowledge and effecting behavioural change but also the appreciation that, intuitively, such activities have a vital co-existence with other (e.g. therapeutic, screening, harm reduction) interventions designed to prevent HCV infection and related disease.

Prevention

HCV is preventable, yet transmission levels remain high. This needs to be addressed.

A vaccine against Hepatitis C, despite important advances in the understanding of host immunity, is unlikely to be available in the foreseeable future^{80,81}. However, there are many ways to interrupt routes of transmission.

Key Issue

In the context of recent evidence indicating that HCV among PWID can be prevented through the provision of a combination harm reduction approach, incorporating OST (Opiate Substitute Therapy), injection equipment (including paraphernalia provision) and, possibly, antiviral therapy (to prevent onward transmission), high levels of transmission among this population group are evident across the EU.

Injecting drug use – multiple safe guards needed

Compelling evidence demonstrates that the provision of **combination OST and needles/syringes, critically at optimal levels, leads to appreciable reductions in HCV transmission among People Who Inject Drugs**^{82,83}.

Experts agree unanimously that a multi-intervention approach – including the provision of i) information and advice, ii) Opiate Substitute Therapy and, iii) injection equipment – is essential for the prevention of HCV transmission among People Who Inject Drugs⁸⁴.

Evidence indicates that the sharing of drug injection paraphernalia (e.g. spoons, filters, swabs) among People Who Inject Drugs contributes to the spread of HCV among this group^{85,86,87,88}.

However, there is a lack of evidence to show that providing sterile needles/syringes **alone** or educational material **alone** to PWID is effective in reducing HCV transmission among this group (although it does reduce injecting behaviours which convey an HCV risk⁸⁹.)

This may be due to the insufficiency of robust, difficult to undertake, investigations to evaluate effectiveness⁹⁰. Similarly, evidence indicating that the provision of Opiate Substitution therapy (OST) **alone** to PWID is effective in reducing HCV transmission is considered tentative⁹¹.

Preventing HCV in prisons

In prisons, a harm reduction service comprising OST (at optimal levels) without injection equipment provision may be sufficient to prevent appreciable transmission of HCV among PWID inmates⁹².

Anti-viral treatment to prevent HCV in current PWID

HCV antiviral treatment may have an important role in preventing HCV transmission among **current** PWID. This is particularly true in instances where the prevalence of HCV infection among PWID populations is under 50%^{93,94,95}; such treatment is deemed to be cost effective in the context of UK/US cost effectiveness thresholds⁹⁶. (see annex 3)

Injecting drug use in the EU – what's happening now?

There are wide variations in both OST and sterile needle/syringe provision/uptake; even among the best performing countries, the provision of needles/syringes is sub-optimal⁹⁷.

Generally, needles/syringes, are unavailable to PWID in prisons; in a few countries, however, such equipment is provided⁹⁸. Guidelines on the provision of needles/syringes in prisons are currently being developed by the United Nations Office on Drugs and Crime.



Other modes of HCV transmission – still an issue in the EU

Progress has been made on infection control in healthcare settings but there is still room for improvement. Within healthcare settings two crucial interventions – blood/organ donor screening for HCV infection and the use of disposable needle/syringes – required to prevent transmission of HCV, are now likely to have been adopted universally^{99,100,101,102}.

Nevertheless, sup-optimal infection control practices, including medical equipment sterilisation, may be responsible for considerable numbers of HCV transmissions in lower income EU Member States; knowledge around the characteristics and extent of such failures is lacking¹⁰³. Equally, interventions to prevent the transmission of HCV from mother to child in-utero/at birth do not exist^{104,105}.

Progress points: screening and safety devices.

To protect patients, a small number of countries in the EU prohibit, through screening, HCV infected healthcare workers (mostly surgeons) from undertaking exposure-prone procedures¹⁰⁶. This policy makes sense bearing in mind that numerous instances of healthcare worker to patient transmission have been documented. Healthcare workers can appreciably reduce their chances of sharps injuries, and thereby the risk of becoming infected with HCV, through the use of safety devices (the EU directive 2010/32 requires countries to adhere to the adoption of such devices by 2013¹⁰⁷).

More EU data needed on safety device usage and tattooing/skin piercing

There is a lack of EU data on safety device usage and the dangers of tattooing.

Tattooing, undertaken in unhygienic, unlicensed settings, conveys a risk of HCV acquisition - the characteristics and extent of the problem in the EU need to be ascertained¹⁰⁸.



RECOMMENDATIONS

ACTION

It is now crucial to develop clear standards for the prevention of HCV (and other BBV) among PWID. These should be used in conjunction with ECDC/EMCDDA guidelines on the prevention of BBV infection among PWID and should incorporate educational/awareness-raising requirements.

EXAMPLE OF ACTION (for illustrative purposes only)

In areas of known injecting drug use, at least one facility providing sterile injecting equipment should be open at some time during a 24 hour period.

OUTCOME

Across the EU, a consistent, acceptable standard of practice for the prevention of HCV (and other BBV) among PWID.

Note (see annex 2) *

Diagnosis

Identifying infected people, especially before they have progressed to severe disease, is crucial. That said, both early and late diagnoses reap benefits for patients. In the context of recent, and likely future, advances in HCV antiviral drug treatment – including the prospect of Highly Effective Interferon-free Antiviral Therapy which can eradicate infection in the majority of instances – only a minority of infected people in the EU have been diagnosed.

Importance and Benefits of Screening

Experts agree that, in the context of the increasing effectiveness of HCV therapy in achieving sustained viral clearance, identifying infected people, especially before they have progressed to severe disease, is considered of paramount importance^{109, 110, 111, 112}. In light of this, they unanimously support awareness-raising about Hepatitis C (conveying details about who is at higher risk and where to get tested) through literature and media channels^{113, 114, 115}.



The US's decision to recommend the screening of millions of individuals born between 1945 and 1965 on the grounds that they have a higher risk of HCV infection demonstrates the importance and benefits of screening^{116, 117}.

Early diagnosis – benefits

- 1) Treatment is likely to be more effective in achieving sustained viral clearance,
- 2) Interventions to help infected individuals avoid the synergistically toxic effects of alcohol can be implemented^{118, 119, 120} and
- 3) The opportunity to impart advice to prevent onward transmission of infection.

Late diagnosis – benefits

- 1) A still high chance of sustained viral clearance,
- 2) The improvement of liver function and,
- 3) The avoidance of impending life-threatening disease¹²¹.

Experts agree that while the diagnosis of everyone who is infected can be fully justified, the diagnosis of people with advanced disease is imperative^{122, 123, 124}.

For both early and late diagnoses (i.e. in people who have been infected for 20+ years), experts agree that the diagnostic process should be coupled with an intention to assess for treatment and then treat with antiviral therapy if the patient is eligible for such therapy and wants to be treated^{125, 126, 127}.

This view is strengthened by the observation that people who know they are infected have a poorer quality of life than infected people who are unaware of their status¹²⁸.

Screening Practice and Policy in the EU – what's happening now?

- Evidence on screening practice and impact, whilst scant, points to only a minority of HCV infected people having been diagnosed; only in a few countries have even half been identified¹²⁹.
- Screening policy varies considerably and, even where it appears similar, interpretation is challenging due to a lack of detail and definition associated with headline information^{130, 131}.
- To support screening practice and decision making in the EU, the ECDC and the EU Commission have commissioned work to develop both an HCV screening cost-effectiveness model and a toolkit to screen migrant populations^{132, 133}. The World Health Organisation is also developing HCV screening guidelines for resource-poor countries¹³⁴; elements of these guidelines may be relevant to EU Member States.

Screening and Cost Effectiveness

Cost-effectiveness should not exclusively dictate whether or not a population should undergo HCV screening.

Uncertainty, stemming from a lack of high-quality evidence, exists about what level of HCV prevalence in a population must be present to justify, from a cost-effectiveness perspective, the systematic screening (involving an individualised, informed approach) of that population. This uncertainty is compounded by the fact that attrition rates through all stages of the clinical pathway from diagnosis to treatment, especially among vulnerable individuals with co-morbidities, can be considerable¹³⁵.

Currently, the cost effectiveness evidence base indicates that the threshold for screening migrant populations is 2% (ie: the estimated population prevalence of the country of origin) and that the offering of a test to general populations (for example at antenatal and genito-urinary medicine clinics) with an HCV prevalence under 1% is not likely to be cost-effective. Conversely, the offering of a test to high prevalence (invariably greater than 10%) PWID populations (in for example drug treatment/harm reduction settings) is likely to be cost-effective^{136, 137, 138}.

However, the playing field is a rapidly changing one with ever increasing therapy effectiveness and ease of administration. In due course, even where HCV prevalences, among patient groups (eg: clinic attendees as above and hospital attendees with or without a raised ALT) undergoing blood sampling for other reasons, are less than 1%, HCV may well be cost effective.

The case for general population screening

General population screening may be particularly relevant to countries where appreciable numbers of individuals are likely to have become HCV infected through healthcare interventions for which infection control measures were sub-optimal. Invariably, such individuals cannot be identified through risk factor interrogation and only rarely can the healthcare source of their infection be confirmed¹³⁹.

Screening children

A similar dilemma applies to the diagnosis of children who acquire infection from their mother in-utero or at birth – particularly in the context of growing therapeutic possibilities for this age group and the fact that a small minority of children will develop severe HCV-related liver disease^{140, 141}. Ensuring that at-risk children are tested is challenging even if the mother is known to be HCV positive.

Screening Technology – what's on offer?

Non-invasive techniques, dried blood spot testing and Rapid Diagnostic Tests all contribute to the screening mix.

- The development of non-invasive techniques to identify liver fibrosis and its extent affords the opportunity to screen populations for advanced liver disease; fibrotic individuals could then be tested for HCV and, if appropriate, fast tracked into treatment. The cost-effectiveness of this approach is still to be determined^{142, 143}.
- Dried blood spot testing, involving the collection of a finger-prick sample of blood on to filter paper, can improve testing uptake, particularly among hard to reach (e.g. PWID) populations. Such sampling can be performed by trained, supervised non-clinical personnel in non-clinical (e.g. drug treatment/harm reduction) settings^{144, 145}.
- Rapid Diagnostic Tests (RDTs) and Point-of-Care tests, avoiding the need for laboratory processing, are sufficiently sensitive, specific and convenient to offer a time and cost-saving alternative to conventional tests¹⁴⁶.



RECOMMENDATIONS

ACTION

It's crucial to establish HCV case-finding standards for the EU. These would be used in conjunction with ECDC & EU Commission (sponsored) materials on HCV screening¹⁴⁷.

EXAMPLE OF ACTION (for illustrative purposes only)

All EU Member States should ensure a 5-10% annual increase in the proportion of their estimated infected populations who have been diagnosed.

OUTCOME

A consistent, EU-wide standard for case-finding.

Treatment and Care

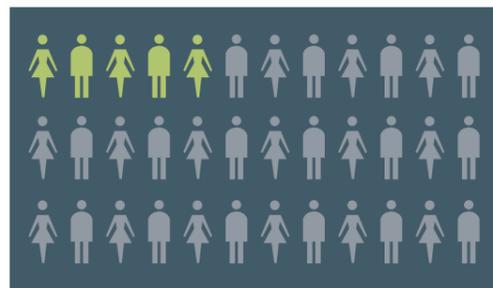
In the context of recent, and likely future, advances in HCV antiviral drug treatment – including the prospect of Highly Effective Interferon-free Antiviral Therapy, which can eradicate infection in the majority of instances, only a small minority of infected people in the EU, even in high income countries, have received therapy.

Critical barriers are failure to:

- i) Diagnose;
- ii) Assist vulnerable, infected people – many with co-morbidities including addictions – through the clinical pathway and;
- iii) Provide the resources needed for assessment and treatment.



ONLY A SMALL MINORITY OF INFECTED PEOPLE IN THE EU HAVE RECEIVED THERAPY



The Importance and Benefits of Therapy – Top 5 facts

Current and imminent HCV antiviral therapy has the potential to eradicate infection among the great majority of HCV infected people^{148,149,150,151}.

1.

Incontrovertible, observational evidence indicates that HCV antiviral therapy dramatically reduces liver-related morbidity and mortality^{152,153,154}.

2.

Antiviral treatment at an earlier stage of infection offers compelling advantages^{155,156}.

3.

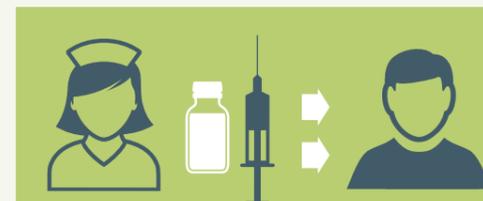
People who have injected drugs have just as good viral clearance outcomes following antiviral treatment as those who have not injected – provided that they do not inject drugs (certainly frequently) during the assessment for, or administration of, therapy; the availability and uptake of OST is critical in this respect^{157,158,159,160,161}.

4.

People who have injected drugs and have cleared their virus following antiviral therapy have a low rate of re-infection^{162,163}.

5.

Good antiviral treatment outcomes can be appreciably compromised by addictive behaviours – injecting drug use¹⁶⁴ and excessive alcohol consumption^{165,166} – which may, through re-infection, lead to progressive liver disease; accordingly the management of these behaviours is crucial.



Current antiviral treatment regimens which always include injectable Interferon can be delivered effectively and safely in the primary care setting by specialist nurses overseen by specialist clinicians

Cost Effectiveness, Delivery and Availability of Therapy

The cost-effectiveness of treatment means that the possibility of eradicating HCV is now being discussed. Experts agree unanimously that during the next five years, HCV antiviral therapy will increasingly become more effective, safe, easy to administer (interferon free) and tailored to the needs of the patient^{167,168,169,170,171,172(a), 172(b)}

Today, all current HCV antiviral therapeutic regimens are cost-effective in the context of UK and US thresholds^{173,174,175}. Further, national procurement of HCV antiviral therapies by Governments/Government agencies can achieve considerable savings¹⁷⁶. In the EU, nearly all countries have approved, and most have launched, direct-acting antiviral therapies (first generation protease inhibitors) for the treatment of genotype 1 patients. Clinical experts agree that optimal therapeutic regimens should be made available to all HCV-infected persons (including those with mild disease) who want it and for whom no clinical contra-indications apply¹⁷⁷. They also agree that people with mild disease could be advised that deferment of therapy, coupled with monitoring, is unlikely to lead to appreciable deterioration in health in the short term.^{172(b)}

Current antiviral treatment regimens which always include injectable Interferon can be delivered effectively and safely in the primary care (e.g. general practice and prison clinic) setting by specialist nurses overseen by specialist clinicians. Accordingly, experts agree that future Interferon-free regimens could be made more accessible to hard-to-reach patients through their delivery in the primary care environment^{178,179,180}.

Learning lessons – the HIV experience.

One of the lessons of the HIV experience – i.e. national and international governmental engagement with the pharmaceutical industry – is critical if antiviral therapy is to be accessed by the many and not just the few¹⁸¹.

STOP What stands in the way of effective therapy?

Expert opinion and data indicate that the principal barriers to therapy uptake are

i)

failure to diagnose infected people, particularly migrants

ii)

failure to support vulnerable diagnosed people who have addictive behaviours and/or co-morbidities through the clinical pathway

iii)

the adverse effects associated with current therapeutic regimens and

iv)

failure of systems to fund the assessment for, and administration of, antiviral treatment in a way which does not incur "out of pocket" cost to the patient^{182,183,184}.

Uptake of Therapy at EU level

At EU level, systematically collected data on i) uptake of HCV antiviral therapy and ii) the barriers to such uptake, do not exist. Nevertheless, limited information from various sources strongly indicates that even in high income countries with funded HCV action plans, a small minority of infected individuals have been treated^{185,186}.

The diversity of EU Member States in terms of wealth, culture, healthcare system and HCV epidemiology (e.g. genotype of infection and age/lifestyle of the host) means that plans to improve treatment access need to be country specific.

RECOMMENDATIONS

ACTION

- The development of HCV Clinical (assessment, treatment and care) Standards for the EU is now a crucial step; these would be used in conjunction with EASL Clinical Guidelines and should incorporate educational/awareness raising requirements.

EXAMPLES OF ACTION (for illustrative purposes only)

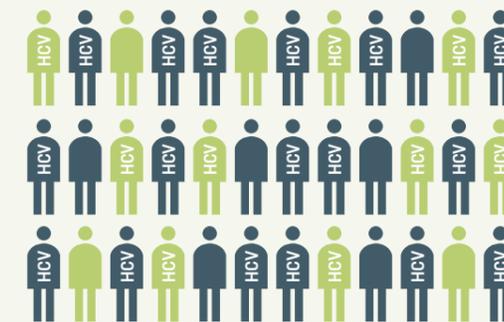
- All individuals diagnosed with chronic HCV infection should be referred to a specialist for assessment.
- All individuals with moderate or severe HCV related liver disease should have unrestricted access to antiviral therapy.

OUTCOME

- A consistent, acceptable standard of HCV case management across the EU.

Monitoring/Surveillance

In the context of millions of people in Europe being infected with a mostly "curable" infection that is now causing increasing morbidity and mortality and continues to spread, existing surveillance to gauge, with reasonable precision i) the extent of the problem and ii) the performance of countries in identifying and treating infected people, is poor.



European & Global Organisations with an HCV & HCV-related data collection role

At EU level, the ECDC has a formal role in monitoring HCV infection; this role commenced relatively recently and is an evolving one. Two major reports on surveillance methods and prevalence of infection were published in 2010 and a third, on HCV diagnoses, is due to be published in 2013^{187,188,189}.

Also at EU level, the EMCDDA has, for many years, published annually a range of data on aspects of drug use including those on the prevalence/incidence of HCV among PWID and on the uptake of harm reduction measures – namely injection equipment and Opiate Substitution Therapy provision – to prevent BBV infections¹⁹⁰.

High-level (and, in certain instances, subjective and generalised) information on country-specific interventions to prevent HCV infection and related disease have been collected recently by WHO (Europe), WHO (Global) in collaboration with the WHA and ELPA (Euro Hepatitis Index); the former two will report in 2013, while the latter reported in 2012^{191,192}. These initiatives should be refined, quality-assured and repeated frequently.

Diagnosed HCV-infected Individuals – inconsistencies in data collection

The ECDC is doing much to promote consistency and quality in HCV data collection but fundamental variations in data collection and collation practice, applicable to all infectious diseases across the EU, presents major challenges.

All EU Member States indicate that they have a surveillance system to monitor diagnosed cases of HCV infection. However, data collection methods, completeness of reporting, types of information collected and quality of data vary considerably among countries. This lack of uniformity and rigour at EU level, coupled with the fact that numbers of diagnoses of HCV – which, often, is an asymptomatic infection at the time of diagnosis – are influenced greatly by very variable intra- and inter-country HCV case-finding measures, means that such data are extremely difficult to interpret.

Data on diagnoses are critical in understanding access to, and uptake of, HCV case-finding interventions but only when placed in the context of estimates of overall numbers of infected persons. If they are not, and diagnoses data only are used to gauge the extent of the problem, there is a risk of seriously and unevenly under-estimating the problem.

Determining the overall size of the infected population

In terms of timeframe and geographical coverage, few countries have a systematic approach to the monitoring of HCV prevalence^{193,194}. All EU countries have undertaken surveys to generate an understanding of the size and characteristics of their HCV-infected population^{195,196}; these surveys vary considerably in terms of geographical coverage, sample size, recruitment approach, and time period. General population studies, invariably, are unrepresentative and small-scale. A large proportion of surveys apply to PWID among whom most new transmissions, certainly in recent times, have occurred.



A relatively new approach to the blood sampling of PWID both in community (e.g. injection equipment distributions sites) and prison settings has been the use of the dried blood spot test. This involves the impregnation of a drop of blood obtained via a finger-prick device, on to filter paper. This enables the recruitment of a more representative, non-hospital clinic based, sample of PWID for study¹⁹⁷.

The importance of monitoring new transmissions of HCV

It is important to monitor new transmissions of HCV so that the effectiveness of interventions to prevent infection can be evaluated.

The monitoring of new HCV transmissions is difficult because HCV infrequently presents as an acute symptomatic illness and no single test indicating recent infection exists. Accordingly, one has to rely on indirect approaches including the estimation of incidence of infection from serial prevalence data and the prospective or retrospective follow-up of HCV negative individuals to determine if they become positive. Incidence work of this type in the EU, particularly among the population at most risk (i.e. PWID), is scanty though islands of good practice do exist.

A new approach to the estimation of HCV incidence among PWID has emerged - the testing of HCV antibody negative blood specimens for HCV RNA to identify very recently acquired infection¹⁹⁸. Also, work evaluating avidity testing which assesses the strength of antibody binding (weak binding of HCV antibody in positive blood samples correlates with recent infection) is being undertaken in Glasgow (Goldberg D, personal communication).

Estimating new transmission as a consequence of sub-optimal infection control associated with healthcare procedures, particularly in southern and eastern European countries which have a higher prevalence and a history of appreciable HCV transmission through this route, is important. No systematic approach to such estimation, however, has been undertaken. One possibility, not yet achievable at EU-level as the data are not systematically collated, is the monitoring of HCV infection among the millions of repeat blood donors routinely tested for HCV in the EU. Absence/very low levels of infection among this population would provide reassurance regarding the risk of acquiring HCV through healthcare procedures.



*".....Member States should ensure.... that all patients are treated equitably on the basis of their healthcare needs rather than on the basis of their Member State affiliation. In doing so, Member States should request the principles of free movement of persons within the internal market, non-discrimination, inter-alia, with regard to nationality and necessity and proportionality of any restrictions on free movement".**

*EU white paper - "Together for Health - a strategic approach for the EU 2008-2013"

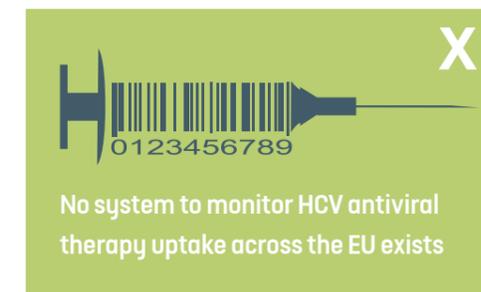
The crucial importance of monitoring people with HCV-related Disease

Across the EU, no surveillance system to monitor serious life-threatening disease or mortality due to, or associated with, HCV exists. A very small number of countries have systems to undertake such monitoring; these usually involve the linkage of HCV infection diagnosis data with data on death and hospital in-patient diagnosis registers^{199,200}.

The impact of life-threatening disease/death, as opposed to HCV infection diagnosis, data should not be underestimated. Where available, these data have helped considerably in generating investment in HCV prevention, diagnosis and treatment/care services²⁰¹. The AIDS case surveillance system, established in 1981 and adopted globally, generated data which drove the remarkable governmental and non-governmental agency public health and research response worldwide.

People receiving HCV Antiviral Therapy

As above, no system to monitor HCV antiviral therapy uptake across the EU exists; a very small number of countries either directly measure or estimate such uptake²⁰². Only where a national HCV Clinical Data System is in place can detailed, accurate information on i) the characteristics of treated individuals, ii) treatment given and, iii) responses to treatment, be monitored over time.



RECOMMENDATIONS

ACTION

- The development of standards for monitoring i) HCV infection transmission and related disease, and ii) the provision of interventions associated with their prevention is a crucial next step.

EXAMPLE OF ACTION (for illustrative purposes only)

All EU member states should report numbers of newly diagnosed cases of HCV related liver failure/cancer and HCV related deaths.

OUTCOME

Across the EU:

- A consistent, acceptable standard of monitoring/surveillance.

Planning and Co-ordination

Funded Action Plans – generally absent among EU Member States – are vital if currently suboptimal Hepatitis C prevention, diagnosis and treatment services are to become fit for purpose. While many EU countries have or report having strategies and plans to improve their Hepatitis C (and sometimes B) services, understanding around the comprehensiveness, intensity and impact of these at an EU level, is sub-optimal^{203,204}.

For two EU countries (France, and Scotland within the context of the UK), formal plans backed by serious Government investment have been implemented to improve Hepatitis C services in recent years^{205,206}.

SCOTLAND

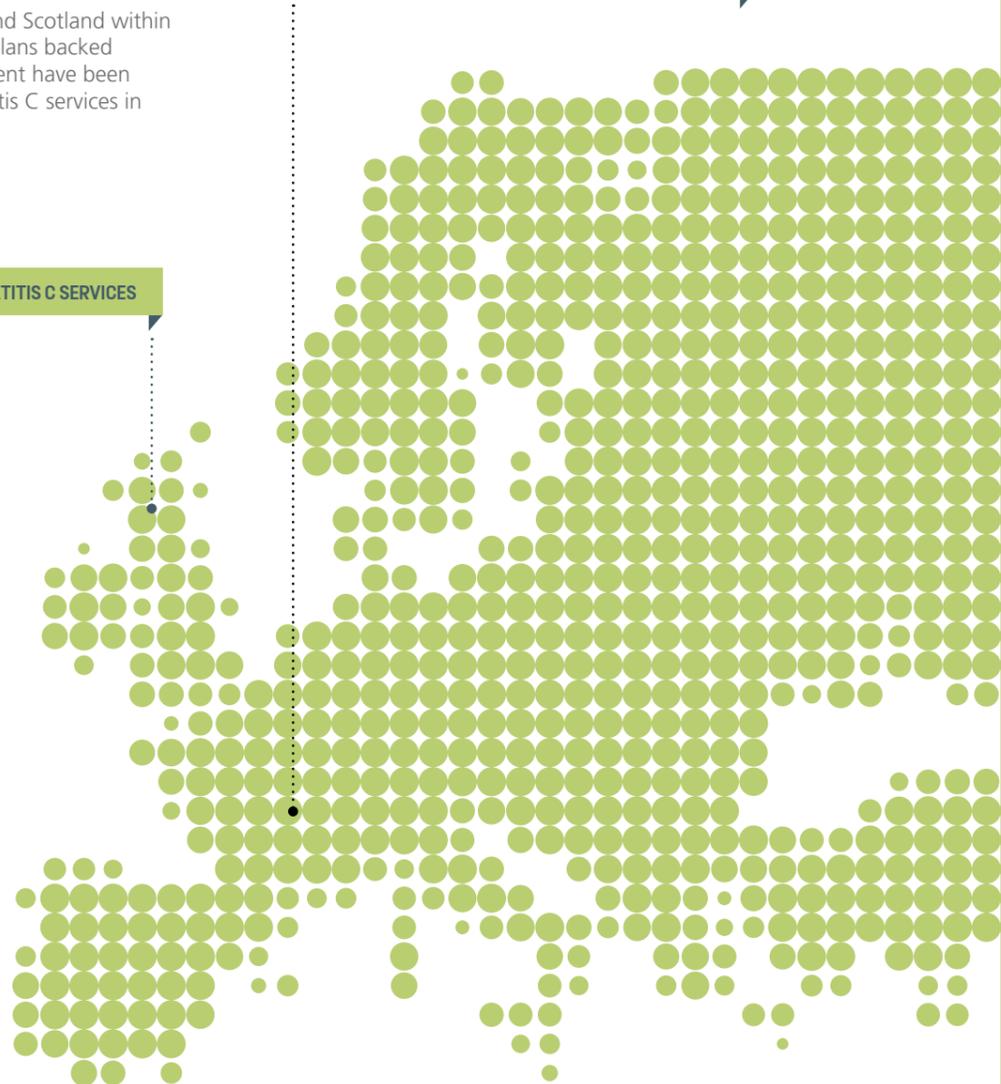
HAS IMPLEMENTED IMPROVED HEPATITIS C SERVICES

“

"The Charter of Fundamental Rights recognised the citizen's right of access to preventive health care and the right to benefit from medical treatment".

FRANCE

HAS IMPLEMENTED IMPROVED HEPATITIS C SERVICES



Case study: Scottish HCV Action Plan

The Scottish HCV Action Plan is worthy of examination^{207,208}. The Plan involved three phases:

- **Pre-Phase I:** Getting Government interested in improving Hepatitis C prevention, diagnosis and treatment/care services.
- **Phase I:** Generating, for Government consideration, a business case to improve Hepatitis C services.
- **Phase II:** Implementing an Action Plan to improve Hepatitis C services.

Pre-Phase I

- Scotland's national infectious disease control and prevention organisation (Health Protection Scotland), in association with partners, conducted epidemiological studies to determine the extent and characteristics of the problem.
- At the request of patient advocacy organisations, a Scottish Parliament All-Party Parliamentary Committee on Hepatitis C was established.
- Public health, clinical and patient advocacy "Hepatitis C Champions" – using data generated by the studies – informed members of the Scottish Parliament and other Government officials, including Scotland's Chief Medical Officer, of the seriousness of the issue.
- A Hepatitis C Consensus Conference was staged and National Clinical Guidelines were developed.
- Scotland's Minister of Health stated in Parliament, that "Hepatitis C is one of Scotland's greatest public health challenges".
- The Scottish Government requested Health Protection Scotland to generate a business case (Phase I) for a Scottish Hepatitis C Action Plan.

Phase I

- A multi-disciplinary task force of experts from Scotland and elsewhere in the UK was established to preside over the development of a business case.

• With the support of three working groups on Prevention, Education/Awareness-Raising and Treatment/Care, the taskforce:

- collated existing, and generated new, knowledge to identify the needs of people with, and at risk of acquiring, HCV infection
- translated this knowledge into proposed actions,
- undertook a consultation exercise to ensure that actions were supported by service providers and users
- costed the actions and presented the costed business case to the Scottish Government for consideration.

- The Scottish Government approved the business case and launched the Action Plan in May 2008.

Phase II

- A governance framework involving a Governance Board, accountable to the Scottish Government, was established. This Board comprised individuals from health authorities given funding by the Scottish Government to improve Hepatitis C Prevention, Diagnosis, Treatment/Care, Monitoring and Co-ordination Services locally and nationally.
- Local Managed Care (Clinical) and Prevention of Hepatitis C Multidisciplinary Networks to implement the Plan locally, were established²⁰⁹.
- National Prevention and Treatment/Care Networks to share best practice among, and provide technical expert advice to, local Networks were created.
- A set of Hepatitis C prevention/clinical health indicators to promote a consistent, high quality delivery of service, were generated²¹⁰.
- A Project Management approach, was adopted; this was underpinned by monitoring systems to generate data so that implementation progress and the impact of interventions could be evaluated.
- The overall co-ordination of the above plan was undertaken by Health Protection Scotland.

RECOMMENDATIONS

Funded Action Plans – generally absent among EU Member States – are vital if currently suboptimal Hepatitis C prevention, diagnosis and treatment services are to become fit for purpose.



ACTION

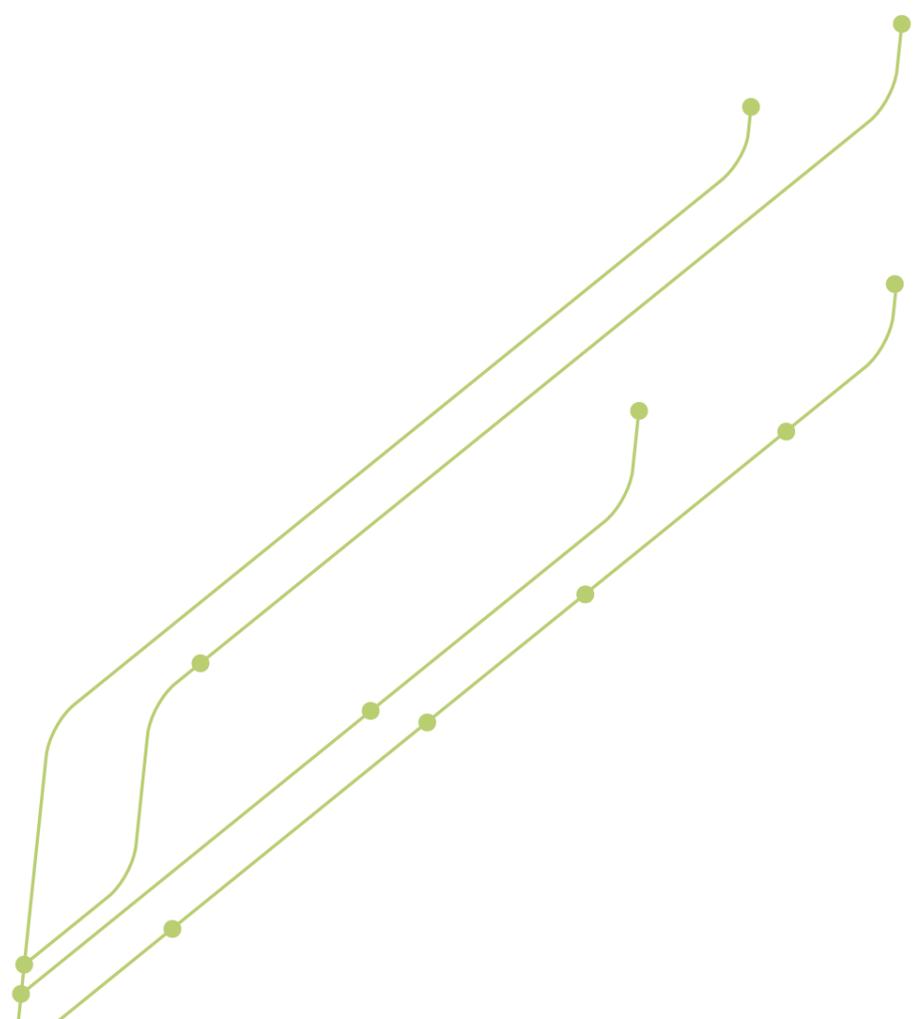
The establishment of standards for the development, coordination and implementation of EU Member State Action Plans to provide optimal Hepatitis C services.

OUTCOME

Across the EU, a consistent approach to service planning and coordination.

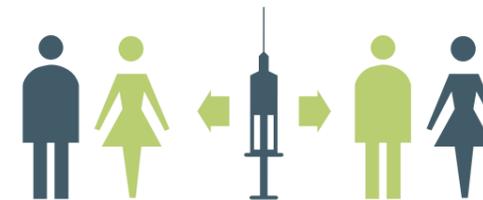
EXAMPLE OF ACTION (for illustrative purposes only)

Each member state should establish multidisciplinary teams nationally and/or regionally to provide leadership and direction.



Section 3: Conclusion

Compelling evidence indicates that HCV has been transmitted among humans for over a hundred years - evolutionary studies suggest it has been circulating for very much longer.



Currently, the sharing of injecting drug use equipment is the dominant mode of HCV transmission in most, if not all, EU Member States.

Epidemic transmission in Europe, however, appears to have been a feature of the second half of the 20th Century. Two major factors have driven the epidemic – sub-optimal infection control associated with healthcare procedures occurring especially in eastern and southern Europe, and injecting drug use particularly in northern and western Europe. Currently, the sharing of injecting drug use equipment is the dominant mode of HCV transmission in most, if not all, EU Member States. The two modes of transmission are very different in that one is associated with an illicit behaviour while the other relates to activities beyond an individual's personal control; nevertheless, they are connected, not only by the inoculation of contaminated blood into human tissue but by the fact that both modes are associated with economic disadvantage. Except for blood and blood-factor-associated transmission pre-1991 and 1986, respectively, all other pervasive healthcare associated transmission has been due to avoidable sub-optimal infection control; such lack of control was and, probably in some instances, still is due to financial constraints resulting in poor education, practice and equipment. The explosion of injecting drug use in Europe during the late 1970s/early 1980s was a consequence of new sources of heroin from Pakistan, Afghanistan and Iran fusing with markets of young, disadvantaged people, mainly men, caught unemployed in the post heavy-industry era.

Further, HCV's propensity to accelerate liver disease progression when accompanied by excessive alcohol consumption and/or HIV (comorbidities, particularly evident among PWID), and to be more prevalent among migrant populations from resource-poor countries, strengthens the bond between HCV infection and disadvantage.

And so, in Europe, HCV infection is a social and economic phenomenon – an infection deeply associated with deprivation and disadvantage. Although the evidence base on how well EU Member States are performing in preventing infection and disease is limited, much more needs to be done, even in the most affluent countries, to tackle a condition which is both preventable and curable; more than two decades after the discovery of HCV, it is an indictment that most infected people remain undiagnosed and only a small minority have been treated²¹¹. Indeed, cirrhosis presentation is often a failure of service provision rather than therapeutic effectiveness or personal behaviour.

It is the association between inequity and HCV acquisition/disease and service provision that makes this proposed Action Plan for the EU so important.

The development of high standards, coupled with the establishment of an EU Hepatitis C Taskforce to monitor and support their implementation and assistance from the European Commission to make cost-effective antiviral therapies affordable, will promote both the quality and consistency of HCV prevention, diagnosis, treatment/care and monitoring service provision across the EU.

The wider societal cost of taking no action regarding hepatitis C in the EU is huge. If serious progress can be made in raising standards of practice and if the trajectory of therapeutic advancement continues, as is very likely, the prospect of near eradication of both infection and related disease will no longer be intangible.

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Annex

1. Estimates of the Prevalence of HCV Antibody Positivity among EU Members*

Member State	Anti-HCV (%)	N	Member State	Anti-HCV (%)	N
Austria	1.0	82000	Latvia	2.2	51000
Belgium	0.9	93000	Lithuania	2.2	75000
Bulgaria	1.8	139000	Luxembourg	1.0	5000
Cyprus	0.5	4000	Malta	1.0	4000
Czech R.	1.5	153000	Poland	2.0	770000
Denmark	0.5	27000	Portugal	1.0	105000
Estonia	5.0	70000	Romania	4.5	1004000
Finland	0.5	26000	Slovakia	1.0	54000
France	1.3	814000	Slovenia	1.0	20000
Germany	0.8	620000	Spain	2.0	906000
Greece	1.5	169000	Sweden	0.5	46000
Hungary	2.2	220000	The Netherlands	1.0	163000
Ireland	1.1	45000	UK ¹	1.1	659000
Italy	3.2	1923000	TOTAL¹	2.0	8194000

Note that the UK estimate has been superseded by an estimate of approximately 288000 antibody positive (216000 chronically infected) individuals; this indicates the uncertainty of EU HCV prevalence estimates.

Assuming 75% of anti-HCV positive individuals are chronically infected with HCV, and accounting for the UK revision, approximately 5.9 million people in the EU are carrying the virus.

- In some countries, appreciable numbers of transmissions may be occurring as a consequence of sub-optimal infection control practices associated with healthcare procedures and tattooing; because i) data, indicating the extent of the problem are lacking, ii) healthcare associated infection control measures are beyond the scope of a Hepatitis C Action Plan, and, iii) the sharing of injection equipment by PWID is considered to be, by far, the dominant risk factor for current HCV transmission in the EU, the standard setting action, as above, applies only to PWID.
- Note that current PWID are individuals who i) would have injected drugs during the 12 months prior to commencing therapy, ii) might occasionally inject drugs during therapy and, iii) might inject drugs after the completion of therapy.

* Lavanchy, D. Evolving epidemiology of Hepatitis C virus. Clin Microbiol Infect 2011; 17: 107-115.

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