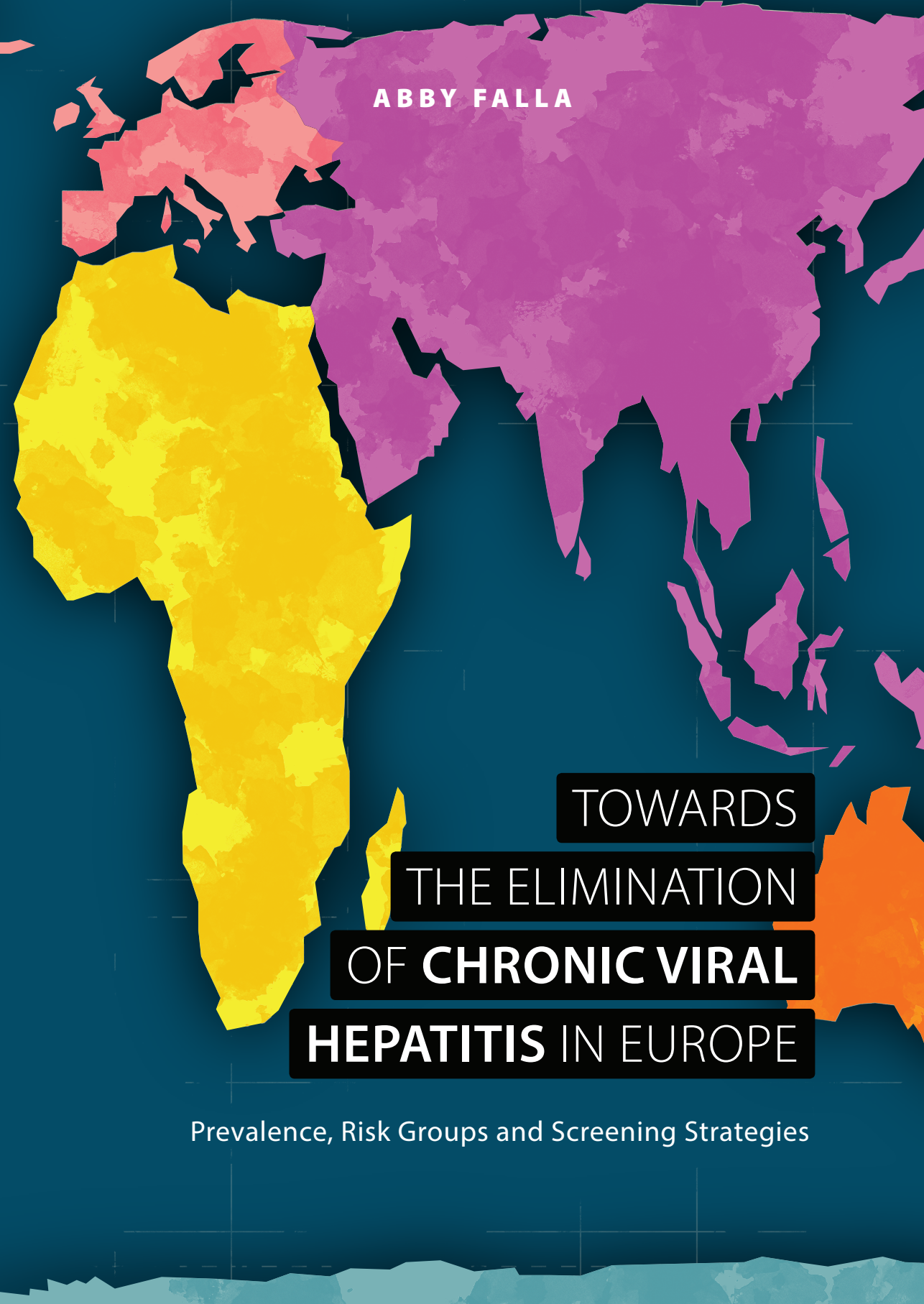
ABBY FALLA
TOWARDS
THE ELIMINATION
OF CHRONIC VIRAL
HEPATITIS IN EUROPE
Prevalence, Risk Groups and Screening Strategies

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Prevalence, Risk Groups and Screening Strategies

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Towards the elimination of chronic viral hepatitis in Europe:
prevalence, risk groups and screening strategies

Werken aan de eliminatie van chronische virale hepatitis in Europa:
prevalentie, risicogroepen en screeningstrategieën

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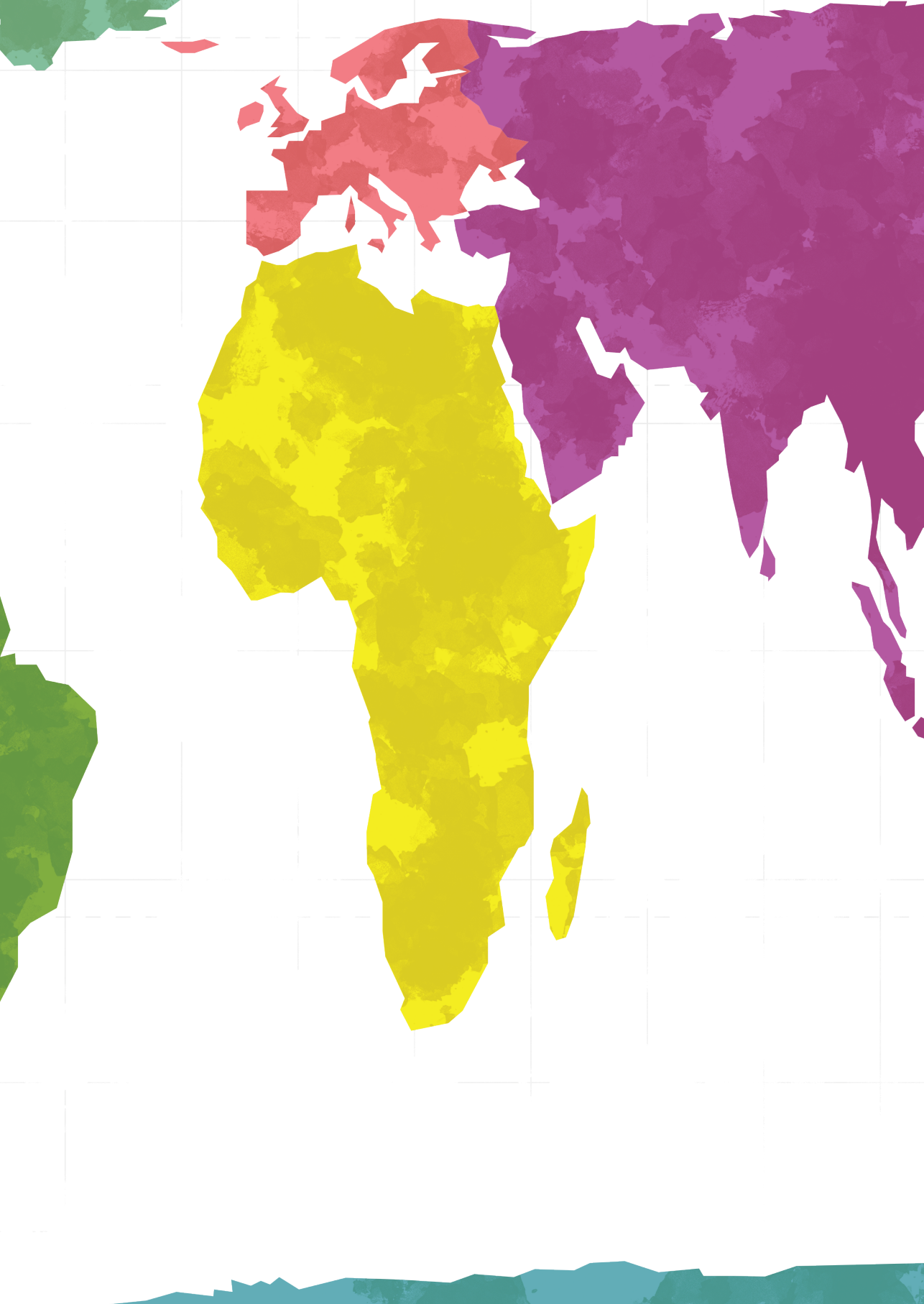

CHAPTER 1

General Introduction

Aetiology and sequelae

Hepatitis B (HBV) and hepatitis C virus (HCV) infections mostly affect the liver and result in a broad spectrum of health outcomes. In rare cases, acute infection can cause liver failure leading to liver transplant and/or death.(1, 2) Infections can spontaneously resolve and lead to immunity after an acute illness with mild symptoms lasting around six months. Infections can also fail to resolve and progress to chronicity. Long term complications of chronic hepatitis B (CHB) or chronic hepatitis C (CHC) infection include extra-hepatic and hepatic manifestations, specifically the risk of disease progression to liver fibrosis, cirrhosis, liver failure and hepatocellular carcinoma (HCC). These complications develop slowly over a period of decades after initial infection.(3) As disease progression is mostly asymptomatic, people infected may be unaware of their infection.(4) Latent disease is an important reservoir of infection as people with chronic viral hepatitis are infectious to others. Chronic infection is also deadly: the Global Burden of Disease study estimated the number of deaths (in 2010) attributed to be 786,000 for hepatitis B and 499,000 for hepatitis C.(5, 6)

Virological markers

Chronic hepatitis B is suspected in the persistent detection of hepatitis B surface antigen (HBsAg) in serum samples over a period of six months, with active chronic infection further confirmed by the presence and level of hepatitis B DNA and unfavourable liver function tests.(7, 8) The presence of hepatitis B e-antigen (HBeAg) correlates with a high viral load and was used as a proxy to confirm chronic infection before the advent of reliable viral load testing.(2, 9) Chronic hepatitis C is suspected in the presence of anti-HCV in serum over a period of six months and further confirmed by the presence of HCV RNA.(8)

Natural history

Whilst HBV and HCV share similarities in aetiology and sequelae, there are important differences in the viruses themselves and in our understanding. Firstly, unlike HCV, HBV is vaccine preventable.(10) A second key difference relates to the risk of developing a chronic infection following viral exposure. The risk of failure to clear an acute HBV infection depends on a number of, and interaction between, virological and environmental factors, but most significantly the state of the host's immune system.(11) Infants and children, whose immune systems are immature, are at the highest risk of developing a chronic infection with perinatal exposure carrying the highest risk (>90%).(12) Outcomes following exposure to HBV as an adult are more favourable with around 5-10% of people infected with HBV developing a chronic infection.(13) Virus-host immune interaction influences viral clearance and progression to chronicity with immuno-compromised people, for instance people living with systemic infectious diseases like human immunodeficiency virus (HIV) or tuberculosis (TB), at highest risk of developing chronic infection following exposure as adults. Outcomes

following exposure to HCV are less favourable with research indicating that between 55-85% of people infected progress to chronic hepatitis C infection.(14) Factors influencing progression to chronic infection with HCV are not well understood, although research indicates a complex interaction of virus-host factors.(1)

Transmission

Both viruses are remarkably successful blood-borne infectious pathogens, and much more infectious than HIV. Both are transmitted parenterally through exposure to infected blood and, in the case of HBV, to other bodily fluids.(2) There are other differences in both transmission routes and individual/population risk factors when comparing HBV and HCV epidemiology.

For HBV infection, drivers of infection also differ in low and in high prevalence areas. In HBV endemic areas, most transmission is perinatal from mother to child (MTCT) and horizontal among infants and children in households.(9) MTCT is responsible for up to one third of all cases of CHB worldwide.(9) As infants and children are more likely to develop a chronic HBV infection, interrupting transmission via these routes through antenatal screening, maternal antiviral treatment (to reduce viral load) and birth dose vaccination is crucial to control the spread of disease.(9, 15) In low prevalence areas, most transmission is via risk behaviour including unprotected sexual contact and injecting drugs using unsterile/shared injecting equipment with HBsAg carriers.(16, 17) In these instances, risk group vaccination and harm reduction interventions are key primary prevention measures.(18) Prior to the introduction of stringent hospital and health care infection control measures, including blood/blood product screening, both HBV and HCV were also acquired via unscreened blood transfusions and contaminated percutaneous medical equipment.(19)

Some of these transmission routes also apply to HCV, notably past/current injecting drug use (IDU), blood transfusion prior to the introduction of blood safety screening (in the early 1990s in most high income countries) and undergoing percutaneous medical procedures in health care services without adequate infection control measures.(20) In many resource-poor countries, transmission via the use of unsafe medical tools remains a key driver of incident infections.(20) There is an ongoing epidemiological debate about the efficacy of sexual contact as a means to transmit HCV. Whilst sexually acquired HCV is described to be uncommon, an increased incidence of chronic HCV infection among HIV positive men who have sex with men (MSM) has been described over the last two decades, largely coinciding with the use of anti-retroviral medication for HIV in the 1990s.(21) High risk sexual activity has been attributed as the main risk factor in most of these non-IDU, HIV positive MSM.(22) Primary prevention measures for controlling the spread of HCV are therefore somewhat

similar for HBV, and notably include health care infection control policies and procedures, the continuation of stringent blood/blood product safety screening and harm reduction measures among people who inject drugs (PWID).(18)

Global epidemiology

Along with serious sequelae for individuals, chronic viral hepatitis is also a serious public health challenge in scale. Global HBsAg prevalence was recently estimated to be 3.6% (95% CI 3.6 – 3.6), corresponding to around 250 million people with a chronic HBV infection.(17) Global viraemic HCV prevalence was estimated at 1.0% in 2015, corresponding to 71.1 million people living with CHC.(23) Together, HBV/HCV caused (in 2013) an estimated 1.4 million deaths (~687,000 deaths due to HBV and ~704,000 due to HCV) and were ranked (in 2013) as the 7th leading cause of death globally.(24) The global statistics describe the scale of disease burden and can motivate resource deployment but they also blur the inequitable distribution of infection and ill-health worldwide. There are wide differences from Global Burden of Disease (GBD) region to region and from country to country in prevalence of chronic infection, disease burden and estimated contribution of CHB/CHC to national/regional mortality.(24, 25)

Almost all Sub-Saharan African countries are reported to be intermediate-high endemicity (HBsAg prevalence >5% to 7.99%) or highly endemic (HBsAg prevalence ≥8.0%) for CHB infection.(17) Most countries in East Asia, South East Asia, Oceania and Central Asia are also intermediate to high endemicity. Countries in North and Latin America are generally of low (<2%) HBsAg prevalence as are most European countries although endemicity levels increase in Europe in an easterly and southerly direction.(16) GBD Regions with the highest anti-HCV/viraemic prevalence are Central and South Asia, much of Sub-Saharan Africa, and Eastern and Central Europe.(23, 26, 27)

Prevalence of both HBsAg and anti-HCV has decreased over time in most countries although the persistently high prevalence in some HBV endemic countries highlights the need for investment in and systematisation of primary prevention especially to prevent MTCT.(17, 28, 29) There is also a strong birth cohort effect reported in HBsAg/anti-HCV epidemiological data for most countries/regions, with the generation born between 1945 and 1965 most affected by CHC infection.(24, 26, 28) Many countries now face a dichotomy: a declining incidence of new infections due to the success of primary prevention alongside a projected increase in chronic viral hepatitis-related mortality due to ageing and disease progression in the most affected birth cohort.(16, 24, 28, 30)

Treatment

Effective antiviral therapy options exist for both CHB and CHC to control and prevent disease progression, and therefore reduce associated morbidity and mortality, in individuals. A number of well-tolerated, effective antivirals are available for the treatment of CHB. (7) The goal of CHB therapy is to suppress viral replication (the main indication for major disease-related complications), induce biochemical remission and prevent liver damage, notably progression to cirrhosis and HCC.(31) However, CHB can only be controlled and not completely cured in individuals.(7)

The goal of CHC treatment is to cure infection, characterised by a sustained virological response (SVR) and undetectable HCV RNA 24 weeks after treatment completion.(20) In the five year course of the research described in these thesis, the field of CHC treatment was completely transformed. Up until 2011, the only treatment regimen available in Europe for CHC infection was peglyated interferon (PegIFN) together with ribavirin, a drug combination with variable efficacy in achieving SVR across the six HCV genotypes (from 40-50% in genotype 1 and 4, and up to 80% in genotypes 2, 3, 5 and 6) and associated with severe side effects.(32) In 2011, telaprevir and boceprevir were licenced by the European Medicines Agency (EMA) for use in Europe in treating HCV genotype 1. These direct-acting antivirals (DAAs) are protease inhibitors to be used in combination with PegIFN/ribavirin. These triple therapy regimens (DAA plus PegIFN/ribavirin) reported relative efficacy in achieving SVR (29-88%) in treatment-naïve and treatment-experienced patients, including previous null responders to dual PegIFN/ribavirin therapy.(20) The second wave of DAAs (daclatasvir, ledipasvir, simeprevir and sofosbuvir) were approved by the EMA for use (in combination with each other and/or with ribavirin) in Europe in 2014 with a third generation of combination DAAs (ombitasvir/paritaprevir/ritonavir, dasabuvir, sofosbuvir/velpatasvir and grazoprevir/elbasvir) approved in 2015-16.(8) These interferon-free oral treatment regimens are of short (8, 12 or 24 week) duration and have reported SVR in more than 95% of patients including treatment-naïve, treatment-experienced, cirrhotic and HIV/HCV co-infected patients.(33) Unlike the previous treatment options, these third generation DAAs are effective across all six HCV genotypes. Further pharmacological innovations were submitted for EMA approval in 2017. Whilst the new DAAs have demonstrable efficacy in curing CHC, they also incur a high (projected) cost of between ~€30,000 to more than €100,000 per cure.(34)

Screening

The potential public health benefits of effective treatment can only be realised by finding (screening), retaining in care and treating people with a chronic hepatitis B/C infection.(35) As chronic infections are mostly asymptomatic, it is unlikely that people with CHB/CHC

will present to health care services with disease-related complaints unless they are in the advanced stages of fibrosis, cirrhosis or liver cancer.(3, 36, 37) Studies estimate that 65-90% of people chronically infected with HBV/HCV are unaware of their infection.(4, 38) As the goal of antiviral treatment is to prevent, halt or cure (in the case of CHC) serious disease as well as to prevent onward transmission (by reducing viral load), early detection before progression to cirrhosis and liver decompensation will deliver the most health benefits both for individuals and in terms of population health. Early detection (secondary prevention) through screening, retention in care and treatment also has the potential to deliver macro-economic productivity gains by preventing premature morbidity and mortality in a working age population. Direct economic costs and productivity are reported to increase with disease progression, further strengthening the rationale for early detection and treatment. (39)

The ethics, public health considerations and clinical characteristics of screening were seminally set out by Wilson and Jungner in 1968: "The central idea of early disease detection and treatment is essentially simple. However, the path to its successful achievement (on the one hand, bringing to treatment those with previously undetected disease, and, on the other, avoiding harm to those persons not in need of treatment) is far from simple though sometimes it may appear deceptively easy."(40) In support of balancing the benefits and harms at a population level, Wilson and Jungner proposed ten criteria to guide the decision making process about whether to organise population-based screening for a disease (Box 1).

These classic criteria have influenced others to develop their own, with more than 50 different sets identified by Andermann et al in a systematic review from 2008.(41) Much of the proliferation was driven by expanded scientific possibility through genetic sequencing and profiling. Equally important motivations were broader trends in Western medicine and the value systems that underpin these societies specifically increased consumerism (valuing freedom of choice), a shift away from paternalism towards informed choice and individualistic decision making, the development of clinical epidemiology as a field of science, and a focus on evidence-based health care from the joint perspectives of clinical efficacy, cost-effectiveness and equity.(41, 42)

Interestingly, the 'classic' criteria also emerged during an epidemiological transition in many industrial nations away from communicable disease as the most important causes of ill-health and death; the Wilson and Jungner criteria were indeed envisaged largely with non-communicable disease screening in mind with limited focus on communicable disease in low- and middle-income countries. These criteria also emerged just after the discovery of HBV (in 1965), more than two decades prior to the discovery of HCV (in 1989) and decades before antiviral treatment and the possibility of HBV/HCV screening became

available. Wilson and Jungner perhaps did not foresee the emergence in high income industrial nations of chronic communicable disease that could be candidates for screening: "measures taken to control endemic communicable disease….are now to a large extent no longer needed in well-developed areas." (p.15(40)) This perhaps explains the lack of explicit mention of prevention of onward transmission and the ability of screening to protect public health as a utility consideration in the criteria.

Box 1. Wilson and Jungner classic screening criteria

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

Key populations

Both as a consequence of the evolving treatment landscape as well as the epidemiological characteristics, there is significant scientific and policy interest in how to design, plan and implement HBV/HCV screening programmes that can effectively reach, diagnose and retain in care people at risk of being chronically infected with HBV/HCV. An important first consideration in screening design concerns the population to be targeted. It is crucial to understand the epidemiology of CHB/CHC to identify the population subgroups that are most affected. Transmission risk factors are fairly well understood and demographic and behavioural risk groups can be defined. Key behavioural risk groups include PWID, MSM, sex workers and people in prison, where the clustering of risk factors due to the criminalisation

of risk behaviour specifically IDU and sex work increase the prevalence.(43-46) Risk factors can also overlap in individuals placing some population subgroups at heightened risk of chronic infection.

Alongside behavioural risk groups, demographic risk groups exposed through origin in high endemic countries can also be defined as population subgroups in which the likelihood of being chronically infected is higher. Exposure risks in high endemic countries affect the general population, placing people born/living in these countries at risk of exposure. A similar logic also applies in low prevalence industrialised countries where specific birth cohorts exposed during a historically higher prevalence period, before primary prevention measures were introduced, are also more likely to be chronically infected as well as being broadly representative of the general population. Migrants from HBV endemic countries may have been exposed to HBV perinatally or parenterally as children (and therefore at high risk of CHB infection). Migrants from HCV endemic countries are at risk of CHC infection due to nosocomial/iatrogenic exposure where health care infection control practices are substandard.(47) In many low prevalence industrialised countries, migrants from high endemic countries are therefore disproportionately affected by chronic viral hepatitis and a key population for HBV/HCV screening and linkage to care. In the European Union/ European Economic Area (EU/EEA), migration within (from high to low prevalence Member States (MS)) and from outside (from higher prevalence countries to lower prevalence MS) is a key contributor to the burden of chronic viral hepatitis.(48-50) There is therefore interest at the EU level in how to reduce chronic viral hepatitis-related morbidity and mortality among migrants as part of the strategic policy pillars relating to cross border threats, improving the health of the European population and reducing inequalities in health.

The HEPscreen Project

As a result of this EU policy interest, the EU Health Programme funded the HEPscreen consortium project during 2011-2014 to research, evaluate and synthesize knowledge on screening for chronic viral hepatitis among migrants.(51) This wide-ranging project spanned 11 EU partners and six EU countries. The scientific work conducted as part of HEPscreen forms the core of this PhD thesis. Alongside the scientific output, an innovative online resource, the HEPscreen Toolkit, was also developed to summarise and synergise good practice knowledge, scientific evidence and 'real-world' experience about how to tackle the public health challenge of chronic viral hepatitis. The Toolkit was produced to assist national and local public health planners and intervention developers to develop good practice-based screening programmes/strategies focused on migrants from endemic countries. Box 2 describes the key features and more can be found at www.hepscreen.eu.

Box 2: Key aspects of the HEPscreen Toolkit

- Videos and animations about the public health challenge of chronic viral hepatitis
- Epidemiological tools to assess the burden of chronic viral hepatitis among migrants
- 'How-to' guides, case studies and videos about the different ways of screening
- A repository of good practice screening projects
- A tool to create multi-lingual leaflets for people offered hepatitis B/C screening – with over 40 languages available
- Tools to support primary care to offer testing to their patients from endemic areas, including a pre-test discussion checklist
- Good practice recommendations for post-test counselling and linkage to specialist care.

Elimination in Europe

The successful implementation of primary prevention to halt transmission together with the potential of secondary prevention through screening, referral and effective antiviral treatment have opened up the possibility for chronic viral hepatitis to be eliminated within decades. The World Health Organisation (WHO) agreed in 2016 the ambitious goal of elimination of chronic hepatitis B and C as health threat by 2030. The journey to elimination is set out in a Global Sector Strategy, an Advocacy Brief and an Action Plan for the health system response for the WHO European Region.(19, 52, 53) The Strategy defines five strategic pillars of elimination:

1. Information for focused action (the "who" and the "where")
2. Interventions for impact (the "what")
3. Delivering for equality ("the how")
4. Financing for sustainability (the financing) and
5. Innovation for acceleration (the future).

AIMS AND OUTLINE OF THE THESIS

This thesis aims to contribute strategic information towards the elimination of chronic viral hepatitis in the EU/EEA. Many EU/EEA countries have successfully controlled the transmission of HBV/HCV and the incidence of new infections is declining.(54, 55) This declining incidence exists alongside a projected increase in mortality due to disease progression and ageing among the infected population.(30, 56) This presents a public health challenge to countries: how to identify and retain in care people with a chronic viral hepatitis infection. The research is focused around the first three strategic pillars of the WHO elimination strategy: the who and where; the what; and the how. There are two broad aims:

1. To understand the epidemiology of chronic viral hepatitis in the general population and among risk groups in the EU/EEA;
2. To understand the health system conditions and screening interventions that effectively reach, diagnose and retain at-risk migrants in health care for viral hepatitis.

Drawing on a range of methodological techniques from both epidemiology, public health and the social sciences, we strive to answer the following three research questions:

1. To what extent are migrants from endemic countries a risk group for chronic hepatitis B and C in Europe?
2. What can be learned from different migrant-focused models of HBV/HCV screening?
3. What are the key conditions to maximise the impact public health of HBV/HCV screening among migrants?

We examine in **Part I** the epidemiology of chronic viral hepatitis infection in the EU/EEA through a series of systematic reviews, meta-analyses and epidemiological studies commissioned by the European Centre for Disease Control (ECDC). In **Chapter 2** we identify and synthesize prevalence estimates among subjects considered representative of the general population, pregnant women and first-time blood donors. Using a study quality assessment framework and an algorithmic approach to select EU/EEA Member State level estimates, we also estimate the prevalence and number of infections for both CHB and CHC at the EU/EEA level. **Chapter 3** is focused on the prevalence in three key populations at higher risk of being chronically infected with HBV/HCV namely people who inject drugs (PWID), men who have sex with men (MSM) and people incarcerated in prison. **Chapters 4 and 5** are focused on people born in endemic countries that migrated to the EU/EEA. In these two parallel studies, we conducted an epidemiological analysis to estimate both the

absolute number of cases among and the relative contribution of migrants from endemic countries to the overall number of chronic HBV/HCV infections in each EU/EEA Member State and across the Union as a whole. We also seek, using systematic review techniques, to assess the validity and reliability of using recent country of birth prevalence estimates as a proxy for the prevalence among migrants.

The focus of **Part II** of the thesis is on screening and linkage to care for chronic viral hepatitis infection and includes scientific work conducted as part of the EU Health Programme-funded HEPscreen Project.(51) **Chapter 6** other describes the outcomes of six pilot studies of different models of screening for HBV/HCV among migrants in four European countries. This is the first study to compare different models of screening for both HBV and HCV that reports on implementation, cost outcomes, results across the cascade of care and on prevalence by country of birth. **Chapters 7 - 12** apply systematic narrative review and DELPHI-method inspired semi-structured survey techniques to understand the health system conditions and patient pathways for screening, referral and treatment for chronic viral hepatitis in the six HEPscreen study countries: Germany, Hungary, Italy, the Netherlands, Spain and the United Kingdom (UK). We explore the availability and awareness of screening guidelines and training among health care professionals (**Chapter 7**). We examine in **Chapter 8** the availability of language support services (translated materials and interpreters) for linguistic minority migrant CHB/CHC patients as well as health professionals' perceptions about what role perceived language barriers play in three different scenarios: why screening is not offered to migrants with country of birth-related risk factors; why at-risk migrants do not take up the offer of screening; and why migrants diagnosed with CHB/CHC do not reach secondary care. **Chapter 9** is focused on defining and synthesising the content and aims of pre-test information provided to people offered HBV/HCV screening. We use primary research and the wider literature to explore the concept of informed choice in HBV/HCV screening and attempt to frame a set of recommendations on how health professionals can provide pre-test information that balances the seemingly polar aims of increasing uptake and securing informed choice in screening. **Chapter 10** examines the patient pathway following a CHB/CHC diagnosis to find out, using the perception of clinical professionals, what actually happens and in which health care services. **Chapter 11** delves deeper into current patient pathways, by exploring the role of the General Practitioner (GP) in screening at-risk groups and in the clinical management of patients with evidence of a CHB/CHC infection.

Chapters 12 and 13 are about treatment restrictions in the six HEPscreen study countries, also using knowledge and perceptions gathered from practising clinicians involved in the care of CHB/CHC patients. We are interested in (**Chapter 12**) restrictions based on patient characteristics, such as asylum seeker patients, undocumented migrants, people without

health insurance and people with state insurance only, and on clinical characteristics such as the abuse of alcohol and injecting illicit drugs. We are also interested in restrictions in (**Chapter 13**) the actual availability in the six study countries of antiviral treatment options available at a European level.

We bring this all together into a **General Discussion (Chapter 14)** and adopt a public health perspective on the cascade of care to address each of the research questions in turn. First, findings from **Chapters 1 - 5** (**Part 1**) are placed into a wider strategic and conceptual context to elucidate the extent to which migrants are a risk group for CHB/CHC infection. Next, the findings and experiences described in the study in **Chapter 6**, along with other studies of screening for HBV/HCV among migrants, are synthesised into an overview of good practices in how to design and deploy screening among migrants. The third research question on how to maximise the public health impact of HBV/HCV screening is addressed using findings gathered across all chapters and from wider literature. We synthesise findings into a series of **Recommendations** for national and European public health policy and practice and for scientific research.

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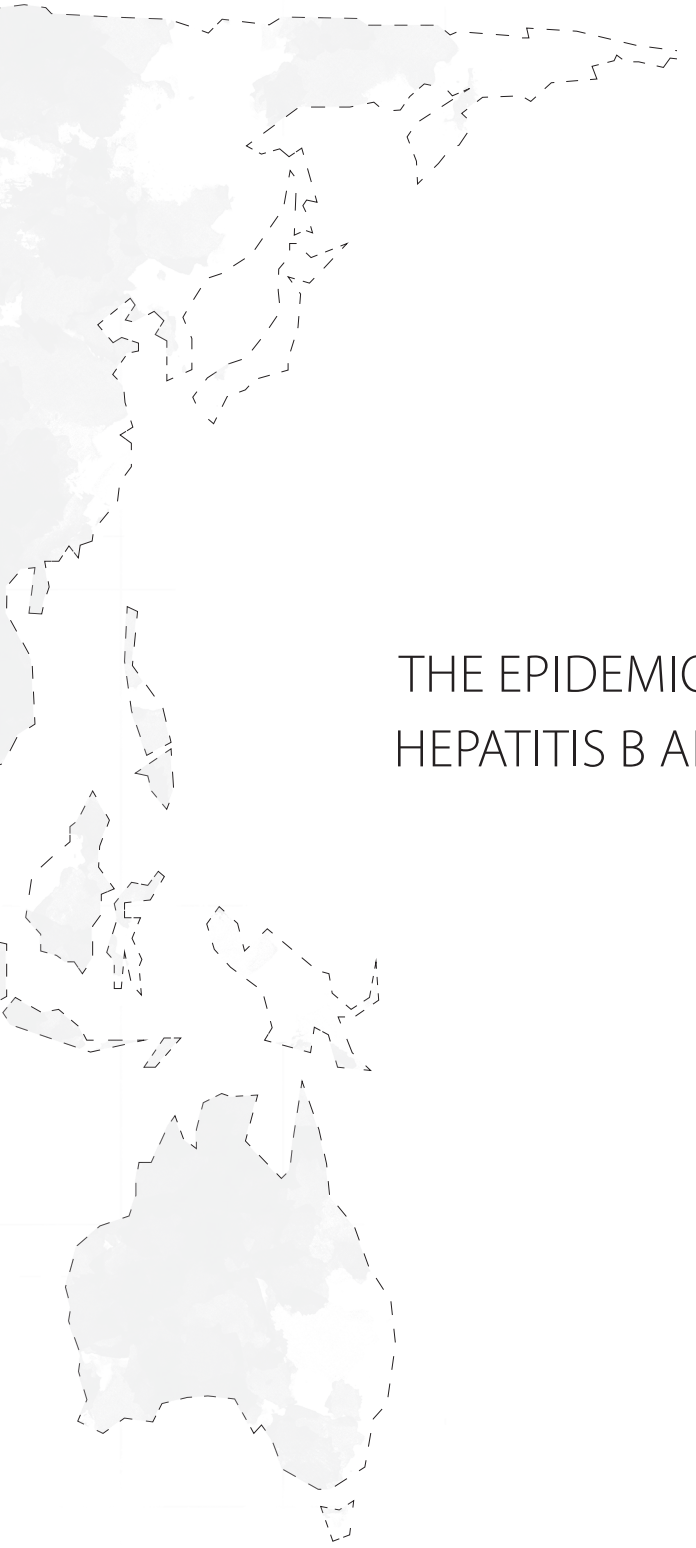
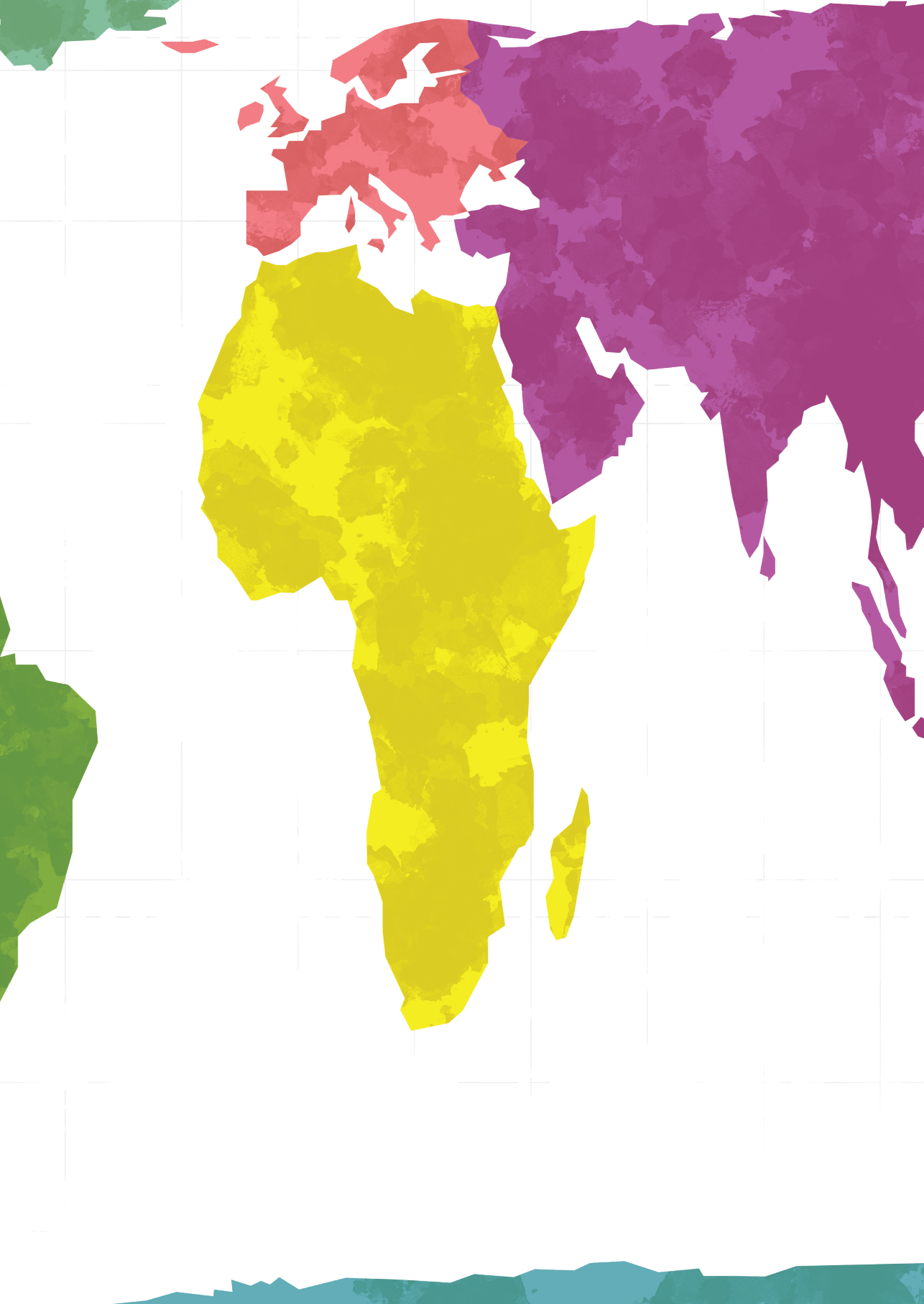


PART I

THE EPIDEMIOLOGY OF CHRONIC HEPATITIS B AND C IN THE EU/EEA



CHAPTER 2

Current prevalence of chronic hepatitis B and C virus infection in the general population, blood donors and pregnant women in the EU/EEA: a systematic review

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SUMMARY

This systematic review aimed at estimating chronic hepatitis B (HBV) and C virus (HCV) prevalence in the European Union (EU) and Economic Area (EEA) countries in the general population, blood donors and pregnant women. We searched PubMed©, Embase© and Cochrane Library databases for reports on HBV and HCV prevalence in the general population and pregnant women in EU/EEA countries published between 2005 and 2015. Council of Europe data were used for HBV and HCV blood donor prevalence. HBV general population estimates were available for 13 countries, ranging from 0·1% to 4·4%. HCV general population estimates were available for 13 countries, ranging from 0·1% to 5·9%. Based on general population and blood donor estimates, the overall HBV prevalence in the EU/EEA is estimated to be 0·9% (95% CI 0·7–1·2), corresponding to almost 4·7 million HBsAg-positive cases; and the overall HCV prevalence to be 1·1% (95% CI 0·9–1·4), equalling 5·6 million anti-HCV-positive cases. We found wide variation in HCV and HBV prevalence across EU/EEA countries for which estimates were available, as well as variability between groups often considered a proxy for the general population. Prevalence estimates are essential to inform policymaking and public health practice. Comparing to other regions globally, HBV and HCV prevalence in the EU/EEA is low.

INTRODUCTION

Both hepatitis B (HBV) and C virus (HCV) affect the liver and can cause acute and chronic hepatitis. People with chronic HBV or HCV infection may transmit the virus to others and are at risk of developing serious liver disease such as cirrhosis or hepatocellular cancer (HCC) [1, 2]. Transmission of HBV and HCV can occur via sexual or blood–blood contact, or vertically (mother-to-child) [3, 4]. In Europe, the high-risk groups for acquisition of HBV include men who have sex with men (MSM) and people who inject drugs (PWID). The key risk groups for HCV include PWID, people in prison and MSM.

The risk of developing chronic HBV infection depends on the age at which people are infected, with 90% of infants infected at birth developing chronic infection, compared with 1–10% of those infected at an older age or as adults [5, 6]. Globally 248 million people were estimated to be chronically infected with HBV in 2010 [7]. Approximately 780 000 people die each year from HBV infection, mostly from chronic HBV infection-related sequelae such as cirrhosis and HCC [8].

Initial infection with HCV is often asymptomatic or mild (70–90% of cases); however, the majority of those infected with the virus (70–80%) develop chronic infection and, over a period of 20–30 years, 10–20% on average will develop cirrhosis and 1–5% will develop liver cancer [2]. An estimated 184 million people globally have chronic HCV infection [9] and 350 000–500 000 deaths are attributable each year to HCV-related liver diseases [8].

In 2011, the European Centre for Disease Prevention and Control (ECDC) started enhanced European Union (EU)-wide surveillance for HBV and HCV, based on annual data collection from EU and Economic Area (EEA) Member States (MS). In 2014, 22442 newly diagnosed HBV infection cases were reported from 30 MS, a rate of 4·2 cases/100 000 population [10]. In the same year, 35 321 newly diagnosed HCV infection cases were reported from 28 MS, a crude rate of 8·8 cases/100 000 population in the EU/EEA [11]. However, because HBV and HCV infections are typically asymptomatic until advanced liver disease develops [1, 2], notification data are known to be incomplete and reflect national screening and testing practices rather than the real number of infections. Supplementary information in the form of reliable and timely prevalence data is therefore important to describe the current burden of disease in the EU/EEA more accurately.

The recent development of more effective HBV and HCV treatment means that elimination of chronic viral hepatitis in Europe is now a possibility [12, 13]. However, 65–90% of infected people remain unaware of their infection and models predict that associated mortality will continue to increase as the current infected population ages [12, 14, 15]. Achieving potential

population health gains through treatment will require significant expansion of screening and treatment among the most affected populations. Robust strategic information will be of even more relevance in view of the recently approved WHO viral hepatitis global health sector strategy, the corresponding European regional action plan, and its monitoring needs [16, 17].

We updated a previous systematic review undertaken by ECDC in 2009 [18] with the aim to assess any changes and estimate the current prevalence of chronic HBV and HCV infection in EU/EEA countries in the general population, blood donors and pregnant women. As a secondary goal, we reviewed the availability, quality and geographical coverage of HBV and HCV prevalence data in the region in view of designing and monitoring future prevention and control initiatives.

METHODS

Search strategy and selection criteria

Original research articles were retrieved from PubMed®, Embase® and Cochrane Library databases in March 2015. The search strategies (Supplementary Fig. S1) combined controlled (MeSH/ Emtree terms) and natural vocabulary (keywords) to define disease-related (HBV/ HCV infection), outcome-related (prevalence) and geographic-related (EU/EEA) search parameters. The search was limited to records published from 1 January 2005 to 12 March 2015. Articles in all EU/EEA languages were included. The results of the search were shared with ECDC National Focal Points (NFP) for viral hepatitis in all 31 EU/EEA MS in May 2015 for review and to validate the list of included references for their country.

Inclusion and exclusion criteria (Supplementary Table S2) encompassed time-related criteria including publishing date (2005 or later); sampling timeframe (data collection ending after 2000 or beginning from 2000 onwards); geographical coverage (EU/EEA MS and/or any of their regions/districts) and disease specific markers (HBsAg/anti-HCV (and DNA/ RNA) prevalence). Only studies reporting original data were included, although reference lists of relevant reviews were consulted for any original articles not captured by the literature search. Articles reporting prevalence in the general population or pregnant women with a sample size of <100 participants were excluded. Articles reporting only self-reported HBsAg/anti-HCV prevalence were also excluded.

To ensure consistent application of the inclusion criteria, two reviewers (SHIH and AMF) independently reviewed the title and abstract of the same random selection of retrieved articles (5%). The inclusion criteria were further refined and a second round of reviewing was

conducted to ensure consistent application (>95% agreement) of the criteria. Following this, title and abstract screening for all articles continued independently using Endnote. The full texts of all publications included after title/abstract screening were assessed for relevance by members of the research team where language comprehension existed (articles in English, Dutch, French, Italian and German) or by ECDC reviewers (other EU/EEA languages). In case of uncertainty about in- or exclusion, the two reviewers consulted each other and cases of disagreement were resolved by consultation with a third team member (IKV).

Definitions

Chronic HBV and HCV were defined as the presence of HBsAg and anti-HCV in serum, saliva or dry blood spot samples, respectively. The general population was defined as people (all ages or adults only) living in a defined geographical area; patients attending community/primary health care settings; and workforce/specific professional groups (e.g. workplace screening) but not healthcare workers. Pregnant women were defined as those women undergoing antenatal care screening, and blood donors were defined as first-time blood donors (Supplementary Table S3).

Data extraction and quality assessment

Data extraction using a pre-defined set of variables (Supplementary Table S4) was performed simultaneously with full-text screening. The unit for data extraction was 'study', defined as a prevalence data report on HBsAg or anti-HCV for a defined population group, in a defined country, over a discrete period; one article may therefore include more than one study. Studies published in more than one article were extracted only once and the article with most details about the study used as the reference.

Each included study was evaluated for risk of selection bias using a framework developed ad hoc by the research team. Separate assessment frameworks were developed for the general population and pregnant women to account for differences in possible sources of selection bias. For general population studies, the domains age, gender, sampling method and response rate, and geographical coverage were considered as possible sources of selection bias (Supplementary Table S5). For pregnant women studies, potential selection bias sources included sampling method and geographical coverage (Supplementary Table S6). Points were awarded in each domain for representativeness or lower risk of bias, and a total score was calculated by summing the values in each domain. This resulted in a score between zero and six for the general population studies and between zero and three for the pregnant women studies. We refer to the total score as study quality score, since a higher

score indicates a lower risk of bias. A general population estimate was considered of high quality when it reached a study quality score 54. A high-quality estimate of prevalence in pregnant women was defined as a study quality score 52.

Data analysis

This review reports HBsAg and anti-HCV prevalence, rather than a viraemic marker of HCV chronic infection, since information on HCV RNA and HBV DNA prevalence was reported in too few studies to conduct an analysis. National weighted or standardized (e.g. for age and/or sex distribution) prevalence estimates, if available (Czech Republic and Belgium for HBV), were preferred over unweighted or crude estimates. Crude estimates for the general population with the highest quality (score 54) were pooled at country level, where available, by summing cases and sample size. Ninety-five per cent confidence intervals (95% CI) were then calculated using the Fisher's exact method in Microsoft Excel©. General population estimates were reported separately for adults and children where available. All higher quality estimates of HBsAg and anti-HCV prevalence (score 54) retrieved for each country for the general population are presented in forest plots (Microsoft Excel©). Higher quality prevalence estimates from pregnant women studies (score 52) were also pooled where possible (using the methodology as described above) and separate forest plots prepared for HBV and HCV. Prevalence maps of Europe for pooled or single higher quality estimates were created using the ECDC Mapping and Multi-Layer Analysis (EMMA) tool [19].

Blood donor data

To assess the HBV and HCV prevalence among blood donors, data from 2014 collected by the Council of Europe were used [20]. The Council of Europe collects comprehensive national data on blood donors. For countries with no data in the 2014 Council of Europe report, the most recent data from previous Council of Europe reports were used. No risk of bias assessment was performed for data on blood donors, as no data were available other than the number of first-time blood donors and the number of infections. When data on number of cases were available, we calculated 95% CI using the Fisher's exact method.

The burden of chronic hepatitis B and C in the EU/EEA

In order to estimate the current burden of chronic HBV and HCV in the EU/EEA, an algorithm combining general population and blood donor data was applied. If a pooled or single higher quality general population prevalence crude estimate was available for a country, this was used to determine the HBV and HCV prevalence in that country; if a higher quality estimate was not available, lower quality general population crude estimates were used (these were pooled when possible); if no general population estimates were available,

prevalence data from blood donors were used. To determine the total number of chronic HBV and HCV cases in each country, total population size (based on Eurostat 2014 data) for each country was multiplied by the estimated HBV and HCV prevalence in each country.

RESULTS

The literature search retrieved 9379 citations. After title/abstract screening, 142 articles for the general population and 50 articles for pregnant women were included. Seventeen MS validated the search results and/or provided additional references, adding nine additional citations for the general population and five for pregnant women. While all 55 full texts were available for pregnant women, three general population articles could not be retrieved. Following full-text screening, 48 articles for the general population and 32 articles for pregnant women were finally included (Fig. 1).

General population

From the 48 articles included, 53 HBsAg prevalence estimates and 45 anti-HCV estimates were extracted. For HBV, multiple estimates were available for 13 of 15 countries covered, with the most estimates (10) available for Italy (Supplementary Table S7). For HCV, more than one estimate was available for nine countries of 16 countries covered, with most estimates (14) again available for Italy (Supplementary Table S8).

From the 53 prevalence HBsAg estimates, 18 estimates in 13 countries (Belgium, Croatia, Czech Republic, France, Germany, Greece, Hungary, Ireland, Italy, the Netherlands, Romania, Slovakia and Spain) were considered to be of higher quality (score 54, Supplementary Table S9). These data are presented in Figures 2 and 3. For Germany, Italy and Spain, multiple higher quality estimates were available and used to calculate a pooled estimate. The HBsAg prevalence in the general population ranged from 0·1% in Ireland [21] to 4·4% in Romania [22] (Fig. 3). Eleven of the 13 estimates were around or below 1%. Several higher quality prevalence estimates were available for Italy which, when pooled, resulted in an estimated HBV prevalence of 0·7%. There is, however, wide heterogeneity among these single study prevalence estimates from Italy, ranging from 0.5% (Apuglia, Southern Italy [23]) to 5.8% (Bergamo, Northern Italy [24]).

Of the 45 anti-HCV prevalence estimates, 19 higher quality (score 54, Supplementary Table S9) prevalence estimates from 13 countries (Belgium, Croatia, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, the Netherlands, Romania, Slovakia and Spain) were available. These data are presented in Figures 2 and 4. Multiple higher quality estimates were available for a pooled estimate in Germany and Italy. The anti-HCV prevalence in the

general population ranged from 0·1% in Belgium [25], Ireland [21] and the Netherlands [26] to 5·9% in Italy (Fig. 4). Relatively high anti-HCV prevalence was also found in Romania (3·2%) [27], Greece (2·2%) [28], Latvia (2·4%) [29] and Slovakia (2·0%) [30]. The estimate for Greece, however, is based on a sample from the population of Crete [28]. Four estimates were available for Spain, of which only one was of higher quality and reported an anti-HCV prevalence of 1·1% [31]. The others ranged from 0·4% in Barcelona [32] and 0·6% in Murcia and Madrid [33] to 1·5% in multiple GP practices around Barcelona [32].

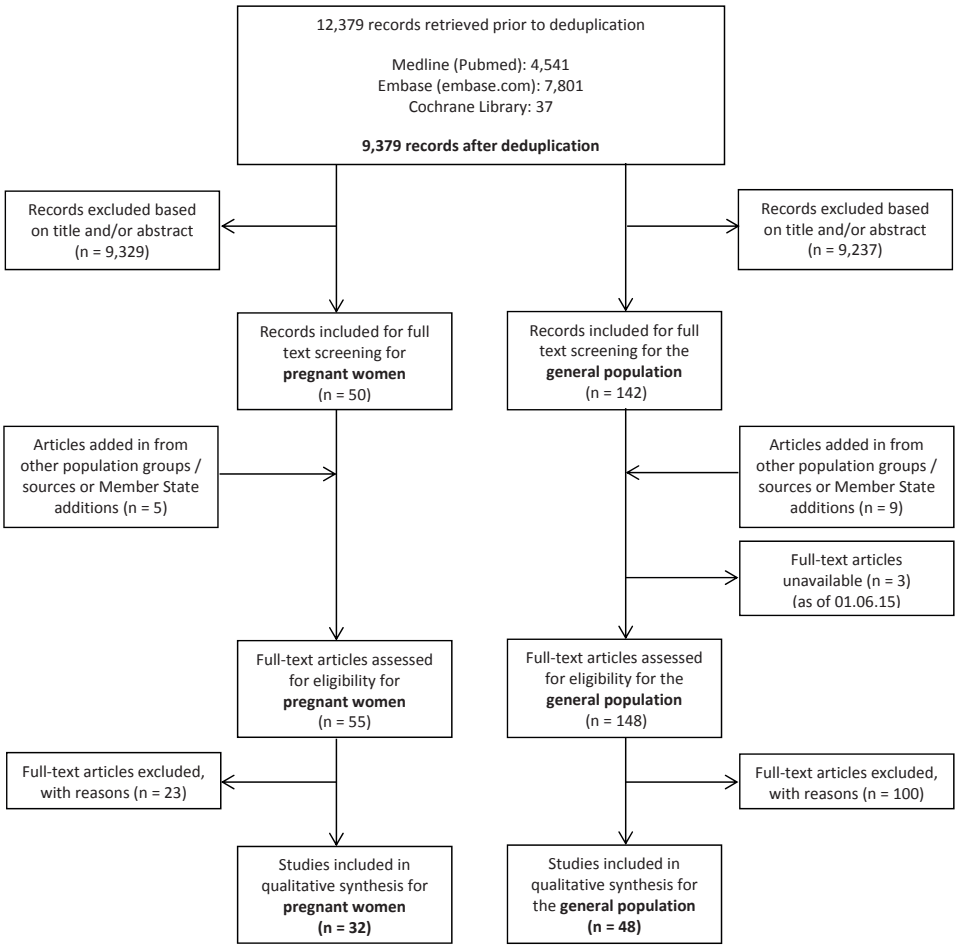

Figure 1. Flow chart of study selection for the general population and pregnant women; EU/EEA countries, 2005–2015.

Figure 2. HBsAg prevalence (left) and anti-HCV prevalence (right) in the adult general population in the EU/EEA, based on studies published between 2005 and 2015.

Pregnant women

To estimate the prevalence in pregnant women, 27 HBsAg estimates from 11 countries (Supplementary Table S10) and 15 anti-HCV estimates from eight countries (Supplementary Table S11) were retrieved from 32 eligible studies. Multiple estimates were available for nine countries, with the highest number of estimates (six) retrieved for Greece. Pooled estimates were available for Denmark, Italy, the Netherlands and the United Kingdom. Higher quality estimates (score ≥2, Supplementary Table S12) of HBsAg prevalence were available for seven countries, ranging from 0·1% in Norway [34] and Spain [35] to 0·8% in France [36] and Italy (Fig. 3). For the Netherlands, HBsAg prevalence in pregnant women increased slightly from 0·3% in 2006 [37] and 2007 [37] to 0·4% in 2008 [37].

Of the 15 HCV estimates for pregnant women, higher quality estimates (score ≥2, Supplementary Table S12) were available for Slovenia, Spain, Italy and Norway, with prevalence ranging from 0·1% in Slovenia [38] to 0·9% in Norway [34] (Fig. 4). The estimate for Slovenia is pooled, calculated using data from 2003, 2009 and 2013, which indicates a slight decrease in anti-HCV prevalence from 0·2% in 2003 to 0·1% in 2009 and 2013 [38].

First-time blood donors

The prevalence of HBsAg and anti-HCV in first-time blood donors was available for 30 countries (Table 1). For Latvia and Portugal, the absolute number of positive cases and first-time blood donors were unavailable, thus no 95% CI could be calculated. The prevalence of chronic HBV infection among first-time blood donors ranged from 0·0% in Finland and Luxembourg to 3·2% in Bulgaria. Most countries (18/31, 58%) had an HBsAg prevalence that was around or below 0·1%. The prevalence of anti-HCV among first-time blood donors ranged from 0·0% in Iceland to 2·2% in Latvia, and 58% of countries had an HCV prevalence that was about or below 0·1%.

European HBV/HCV prevalence estimates

Using prevalence estimates for the general population and blood donors, the HBsAg prevalence in the EU/EEA as a whole is estimated to be 0·9% (95% CI 0·7–1·2), equivalent to almost 4·7 million chronic HBV cases. An overview of the estimated prevalence and data used for each country is in Supplementary Table S13. The United Kingdom has the largest estimated burden of chronic HBV in the EU/EEA with over a million cases, followed by Romania (877 682), and Spain, France and Italy (each with between 400 000 and 500 000 cases).

Table 1. Prevalence of HBsAg and anti-HCV in first-time blood donors, EU/EEA*

Country	Prevalence of HBsAg (95%CI)	Prevalence of anti-HCV (95%CI)	Council of Europe Report
Austria	0.099% (0.072–0.132)	0.039% (0.023–0.061)	2010
Belgium	0.077% (0.055–0.104)	0.039% (0.024–0.060)	2011
Bulgaria	3.224% (3.039–3.418)	0.342% (0.282–0.410)	2011
Croatia	0.233% (0.142–0.359)	0.140% (0.072–0.244)	2011
Republic of Cyprus	0.441% (0.270 -0.681)	0.221% (0.106–0.405)	2008
Czech Republic	0.059% (0.040–0.085)	0.216% (0.177–0.261)	2011
Denmark	0.016% (0.004–0.040)	0.016% (0.004–0.040)	2011
Estonia	0.267% (0.128–0.490)	0.959% (0.673–1.326)	2011
Finland	0.000% (0.000–0.019)	0.025% (0.008–0.059)	2011
France	0.070% (0.062–0.079)	0.034% (0.028–0.040)	2011
Germany	0.116% (0.107–0.126)	0.062% (0.055–0.069)	2011
Greece	1.374% (1.280 -1.473)	1.202% (1.114–1.295)	2011
Hungary	0.009% (0.003 -0.021)	0.159% (0.128–0.195)	2011
Iceland	0.072% (0.002–0.398)	0.000% (0.000–0.264)	2011
Ireland	0.039% (0.013–0.090)	0.008% (0.000–0.043)	2011
Italy	0.168% (0.155–0.181)	0.094% (0.085–0.104)	2011
Latvia†	1.127%	2.170%	2003
Liechtenstein	-	-	n/a
Lithuania	0.560% (0.468–0.665)	1.537% (1.382–1.704)	2011
Luxembourg	0.000% (0.000–0.406)	0.221% (0.027–0.794)	2011
Malta	0.174% (0.047–0.445)	0.043% (0.001–0.242)	2011
The Netherlands	0.034% (0.018–0.060)	0.020% (0.008–0.041)	2011
Norway	0.028% (0.009–0.065)	0.033% (0.012–0.073)	2011
Poland	0.450% (0.425–0.476)	0.742% (0.710–0.775)	2010
Portugal	0.094%	0.165%	2006
Romania	3.078% (2.965–3.195)	0.590% (0.541–0.643)	2011
Slovakia	0.072% (0.048–0.104)	0.025% (0.012–0.046)	2011
Slovenia	0.087% (0.043–0.155)	0.016% (0.002–0.057)	2009
Spain	0.168% (0.152–0.185)	0.099% (0.086–0.112)	2011
Sweden	0.043% (0.026–0.065)	0.059% (0.040–0.085)	2009
United Kingdom	0.038% (0.030–0.047)	0.037% (0.030–0.047)	2011

* Adapted from Table 1 and 7.1, Council of Europe Report 2014. [20] † Latvia: No data are available after 2003.

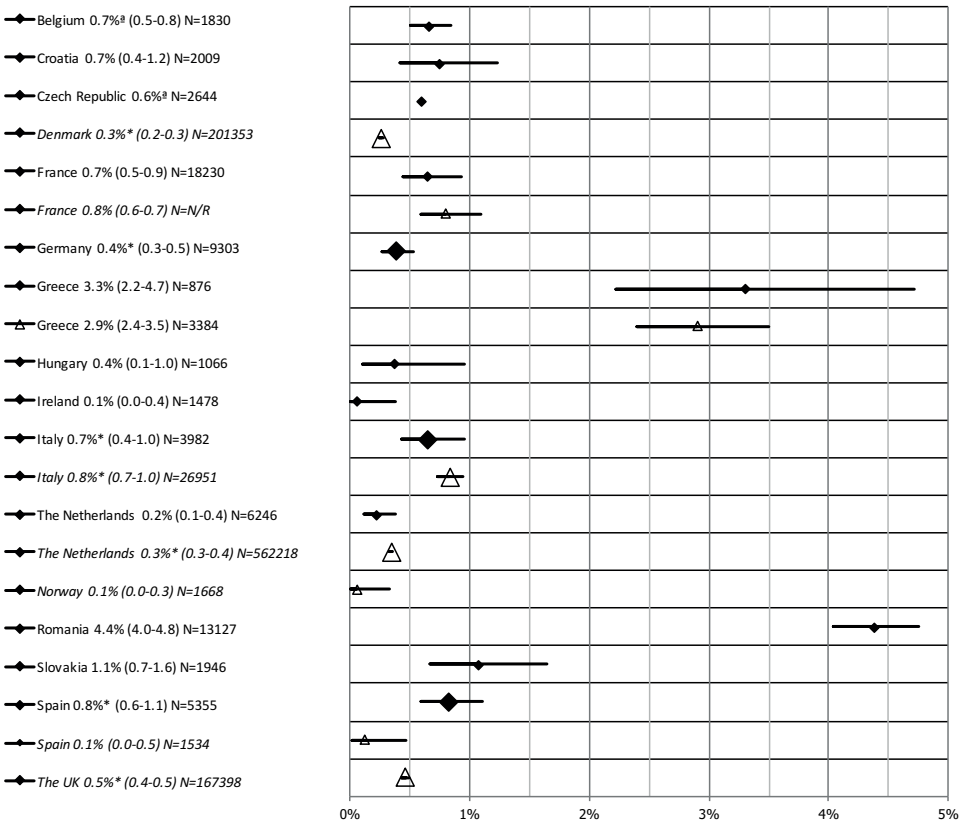

Figure 3. HBsAg prevalence estimates from studies with a lower risk of bias for the general population (study quality score ≥4) and for pregnant women (study quality score ≥2), in the EU/EEA, 2005–2015

Legend: country, prevalence estimate (95% CI) and sample size (N), general population estimates represented by diamond data points, pregnant women estimates represented in italics with triangle data points. [a]Standardized estimate *Pooled estimate.

The anti-HCV prevalence in the EU/EEA is estimated at 1·1% (95% CI 0·9–1·4) equivalent to approximately 5·6 million anti-HCV-positive cases. Of these, an estimated 70% are chronically infected, i.e. viraemic replication with detectable HCV RNA [17]. France, Italy, Poland, Romania, Spain and the United Kingdom have the largest burden of chronic HCV with between 350 000 and 2·5 million anti-HCV positive people.

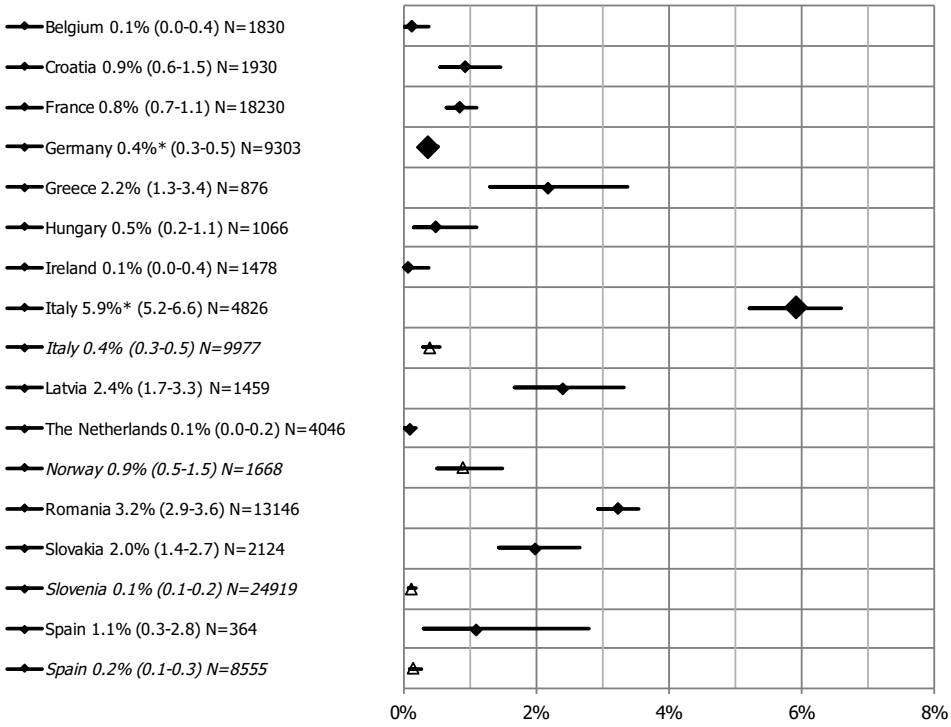

Figure 4. Anti-HCV prevalence estimates from studies with a lower risk of bias for the general population (study quality score ≥4) and for pregnant women (study quality score ≥ 2), in the EU/EEA (2005-2015).

Legend: Country, prevalence estimate (95%CI) and sample size (N), general population estimates represented by diamond data points, pregnant women estimates in italics with triangle data points)*Pooled estimates.

DISCUSSION

In this review, we have compiled recent evidence available on the prevalence of chronic HBV and HCV infection in the general population, pregnant women and blood donors from EU/EEA countries to provide further information on the epidemiology of these infections and to identify gaps in the available evidence. The prevalence of chronic HBV and HCV in the general population varies widely across the 16 EU/ EEA countries for which estimates were available, with a higher HBsAg and anti-HCV prevalence in countries in the Eastern and Southern part of the EU/EEA. There is great diversity across the region and the estimated prevalence in the country with the highest HBsAg estimate in the EU/EEA (Romania) is 44 times higher than in the country with the lowest estimated prevalence (Ireland). We also found that the highest single estimated anti-HCV prevalence (in Italy) is nearly 60 times

higher than estimates from countries with the lowest prevalence (Belgium, Ireland and the Netherlands). Differing risk factors and transmission routes might partially explain this variation across countries, as well as different implementation of prevention and control strategies.

This study updates the previous ECDC systematic review [18] and adds new estimates of HBsAg in the general population for six countries (Germany, Greece, Ireland, Italy, the Netherlands and Romania). Although we did not conduct a statistical analysis of differences between the reviews, there is evidence of change over time in all countries except Ireland. A decline in HBV prevalence was observed in Germany (0·6–0·4%) and Romania (5·6–4·4%). Improved primary prevention programmes including antenatal screening and HBV vaccination are likely explanations for this decline, especially in Romania. A decline in estimated prevalence is also likely for Italy, but with only regional prevalence estimates reported in 2009 (due to heterogeneity across North, Central and South Italy), we cannot compare the pooled 0·8% HBsAg prevalence estimate derived from the samples included in this study. This study also observed heterogeneity in the estimates for Italy derived from higher quality studies (0·5–5·8%). An increase in estimated prevalence was observed in Greece (2·1–3·3%) and the Netherlands (0·1–0·2%). Limited geographical coverage is a likely explanation for the increase in Greece as neither estimate is from a national sample (the 2009 study covered the Peloponnesus [39]; the study in this review was conducted in Crete [28]). The slight increase in the Netherlands can be explained by the increase of the migrant population in the country, as was reported in the original study [40].

New high-quality anti-HCV prevalence estimates were available for five countries (France, Germany, Greece, the Netherlands and Spain). Again, although no statistical testing was conducted, results suggest that while the chronic HCV prevalence remained at 0·4% in Germany, it declined over time in France, the Netherlands and Spain, and increased in Greece. As with HBsAg prevalence, it is possible that the increase in Greece is mostly a reflection of the restricted geographical coverage of both the current estimate (Crete [28]) and the two reported in 2009 (Peloponnesus [39] and Zakynthos [41]). The new estimates for France and the Netherlands are derived from large-scale national random samples, whereas in 2009, the estimates were derived from regional/city specific estimates where higher risk populations are over-represented. New estimates not previously available in 2009 were available for Hungary, Ireland, Croatia (not in the EU/EEA in 2009) and Latvia.

Both Ott et al. [42] and Schweitzer et al. [7] found that HBsAg prevalence increases eastwards across the EU/EEA; Schweitzer et al. reports the highest estimated prevalence found in Romania. While most HBsAg prevalence estimates are comparable, there are some notably different estimates reported by Schweitzer et al. for the 1990–2015 period, particularly for

Greece (0·97% vs. 3·3% in this review) and the United Kingdom (0·01% vs. 1·74% in this review). Methodological differences, specifically the inclusion of a wider timeframe and a broader definition of the general population to include blood donors, pregnant women and health care workers, could explain these differences.

For anti-HCV, an increase in Eastern and Southern EU countries was also reported. Similar to the findings from this review, Gower et al. found the highest prevalence estimates for Romania (3·2%), Lithuania (2·9%) and Latvia (2·4%) [43]. However, there is some divergence in the reported estimates for Italy. Our pooled 5·9% prevalence is considerably higher than the published 2·2% [43], yet the wide 'uncertainty range' (notably not a CI) reported by Gower et al. does include 5·6%, suggesting some comparability. In our study, 14 highly heterogeneous estimates (0·6% [44] to 27·6% [45]) met the inclusion criteria, four of which were pooled. Gower et al., however, selected one 'best estimate' to represent a country. Ultimately, our findings suggest that the prevalence in Gower et al. could be an underestimate; on the other hand, our estimate for Italy might be skewed upwards by included studies conducted in remote areas of the centre of the country.

HCV estimates presented in Cornberg et al. for France, Germany, Hungary and Romania were very similar to the estimates in this paper or the same study was identified as the most reliable estimate [46, 47]. Cornberg et al. suggest that the best prevalence estimate for Italy is 4·4% (all ages) and 5·2% for adults, similar to the 5·9% we found. Cornberg et al. most diverges with our findings for Spain (2·6% vs. 1·1% in this review) [31]. Although they also present other estimates they conclude, along with Esteban et al., that the prevalence in Spain is around 2·5% [48], suggesting our findings may be an underestimate of the true prevalence in the country.

The differences in prevalence between countries and over time are difficult to interpret, because comparability between studies is limited by the use of different study designs, probabilistic and non-probabilistic sampling strategies, and use of different laboratory tests and sample types. In addition, geographical representativeness is limited as most studies were performed at sub-national level. Representative seroprevalence studies for the general population are thus needed for valid comparison.

Pregnant women

Pregnant women are commonly considered as proxy for the general population, albeit to a different extent for HBV and HCV. The majority of EU/EEA MS offer antenatal HBV screening. Estimates of HBsAg prevalence among pregnant women, although slightly higher, mostly align with observed general population estimates in most countries, except in Greece and Spain, where the prevalence among pregnant women is lower. This is consistent with results of the 2009 systematic review [18]. The prevalence data for pregnant women in Spain are more recent than the general population estimates, so the difference between these groups might reflect a change in prevalence over time. For Greece, the prevalence data for pregnant women are from a national sample, while the general population data are derived from a regional sample. While a lower HBV prevalence could be expected in pregnant women, based on gender and age differences, groups with a higher risk of chronic viral hepatitis, such as migrants, are often under-represented in general population studies and may possibly be overrepresented among samples in pregnant women.

Anti-HCV prevalence in pregnant women, where available for comparison with higher quality general population estimates, was found to be considerably lower. Chronic HCV infections in many EU/EEA countries have an age- and gender-specific prevalence distribution, with some studies from Southern Europe suggesting that 60% of the infected population is over 65 years of age [46]. Older and male populations, mostly infected through injecting drug use, contaminated blood or blood products, or improper infection control practices in health care, are not represented in studies in pregnant women [46], and our findings suggest that pregnant women are not a reliable proxy population to estimate prevalence in the general population.

First-time blood donors

HBV and HCV seroprevalence data in first-time blood donors are readily available for most EU/EEA countries and are the most complete population prevalence source. Although blood donors are often used as a proxy population, this subgroup is generally considered not to be a representative sample due to self-selection of blood donors and strict regulation by blood banks [49]. These selection biases are reflected in our findings, which show that prevalence in first-time blood donors is considerably lower than general population estimates for all countries, although some confidence intervals overlap. Latvia may be the notable exception with a reported anti-HCV seroprevalence of 2·2% among first-time blood donors in 2003 (the latest estimate available), largely comparable with the higher quality estimate of 2·4% in 2008 in the general population [29].

The burden of chronic hepatitis B and C in the EU/EEA

The HBV and HCV prevalence in the EU/EEA as a whole is estimated to be around 0·9% and 1·1%, respectively, resulting in an estimated total of 4·7 million chronic HBV cases and 5·6 million anti-HCV positive cases. Considering that an estimated 70% of anti-HCV-positive cases are chronically infected [17], this corresponds with approximately 3·9 million chronic HCV cases.

The robustness of these figures is influenced not only by the intrinsic limitation of using prevalence estimates derived from an array of diverse studies, but also by the inclusion of prevalence estimates among blood donors as a proxy for the general population in the absence of other evidence. However, when taking into account both HBV and HCV data, general population estimates obtained from included studies accounted for approximately 83% of the total European population, with the remaining 17% covered by blood donor estimates.

Other than perhaps the population size of the country, no clear distribution across the EU can be observed in the availability of (higher quality) estimates in any of the targeted population groups. For one country, Liechtenstein, no information about HBV and HCV prevalence was available for any of the population groups. For Cyprus, Iceland and Malta, only prevalence data on first-time blood donors were available, and for Austria, Estonia, Lithuania, Poland and Sweden, only low-quality estimates were available.

Strengths and limitations

An important strength of this review is that publications in all EU/EEA languages were included. In addition, consultation with MS further supplemented and validated the evidence retrieved. We feel that the lower sensitivity in the literature search due to the use of a geographical filter was effectively offset by the MS consultations. Another strength is that small sample studies were excluded, a risk of bias assessment was developed and applied, and only high-quality estimates were selected and pooled (if multiple were available) for the analyses, to ease inter- and intra-country comparisons. The risk of bias assessment tool, however, has not been previously tested. An untested assumption in the tool is the equal weight given to each domain to calculate a final quality rating. For first-time blood donors, another data source was used rather than studies identified via a systematic review and the source was not assessed for bias.

This systematic literature review confirms the diversity in prevalence of chronic HBV and HCV infections across the EU/EEA, as well as the variability between groups often considered to provide a good proxy for the general population. Our findings suggest that using blood donor or pregnant women data as a proxy for HCV and, to a certain extent, HBV prevalence

estimates for the general population is not desirable. Comparing to other regions globally, HBV and HCV prevalence in the EU/EEA is low, with some sign of decline, at least for HBV. The availability of studies with relatively recent data on the prevalence in the general population is limited, with data for around half of the 31 countries in the EU/EEA, reporting higher HBV and HCV prevalence in countries in the Eastern and Southern part of the region. The epidemiology of HBV and HCV is constantly changing, in part due to the impact of prevention and control programmes and changes in risk factors, but many countries lack recent robust epidemiological studies that provide reliable estimates of the burden of chronic viral hepatitis. The lack of high-quality, recent, nationwide prevalence estimates and the heterogeneity of available studies makes it challenging to gain an EU/EEA overview of the current epidemiological situation regarding chronic viral hepatitis. The need for high-quality strategic information on the burden of HBV and HCV is compelling, not only for scaling up secondary prevention services appropriately, but also to inform regional and global activities that will shape the response to these epidemics in years to come. This could be achieved by complementing case-based surveillance with alternative data sources with adequate standardization levels across the region. A standardized seroprevalence survey performed across the EU/EEA, while resource intensive, may be a well-needed intervention to consider.

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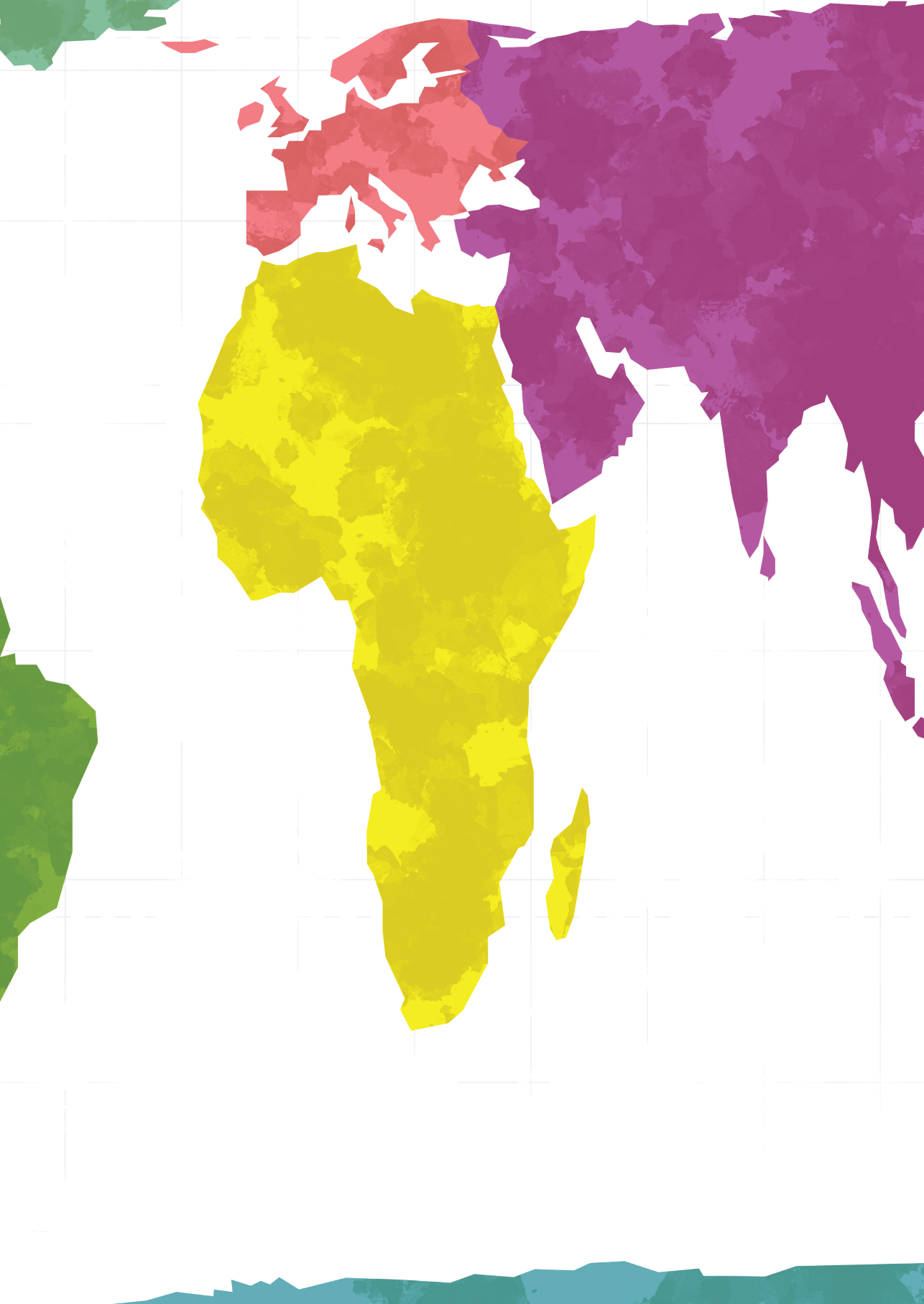

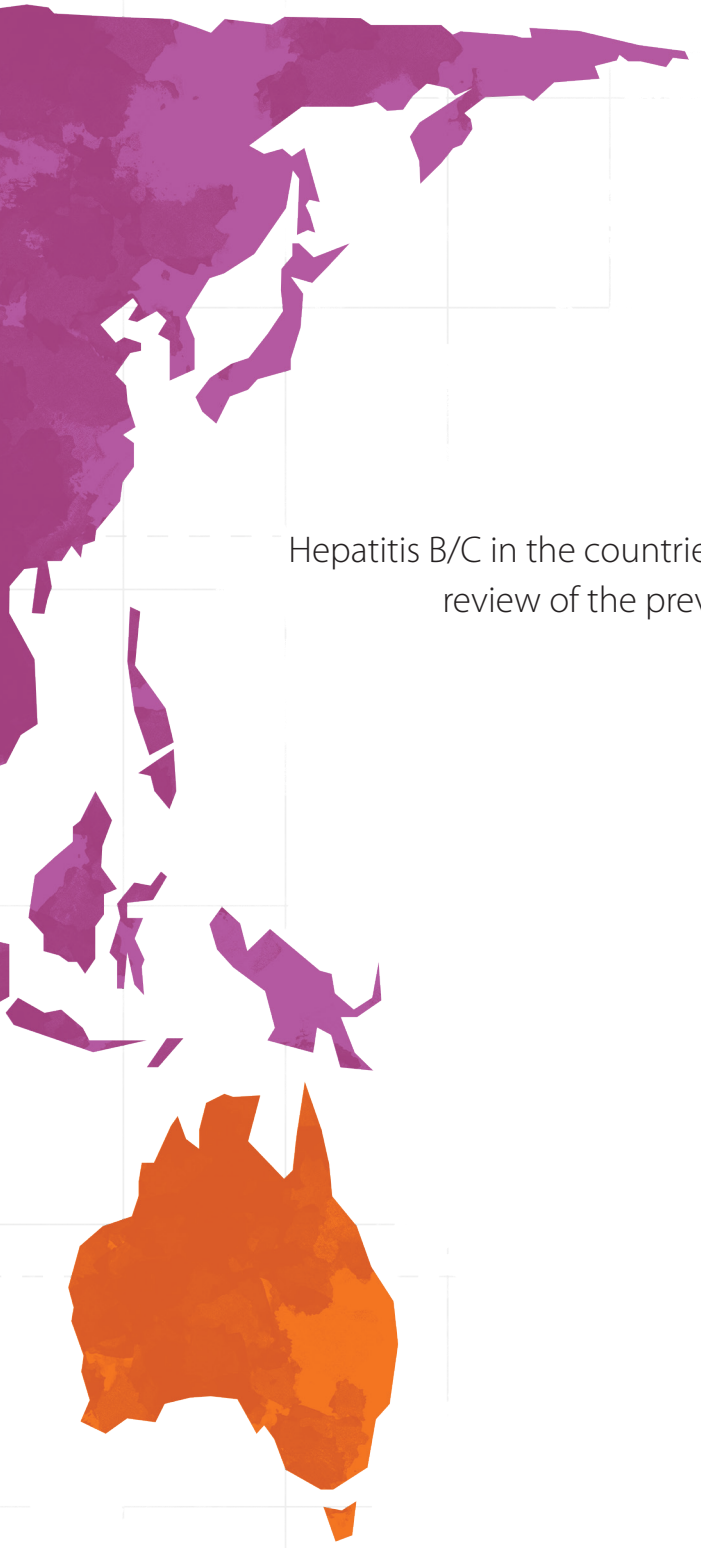

CHAPTER 3

Hepatitis B/C in the countries of the EU/EEA: a systematic review of the prevalence among at-risk groups

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ABSTRACT

Background: In 2016, the World Health Organisation set a goal to eliminate viral hepatitis by 2030. Robust epidemiological information underpins all efforts to achieve elimination and this systematic review provides estimates of HBsAg and anti-HCV prevalence in the European Union/European Economic Area (EU/EEA) among three at-risk populations: people in prison, men who have sex with men (MSM), and people who inject drugs (PWID).

Methods: Estimates of the prevalence among the three risk groups included in our study were derived from multiple sources. A systematic search of literature published during 2005-2015 was conducted without linguistic restrictions to identify studies among people in prison and HIV negative/HIV sero-status unknown MSM. National surveillance focal points were contacted to validate the search results. Studies were assessed for risk of bias and high quality estimates were pooled at country level. PWID data were extracted from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) repository.

Results: Despite gaps, we report 68 single study/pooled HBsAg/anti-HCV prevalence estimates covering 23/31 EU/EEA countries, 42 of which were of intermediate/high prevalence using the WHO endemicity threshold (of ≥2%). This includes 20 of the 23 estimates among PWID, 20 of the 28 high quality estimates among people in prison, and four of the 17 estimates among MSM. In general terms, the highest HBsAg prevalence was found among people in prison (range of 0.3% - 25.2%) followed by PWID (0.5% - 6.1%) and MSM (0.0% - 1.4%). The highest prevalence of anti-HCV was also found among people in prison (4.3% - 86.3%) and PWID (13.8% - 84.3%) followed by MSM (0.0% - 4.7%).

Conclusions: Our results suggest prioritisation of PWID and the prison population as the key populations for HBV/HCV screening and treatment given their dynamic interaction and high prevalence. The findings of this study do not seem to strongly support the continued classification of MSM as a high risk group for chronic hepatitis B infection. However, we still consider MSM a key population for targeted action given the emerging evidence of viral hepatitis transmission within this risk group together with the complex interaction of HBV/HCV and HIV.

INTRODUCTION

Chronic infection with the hepatitis B (HBV) or hepatitis C virus (HCV) is a significant cause of liver disease-related morbidity and mortality in the European Union/European Economic Area (EU/EEA).(1) Both viruses are transmitted through contact with infected blood, blood products and other bodily fluids. HBV is vaccine preventable which, along with other primary prevention measures including health care infection control and antenatal screening, have led to a decrease in acute and chronic hepatitis B (CHB) incidence in many EU/EEA countries.(2) Health care infection control together with harm reduction programmes among people who inject drugs (PWID) have also led to some decrease in the HCV incidence in many countries.(3) Many EU/EEA countries now face a dichotomy: a declining incidence of new HBV/HCV infections in the general population due to the success of primary prevention (2, 4) alongside a projected increase in liver disease-related morbidity and mortality due to ageing of the chronically infected population.(5, 6) With the availability of antiviral treatment that can effectively halt disease progression in CHB, including progression to cirrhosis and hepatocellular carcinoma, and new direct acting antivirals for chronic hepatitis C (CHC) that report cure rates in more than 90% of cases (7, 8), elimination of chronic viral hepatitis is a possibility. Elimination requires expanded access to screening, efficient linkage to care and retention in treatment among risk populations. Timely, reliable prevalence data are needed to understand which populations are most affected to better target screening and treatment programmes, and to monitor the performance and impact of these activities at a strategic level. Indeed, for screening to have a more favourable cost-effectiveness ratio and lead to an overall net gain in population health, current evidence indicates that it should be targeted to higher prevalence populations including PWID and other risk populations, where the expected case yield would be highest.(9, 10) However, the prevalence threshold above which a favourable cost effectiveness ratio varies considerably between EU/EEA countries.

In terms of key at-risk populations, men who have sex with men (MSM) are considered a high risk population for viral hepatitis due to the efficacy of sexual contact in transmitting HBV and the high prevalence of other sexually transmitted infections especially Human Immuno-Deficiency Virus (HIV). Whilst sexual contact was historically considered an ineffective route of HCV transmission, an increased HCV incidence among MSM who have not/do not inject drugs has been reported since the early 2000s. There is increasing evidence of permucosal transmission of HCV, especially among HIV positive MSM, although sexually acquired HCV infection remains rare in HIV negative, non-injecting MSM.(11, 12) Hahné et al reported Hepatitis B surface Antigen (HBsAg) and anti-HCV (measures of evidence of chronic HBV and chronic or resolved HCV infection respectively) prevalence among MSM in the EU/EEA ranging from <1% to 4% and from >1% to 2.9%, respectively.(13)

People detained in prison settings are considered a high risk population for blood-borne virus infection due the criminalisation of high transmission risk behaviour such as injecting drug use and sex work, coupled with pre-detention social vulnerability (such as experience of domestic abuse, poverty and homelessness) among many people detained and convicted. Prison-acquired blood-borne virus infections may also occur due to the continuation of transmission risk behaviour, the limited availability of harm reduction services and the lack of adequate infection control practices.(14, 15) Dolan et al meta-analysed data in Global Burden of Disease regions: in Western Europe, HBsAg and anti-HCV prevalence among people in prison was reported to be 2.4% and 15.5%, respectively, while in Eastern Europe it was 10.4% for HBsAg and 20.2% for anti-HCV.(16) HBsAg and anti-HCV estimates are also available for nine and 13 EU/EEA countries, respectively, although no study quality assessment nor country-level metaanalysis/pooling were performed.

Of the three at-risk populations included in this study, PWID are considered at highest risk due to the efficacy of unsafe injecting behaviour in transmitting HBV and HCV. This together with clustering of social and environmental risk factors in this marginalised population such as a history of incarceration, poverty, homelessness and multi-morbidity compound their vulnerability.(17) Nelson et al conducted a global review of HBsAg and anti-HCV prevalence among PWID in 2010, and reported prevalence data for 30 EU/EEA countries for anti-HCV and for 26 EU/EEA countries for HBsAg. The prevalence of anti-HCV ranged from 21.1% in Finland to 90.5% in Latvia, whereas HBsAg prevalence ranged from 0.0% in Ireland and Cyprus to 21.3% in Estonia.(17) Wiessing et al performed a systematic review of various epidemiological measures of the HCV epidemic among PWID in Europe.(18) Although anti-HCV prevalence was not an included outcome, their findings across the cascade of care show that 72% of anti-HCV infected PWID are viraemic; that 49% are unaware of their infection; and that 9.5% of diagnosed cases are reported to be on treatment. A review focused on the EU/EEA in 2009, Hahné et al reported HBsAg prevalence among PWID to be between 0.0% and 21.3% and anti-HCV prevalence to be between 5.3% and 90%.(13) An updated synthesis of the prevalence in this priority population is required.

Our study is part of a larger project funded by the European Centre for Disease Prevention and Control (ECDC) that seeks to provide a timely update on available estimates across a number of low risk populations (the general population, pregnant women and first-time blood donors) and as a comparator/contrast to collate prevalence estimates in high risk populations. We describe the results of the study into chronic viral hepatitis low risk populations and among migrants elsewhere.(19, 20) In the study reported here, we seek to update and expand the work of the previous ECDC systematic review (from 2009) by Hahné et al. (21) of prevalence estimates for markers of hepatitis B (HBsAg) and C (anti-HCV) in three key risk groups: MSM, people who inject drugs and people incarcerated in prison.

Our study seeks to contribute to the elimination of viral hepatitis in Europe by providing information to support the design and management of primary and secondary prevention strategies.

METHODS

Data sources

Estimates of the prevalence among the three risk groups included in our study were derived from multiple sources. A systematic literature search was conducted according to PRISMA guidelines (22) to retrieve, assess and synthesize available data published in the period 2005-2015 on the prevalence of HBsAg and anti-HCV infection in MSM and people in prison. Data on the prevalence among PWID were retrieved from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA).(23, 24)

Definitions

The key outcome was prevalence, which was defined as the proportion of study subjects with a positive finding of HBsAg or anti-HCV in serum, saliva or dry blood spot samples. MSM were not formally defined beyond the search term/inclusion criterion of 'MSM' and in practice this conceptualisation included men participating in studies in MSM-specific venues (e.g. saunas). People in prison were defined as people incarcerated in prison settings including prisons, remand centres, youth detention centres and psychiatric prison hospitals but excluding formerly incarcerated populations and other non-custodial secure institutions (such as secure psychiatric hospitals). PWID were defined by the EMCDDA as any person who has ever in their lifetime injected a drug for non-medical purposes.(25)

The prevalence in MSM and people in prison: systematic review

Search strategy

A systematic search to retrieve original research articles was conducted in PubMed®, Embase® and Cochrane Library bibliographic databases in March 2015. The search strategy (described in the online supplementary file) combined controlled (i.e. MeSH/Emtree terms) and natural vocabulary (i.e. keywords) to define disease-related (HBV or HCV infection), outcome-related (prevalence), and geographic-related search parameters (EU/EEA). To maximise the yield of the search, no population-specific search terms were included. Population relevancy was instead assessed at the title/abstract and full text assessment stages, as described below. The search was limited to records published from 1 January 2005 to 12 March 2015. Articles in all EU/EEA languages were included. The results of the search were shared with ECDC National Focal Points (26) for viral hepatitis in all EU/EEA

Member States in May 2015 to review and validate the list of included references for their country. The data extraction, risk of bias assessment and data analysis described below were all performed in Microsoft Excel.

Inclusion/exclusion criteria

Inclusion/exclusion criteria included publication and data collection date ranges, geographical relevancy, the reporting of specific markers of hepatitis B/C infection, population relevancy (as outlined in the definitions section above) and study design. Criteria related to study design included the actual measured presence of viral markers in bodily fluid/dried blood spot samples (and thus the exclusion of self-reported infection) in human subjects, prevalence as an outcome measure, the exclusion of modelled data only, and the exclusion of guidelines, meta-analyses, systematic reviews and commentary/opinion pieces. These criteria were twice piloted and refined by two reviewers (AF/SHIH) on a random sample of 5% of articles in order to reach >95% concordance. Following this, the title/abstract screening continued separately using Endnote. The full text of all publications included during title/abstract screening were individually assessed for relevance by members of the research team (for articles in Dutch, English, French, German and Italian) or by ECDC reviewers (for articles in other EU/EEA languages). Reviewers consulted each other in cases of uncertainty about in- or exclusion, and with a third team member (IV) to resolve further disagreement. The full search strategy, the in- and exclusion criteria and the PRISMA checklist are available in the supplementary information accompanying this article. See Figure 1 for the PRISMA flowchart (reasons for full text exclusion are detailed in the online supplement).

Data extraction

Data extraction using a pre-defined set of variables was performed simultaneously with full text screening. The unit for data extraction was study, not article. A study was defined as the report of prevalence data on HBsAg or anti-HCV for a defined population group, in a defined country, over a discrete period of time and one article may therefore include more than one study. Studies published in more than one article were extracted only once and the article with the most detail about the study used as reference. For studies retrieved reporting the prevalence in MSM, only data on HIV negative or unknown/unmeasured HIV sero-status MSM were extracted. All results reported in the study relating to MSM are therefore among HIV negative or unknown HIV sero-status MSM.

Risk of bias assessment

For MSM and the prison population each study was evaluated for the risk of selection bias using a specifically developed assessment framework. To account for differences in sources of selection bias, separate assessment frameworks were developed for MSM and people in prison to determine the representativeness of sample for that specific target population and the robustness of the estimates in each study. For studies in MSM, just one domain was included, 'sampling venue coverage', where the risk of bias was considered smaller for studies in multiple venues or multiple venue types. For studies in the prison population, the domains of age, gender, proportion of PWID, sampling method and geographical coverage were considered as possible sources of selection bias. Points were awarded in each domain for representativeness or a lower risk of bias, and a total score calculated by summing the values in each domain. This resulted in a score of between zero and two for MSM and between zero and six for the prison population. We refer to the total score as study quality score, since a higher score indicates a lower risk of bias.

Data analysis

We recalculated 95% confidence intervals (CIs) for all crude and pooled estimates using the Fisher's Exact method. All prevalence estimates retrieved for MSM, irrespective of the study quality score, are presented in separate (one for hepatitis B and one for hepatitis C) forest plots prepared using Microsoft Excel. HBsAg and anti-HCV prevalence estimates obtained from studies among adults in prison with a high study quality score (≥3) were pooled, when possible, by summing cases and sample size. Pooled or single study-derived high quality estimates retrieved for people in prison are presented in a forest plot, unless a study reported data over time whereby the most recent estimate was selected. Adult and juvenile (as defined by the included studies) estimates for the prison population are shown separately.

The prevalence in PWID: extraction from the EMCDDA data repository

The EMCDDA systematically retrieves, synthesizes and publishes comprehensive (and often unpublished) data on the prevalence of viral infections among PWID.(23, 24) We opted to draw on this repository due to its extensive scope as well as the potential to retrieve unpublished data that would be unavailable in scientific literature. The full data set retrieved for use in this study included country, year of study, geographical coverage, sample size and prevalence as well as limited information about study design and recruitment method/setting. We included only national level estimates, and where multiple national estimates were available for a country, the most recent estimate was selected. We did not assess the quality of the study beyond these parameters of geographical coverage and recency. Number positive was back calculated using prevalence and sample size, and a 95% CI re-

calculated using the Fisher Exact method. Samples in fewer than 10 subjects were excluded and multiple nationallevel estimates (if available from a specific year for an EU/EEA country) were pooled by summing cases and sample size.

RESULTS

Literature/database search retrievals

The literature search retrieved 9,379 citations, from which 17 citations were included for MSM and 57 for people in prison based on title/abstract. Seventeen MS validated our search results or provided additional references. For people in prison, seven publications were added either through a manual search of retrieved studies or through the national viral hepatitis ECDC focal points. An additional three citations were added for MSM. Whilst all 20 full texts were retrieved for MSM, three of the 64 included for people in prison were unavailable. Following full text screening, 13 articles were included for MSM and 32 for people in prison. The database search of the EMCDDA data repository retrieved seven national level HBsAg and 16 national level anti-HCV prevalence estimates.

The prevalence of HBsAg and anti-HCV among HIV negative/unknown HIV sero-status MSM

A total of 17 prevalence estimates, six for HBsAg and 11 for anti-HCV, were extracted from the 13 included studies about *HIV negative/unknown HIV sero-status* MSM. Key study details, including the risk of bias assessment, for all reported estimates among MSM are available in Annex 8 (HBV) and 9 (HCV) in the supplementary file for this article.

The six HBsAg prevalence estimates covered four countries: one each from Croatia and France and two each from Estonia and the United Kingdom (UK). HBsAg prevalence ranged from 0.0% - 0.1% in Estonia (27, 28) and the UK to 1.4% in France (Figure 2). The prevalence in the UK was derived from STI clinics in Scotland in 2001-2003 and ranged from 0.0% (29) to 1.0% (30), with the sample size of the study for the latter estimate considerably larger than the former study (N=575 vs N=81). The estimate from France is based on a large (N=876), multi-centre, multi venue type study from 2009.(31)

The 11 anti-HCV estimates covered seven countries and the prevalence ranged from 0.0% in Italy (32) to 4.7% in Estonia (Figure 3), with eight of the 11 data points ≥1%. Single estimates were available for France(31), Italy(32) and Sweden(33) whereas multiple estimates were available for Croatia, Estonia, the Netherlands and the UK. For Estonia, the two anti-HCV estimates range from 4.7% (in 2013) to 1.8% (in 2014-15).(27, 28) The two estimates for Croatia range from 2.5%(34) to 2.9%(35) and cover broadly the same time period

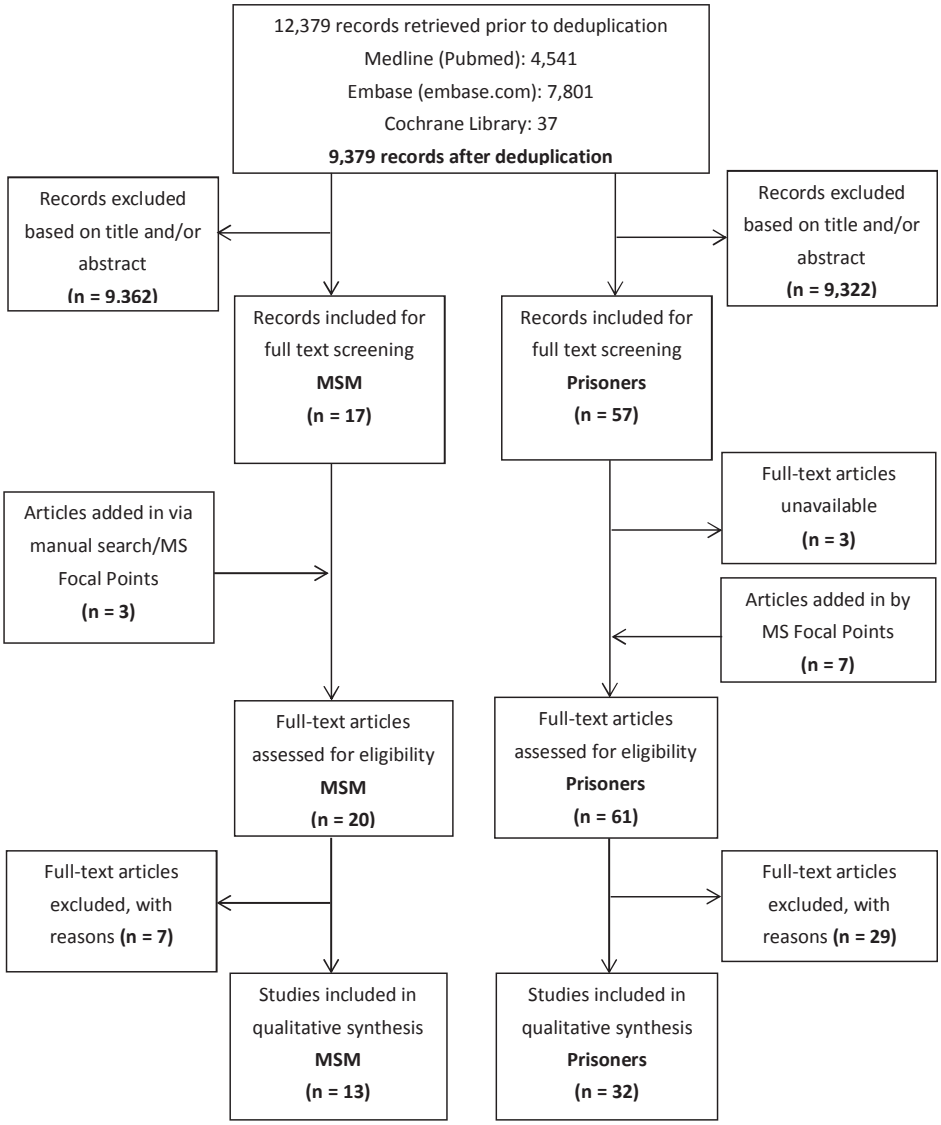

Figure 1. PRISMA flowchart for studies retrieved for MSM and prisoners

(2003-2006) although the former sampled the population of Zagreb only while the latter covered seven cities. The two estimates from the Netherlands range from 0.7% to 1.3% and were derived using different study designs among the MSM population in Amsterdam; men attending a STI clinic opting out of HIV testing in 2007(36) and a cohort study over the period 1984-2003, respectively.(37) The two estimates for the UK were: 2.2%, found

in a multi-centre study between 2008/9 (N=1121) in London gay bars, clubs and saunas; and 1.6% found among STI clinic attendees in Sheffield in 2009-2011 (N=3395).(38, 39) In summary, prevalence among MSM ranged from 0.0% to 1.4% for HBsAg and from 0.0% to 4.7% for anti-HCV.

The prevalence of HBsAg and anti-HCV among people in prison

Fifteen HBsAg prevalence estimates for 12 countries were extracted from the 32 included articles, only one of which (in Romania) scored <3 in the study quality assessment. Single estimates of HBsAg prevalence were retrieved for Bulgaria, Finland, France, Hungary, Ireland, Italy, Luxembourg, Portugal and Spain. Multiple (and therefore pooled) estimates were found for Croatia and the UK (Figure 4). These data show considerable heterogeneity in HBsAg prevalence in the prison population in the EU/EEA from <1% in the UK, Ireland(40), Finland(41) and France(42) to 6.7% in Italy(43), 7.0% in Luxembourg(44), 10.7% in Portugal(45) and 25.2% in Bulgaria(46). Two estimates for Croatia obtained over 2004-2006 and 2005-2007 both report a HBsAg prevalence of 1.3% in adult inmates, with a third study from 2005-2007 reporting 1.4% among juvenile inmates. Two estimates obtained in the UK, one in a maximum security psychiatric hospital prison (reporting 0.0%) and the other in a general prison in London (reporting 2.0%), were pooled into an estimate of 1.6% (95% CI 0.8-2.9). Whilst diversity in sampling design was seen across the 14 high quality HBsAg prevalence estimates, just one study (44) was biased towards exclusive recruitment of PWID or use of injecting drug use as a sampling criterion. Key study details, including the risk of bias assessment, for all reported estimates among people in prison are available in Annex 10 (HBV) and 11 (HCV) in the online supplementary file for this article.

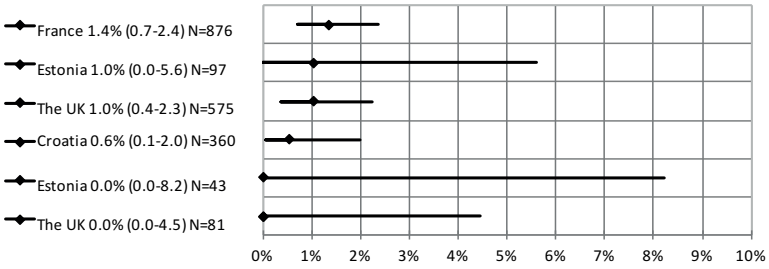

Figure 2. HBsAg prevalence among MSM

Legend: Country, prevalence estimate (95% CI) and sample size (N)

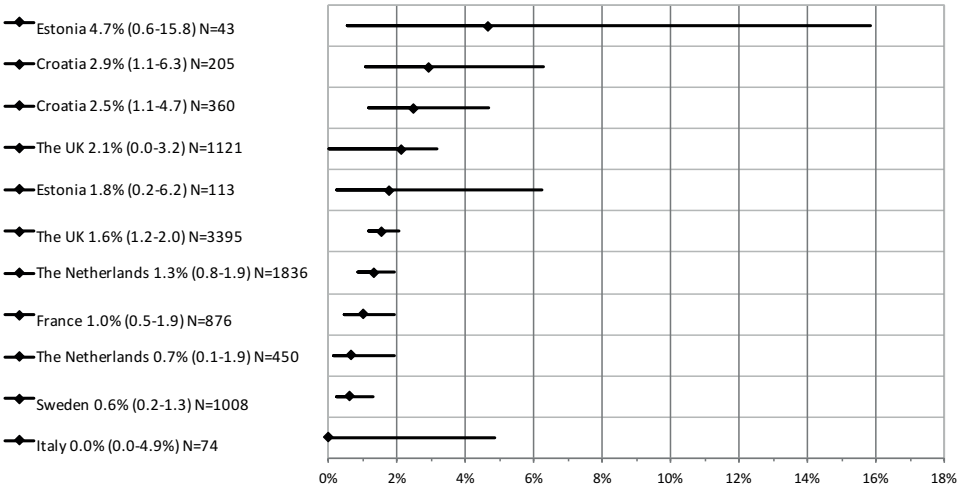

Figure 3. Anti-HCV prevalence among MSM

Legend: Country, prevalence estimate (95% CI) and sample size (N)

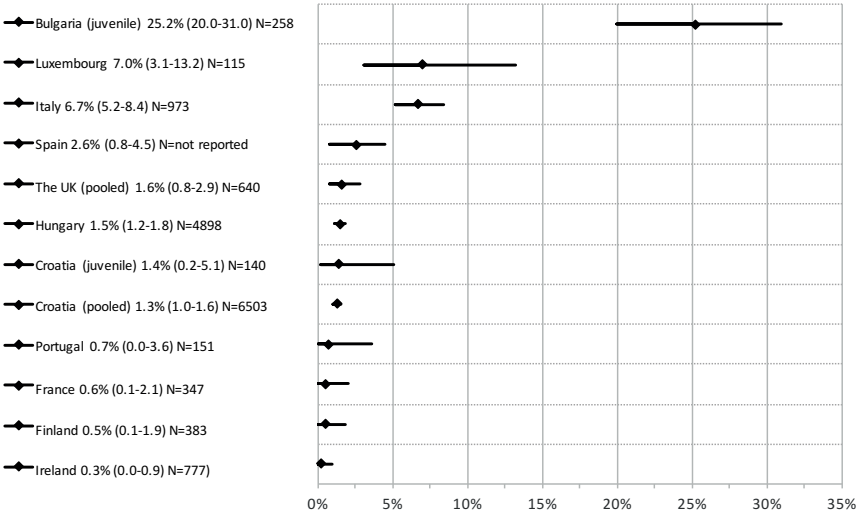

Figure 4. HBsAg prevalence among people (adults unless noted as juveniles) in prison

Legend: Country, prevalence estimate (95% CIs) and sample size (N)

Forty-five estimates of anti-HCV prevalence were retrieved from the included studies of which 37 estimates for 11 countries were considered high quality (i.e. a study quality score of ≥3). In 17 of the 45 anti-HCV estimates, injecting drug use was a study inclusion criterion or current/former PWID formed the majority of subjects. Figure 5 shows the final 16 single study/pooled high quality estimates included.

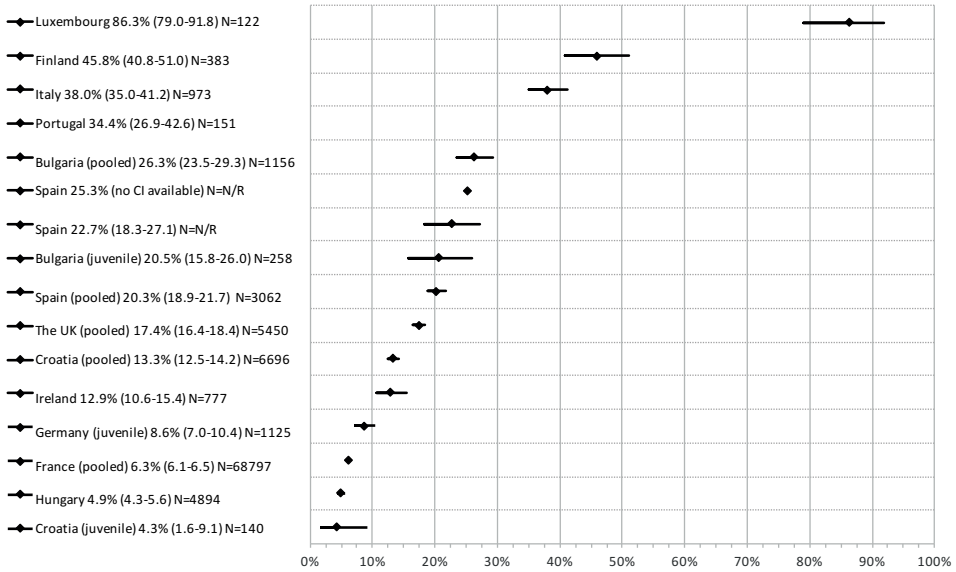

Figure 5. Anti-HCV prevalence among people (adults unless noted as juveniles) in prison

Legend: Country, prevalence estimate (95% CIs) and sample size (N)

There is considerable heterogeneity in the (mostly high i.e. ≥8%) prevalence among people in prison across the EU/EEA; all but four estimates (from Croatia (juvenile), France, Germany (juvenile) and Hungary) were above 10%, with an estimate from Luxembourg as high as >80% prevalence.(44) Multiple high quality (and therefore pooled) estimates were available for Bulgaria, Croatia, France, Spain and the UK. Alongside a pooled estimate of 20.3% (47, 48), consecutive annual estimates report a decrease in anti-HCV prevalence in Spain from 44.9% in 2000 to 25.3% in 2009.(49) Two multi-centre study-derived estimates from Bulgaria were pooled into an estimate of 26.3% (95% CI 23.5- 29.3).(50, 51) Four estimates from the UK were pooled into an overall prevalence of 17.4% (95% CI 16.4-18.4) (52-55). The pooled prevalence of 6.3% for France is derived from seven studies screening more than 68,000 people in prison. The three estimates among juvenile inmates show considerable heterogeneity, from 20.5% prevalence in Bulgaria (46) to 8.6% in Germany (56) and 4.3%

in Croatia (57). To summarise, prevalence extracted (and pooled where possible) from the high quality studies ranged from 0.3% to 25.2% (for HBsAg) and from 4.3% to 86.3% (for anti-HCV).

The prevalence of HBsAg and anti-HCV among PWID

The most recent, national level estimates of HBsAg and anti-HCV prevalence among PWID are presented in Table 1. National estimates of HBsAg prevalence were available for seven countries (Croatia, Cyprus, Greece, Hungary, Ireland, Latvia and Portugal), four of which were from studies conducted in 2013. The reported national prevalence ranges from 0.5% in Croatia, Hungary and Ireland, to more than 6% in Hungary and Portugal. National estimates of anti-HCV prevalence in the PWID population were available for 16 countries: Austria, Croatia, Cyprus, Czech Republic, Denmark, Finland, Greece, Hungary, Ireland, Italy, Latvia, Malta, Norway, Portugal, Slovenia and the UK. Anti-HCV prevalence was ≥30% in 13 of these countries and ≥50% in seven. In sum, the prevalence among PWID ranged from 0.5% to 6.1% (for HBsAg) and from 13.8% to 84.3% (for anti-HCV).

DISCUSSION

This is the first review to collate, assess and compare prevalence estimates across these three key at-risk groups in the EU/EEA. Although gaps in evidence exist, this study reports 68 HBsAg/anti-HCV single study/pooled prevalence estimates from 23 of 31 EU/EEA countries, 42 of which are considered as intermediate/high prevalence using the WHO endemicity threshold for HBV/HCV (≥2%)(58). This includes 20 of the 23 estimates among PWID, 20 of the 28 high quality estimates among people in prison, and four of the 17 estimates among *HIV negative/unknown HIV sero-status MSM*. Geographical trends are difficult to determine due to heterogeneity of, and gaps in, evidence, although the reported data here are suggestive of higher prevalence among MSM (for anti-HCV) and among PWID (for both viruses) among countries in eastern and southern Europe.

Limitations in the estimates reported for people in prison and MSM relate to geographical and population coverage, study quality and heterogeneity of the included estimates. To retrieve estimates for people in prison and for MSM, we conducted a very broad search of the published literature with no language or population restrictions, and validated retrievals directly with countries, yet found many geographical gaps in the data. Indeed, only a third of EU/EEA countries are represented among the studies that met the inclusion criteria for people in prison and only seven countries reported estimates among MSM. It is unlikely we failed to identify and include all existing high quality data, and consider it most likely that the data just do not exist or are not published.

Table 1. HBsAg and anti-HCV prevalence in PWID in the EU/EEA

Country	HBsAg					Anti-HCV				
	Year	Sample size	Prevalence (95% CI)	Study design	Setting	Year	Sample size	Prevalence (95% CI)	Study design	Setting
Austria	-	-	-			2013	48	31.3 (18.7 - 46.3)	DT	ODD
Croatia	2007	200	0.5 (0.0 - 2.8)	SP	PRI	2007	200	44 (37.0 - 51.2)	SP	PRI
Cyprus	2013	82	6.1 (2.0 - 13.7)	DT	DTC	2013	82	47.6 (36.4 - 58.9)	DT	DTC
Czech Republic	-	-	-			2013	1,889	14.6 (13.1 - 16.3)	DT	NSP
Denmark	-	-	-			2008	223	52.5 (45.7 - 59.2)	SP (UAT)	ODD
Finland	-	-	-			2009	682	60.5 (56.8 - 64.3)	SP (UAT)	NSP
Greece	2013	1,337	3.0 (2.2 - 4.1)	DT	DTC; LTS; OTH; PHL; PRI; STR	2013	1,309	68.1 (65.5 -70.6)	DT	DTC; LTS; PHL; PRI; OTH STR;
Hungary	2011	664	0.5 (0.1 - 1.3)	SP	DTC, NSP	2011	652	24.1 (20.8 - 27.6)	SP	DTC; NSP
Ireland	2010	200	0.5 (0.0 - 2.8)	SP	PRI	2010	200	41.5 (34.6 - 48.7)	SP	PRI
Italy	-	-	-			2010	743	60.5 (56.8 - 64.0)	DT	DTC
Latvia	2013	562	2.1 (1.1 - 3.7)	DT	DTC	2013	522	70.1 (66.0 - 74.0)	DT	NSP
Malta	-	-	-			2013	109	13.8 (7.9 - 21.7)	DT	ANT; DTC; HTC; OHC; PHL; STI
Norway	-		-			2013	6,342	63.0 (61.8 - 64.2)	SP	DTC
Portugal	2013	399	6.3 (4.1 - 9.1)	DT	DTC	2013	414	84.3 (80.4 - 87.7)	DT	DTC
Slovenia	-	-	-			2009	112	32.1 (23.6 - 41.6)	DT	DTC
United Kingdom	-	-	-			2013	3,144	49.1 (47.4 - 50.9)	SP (UAT)	DTC; LTS; OTH; NSP

Acronyms (study design): DT = diagnostic testing; SP = specific prevalence study (UAT = unlinked anonymous testing)
Acronyms (setting): ANT = Antenatal Clinics; DTC = Drug Treatment Centres; HTC = HIV Testing Centres; LTS - Low Threshold Services; ODD = Overdose Deaths; OHC = Other Hospitals or Clinics; OTH = Other; NSP Needle Exchange Programmes; PHL = Public Health Laboratories; PRI = Prisons; STI = STI clinics STR = Street.

In the absence of larger, more robust studies from which prevalence can be derived, we consider the data reported here are the best available although there may have been more recent estimates published since the date of our search (March 2015). Significant heterogeneity in study design within and between risk groups hamper the statistical comparison and pooling of prevalence across countries and populations. To control for strong sources of bias in studies among people in prison when pooling data, we developed and applied a study quality assessment. The five domains were considered equally important sources of bias and it is possible that estimates included in the analysis have residual selection biases. Further, our study quality assessment did not consider sample size and there is clearly more uncertainty in the estimates derived from smaller studies.

For pragmatic reasons, we extracted prevalence estimates for PWID from the data repository coordinated by EMCDDA. With limited methodological information accompanying the EMCDDA data sets, it is possible that this data set is not exhaustive. However, EMCDDA were recently identified by another wide-ranging systematic review as the source of the most routinely collected, European-level data on the viral hepatitis prevalence among PWID.(18) We adopted an algorithmic approach favouring the most recent national level data to select estimates, and found estimates meeting this criteria for just seven MS for HBsAg and 16 MS for anti-HCV. As with the retrievals from the systematic search, there is considerable eterogeneity in study design (intervention-related and observational), sampling method (single and multi-centre sampling methods) and sample size (from <50 to >6,000 participants) across these 23 estimates. Beyond favouring the geographical and time-frame parameters, we did not systematically assess the quality of these studies and selection biases relating to study setting, population and sample size are likely to exist.

Using 2% prevalence as the endemicity threshold set out in the 2017 WHO HBV and HCV testing guidelines, (58) by comparing risk group prevalence with the general population prevalence (from previously published reviews of the literature (59-64)) and by comparing across risk groups, our findings generally support the continued classification of PWID and people in prison as the key populations for both chronic hepatitis B and C infection. Whilst this study does not seem to support the continued classification of *HIV negative/unknown HIV sero-status* MSM as a high (>2%) prevalence population for chronic hepatitis B infection, we are cautious in this conclusion given the wide confidence interval (that sometimes includes the 2% threshold) around the MSM-derived HBV estimates. We therefore still consider MSM a key population for targeted action, given that anti-HCV prevalence in MSM is higher than in the general population, the evidence of the ongoing transmission of viral hepatitis among MSM populations and the complex interaction of viral hepatitis and HIV. (11, 12) Both infection with, and antiretroviral treatment for, HIV are suspected to increase progression to chronicity as well as to accelerate fibrosis.(11, 12) Global anti-HCV prevalence

among HIV positive MSM has been estimated as high as 6.4% (65), and end-stage liver disease is a leading key cause of death among co-infected HIV positive patients in some high income countries.(66) A cohort study found an unexpectedly high proportion of MSM (23% compared to the 5-10% chronicity rate expected in the general adult population(67)) develop a chronic hepatitis B infection following HBV exposure regardless of HIV status, with a younger (adult) age at infection significantly associated with an increased risk of developing CHB.(68) It would therefore seem an effective use of health resources to (continue to) offer HCV screening to HIV positive men in addition to MSM-wide HBV vaccination.(69) Specific cost-effectiveness analyses of offering individual or combined blood-borne virus screening in MSM would also greatly aid public health decision making and be a useful addition to the evidence.

Differences in the prevalence among people in prison between countries are related to the differential distribution of risk factors among the prison population together with differences in prison conditions, such as the availability of harm reduction interventions and infection control practices and infrastructure across the EU/EEA countries represented in this study.(16) The high prevalence of HBsAg in the prison population in some countries could be attributable to the incarceration of people born in intermediate or high prevalence countries and consequent over-representation of migrants in the incarcerated population. Recent estimates suggest that the proportion of the prison population that is foreign-born ranges from <5% in Bulgaria and Hungary, to more than 15% in France, Germany, Italy, Portugal and Spain, and up to 72% in Luxembourg. (70) It is possible that the incarceration of foreign-born migrants is a driver of the high prevalence of chronic hepatitis B and C infection in prisons although as there is no systematic EU-wide data collection on the demographic profile of the incarcerated population, our understanding of the dynamics of migration, incarceration and chronic infection is limited. (70)

Our study seeks to contribute to the elimination of viral hepatitis in Europe by providing information to support the design and management of primary and secondary prevention strategies. However, expected prevalence is just one of a number of factors that affects the cost-effectiveness of testing strategies. Programme-related factors such as ease of reaching the target population, uptake of screening, actual (viraemic) prevalence, linkage to care and treatment initiation also playing a key role.(9, 10, 13)

We see four key public health implications emerging from our experience in this study. The first is the indication for systematic screening and linkage to care of people in prison given the high prevalence, the overlap with the PWID population, and the possible continuation of risk behaviour. Secondly, we see significant public health benefits of providing treatment as prevention, especially for CHC, among populations that share risk behaviour, in line with

national and international clinical and public health guidelines.(58) Analyses have shown that treatment among high-risk dynamically interactive populations such as PWIDs, is costeffective, especially given the shorter and more tolerable treatment regimens.(8) Thirdly, the need for diagnostic testing and treatment is particularly important for PWID where the prevalence, and therefore risk of intra-population transmission, of hepatitis C is very high.

PWID screening in accessible locations as part of broader harm reduction measures may help break down barriers of stigma and among this vulnerable and high risk population.(16, 71) The criminalisation of drug use has been suggested to be as the single most important determinant of the high blood-borne virus prevalence among people in prison.(16) Finally, the lower prevalence of CHB we found among some risk populations in some countries is likely a direct result of the adoption and implementation of primary prevention measures, especially childhood immunisation, in the general population.(72) This highlights the importance of adequately resourcing primary prevention measures as well as continuing to offer HBV vaccination to risk groups to protect public health.

The limitations of this study also provide ideas for future research, specifically the improvement in the design of studies and greater geographical representation to fill the gaps in evidence. The development and consistent application of an EU/EEA or international standard for the design and quality assessment of seroprevalence studies to inform pooling and/or statistical comparison of data across studies and populations would also greatly improve understanding of prevalence across countries and populations. Finally, and probably most importantly, there is clear and urgent need for more implementation studies to determine the features of screening programmes and strategies among risk populations that effectively reach, diagnose and link to care people infected with chronic viral hepatitis.

CONCLUSION

Our study highlights the heterogeneity in prevalence across risk groups across Europe. Prevalence generally increases in an Eastern and Southern direction. There are also many countries, especially in the Eastern and Southern part of Europe, that are not represented in our results, highlighting the need to build capacity for and resource the development of robust epidemiological studies among key risk groups. Step One of elimination action planning is to know your epidemic, the 'who' and the 'where',(73) and both the evidence and the data gaps contained in this review should contribute to this strategic aim.

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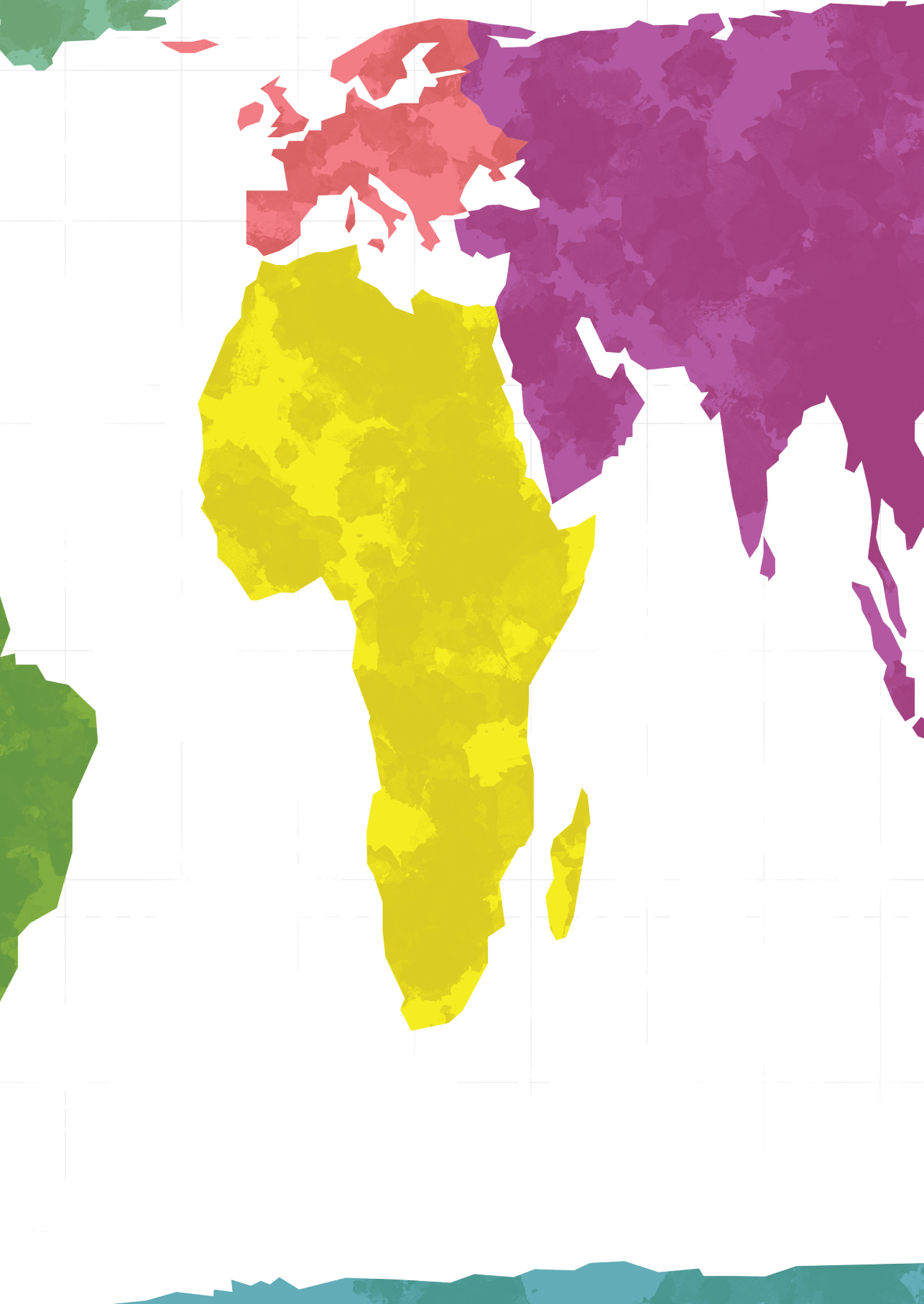

CHAPTER 4

Estimating the scale of chronic hepatitis B infection among migrants from endemic countries in EU/EEA countries

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ABSTRACT

Background: Chronic hepatitis B (CHB) related morbidity and mortality can be reduced through risk group screening, linkage to care and anti-viral treatment. This study estimates the number of CHB cases among foreign-born (migrants) in the European Union and European Economic Area (EU/EEA) countries in order to identify the most affected migrant populations.

Methods: The CHB burden was estimated by combining: demographic data on migrant population size by country of birth in the EU/EEA, extracted from European statistical databases; and CHB prevalence in migrants' countries of birth and in EU/EEA countries, derived from a systematic literature search. The relative contribution of migrants from endemic countries to the total CHB burden in each country was also estimated. The reliability of using country of birth prevalence as a proxy for prevalence among migrants was assessed by comparing it to the prevalence found in studies among migrants in Europe.

Results: An estimated 1–1.9 million CHB-infected migrants from endemic countries (prevalence ≥2%) reside in the EU/ EEA. Migrants from endemic countries comprise 10.3% of the total EU/EEA population but account for 25% (15%–35%) of all CHB cases. Migrants born in China and Romania contribute the largest number of infections, with over 100,000 estimated CHB cases each, followed by migrants from Turkey, Albania and Russia, in descending order, with over 50,000 estimated CHB cases each. The CHB prevalence reported in studies among migrants in EU/EEA countries was lower than the country of birth prevalence in 9 of 14 studies.

Conclusions: Migrants from endemic countries are disproportionately affected by CHB; their contribution however varies between EU/EEA countries. Migrant focused screening strategies would be most effective in countries with a high relative contribution of migrants and a low general population prevalence. In countries with a higher general population prevalence and a lower relative contribution of migrants, screening specific birth cohorts may be a more effective use of scarce resources. Quantifying the number of CHB infections among 50 different migrant groups residing in each of the 31 EU/EEA host countries helps to identify the most affected migrant communities who would benefit from targeted screening and linkage to care.

INTRODUCTION

Migration flows in the first half of the twentieth century were predominantly from Europe towards America. Since the Second World War, economic and geopolitical factors such as decolonisation, labour migration, the collapse of communism, air travel, economic growth and political crisis have changed this and migration to Europe has increased.(1) Much of this migration has been from low- and middle-income countries in Asia and Africa, many of which have a high prevalence of hepatitis B and C.(2, 3) Existing case-based surveillance systems such as the European hepatitis B and C surveillance system managed by the European Centre for Disease Prevention and Control are unable to accurately quantify the number of chronic viral hepatitis cases among migrants on account of different reporting, testing and screening practices among member states. Additional information sources and epidemiologic research are needed to estimate the scale of chronic hepatitis B virus infection in this population.(4)

Hepatitis B virus (HBV) infection primarily affects the liver. It usually has an insidious onset and can remain undetected for many years. Up to 5% of HBV infections in adults (up to 90% in young children) can progress to become chronic and up to 30% of chronic cases may develop liver cirrhosis.(5)

Public health measures, including antenatal screening, childhood HBV vaccination, stringent testing of blood products, improved infection control practices and harm reduction programmes, have led to a significant reduction of viral hepatitis transmission and a decline in the number of acute HBV cases reported in many European Union/European Economic Area (EU/EEA) countries.(6) Limited or more recent implementation of these primary prevention measures explains the high prevalence of viral hepatitis seen in many parts of the world, but especially in South East Asia, Sub-Saharan Africa and Eastern Europe.(7) Vertical transmission from mother to child and nosocomial transmission are considered to be the main routes in intermediate (2–8%) and high (>8%) HBsAg prevalence countries.(5, 7)

Worldwide viral hepatitis related mortality in absolute terms increased by 63% between 1990 and 2013, while the associated disability adjusted life years increased by 34% during this time.(8) This global increase is largely the result of inadequate prevention measures combined with population growth in hepatitis endemic areas.(8) An estimated 13 to 14 million people in the WHO European region are chronically infected with hepatitis B (9, 10) and about 36,000 people die every year as a consequence.(9) In Europe, chronic HBV infection is a major cause of liver cirrhosis and 10–15% of hepatocellular carcinoma (HCC), cases are attributed to chronic hepatitis B (CHB).(10)

Antiviral treatment with nucleot(s)ides such as tenofovir or entecavir can prevent the development of cirrhosis and HCC and can suppress viral replication in a very high proportion of cases.(3) However, because of the largely asymptomatic nature of the infection until late stages, it is estimated that between 40% and 80% of people infected are unaware of their infection and many are not diagnosed until after liver damage has occurred.(10, 11) The population health benefits of effective treatment can only be realised by improving early detection of infection through targeted testing among risk groups.

The WHO recently ratified the strategic goal to eliminate chronic viral hepatitis as a health threat in Europe by 2030. The strategy and action plan published to support countries and the region to achieve this goal highlight 'the who' and 'the where' as the first two strategic pillars of elimination.(12, 13) Whilst it is suspected that a large proportion of migrants to the EU come from hepatitis B (HBsAg) intermediate (2%–8%) and high (>8%) endemicity countries (2, 3), little is known about the epidemiology of CHB among migrants. Specifically lacking are robust estimates of the number of infections among migrants and knowledge about which groups are most affected. Estimates of which migrant groups are most affected and would therefore benefit most from (linguistically/culturally/specifically) targeted screening programmes, early detection and treatment are required if Europe is to achieve this ambitious elimination goal.

The aims of this study are: 1) to estimate the number of CHB cases among the foreign-born population originating from intermediate and high HBV endemicity countries residing in the 31 countries of the EU/EEA; 2) to estimate the relative contribution of migrants to the overall burden of CHB in Europe; and 3) to identify the migrant groups among whom the largest number of cases are found so as to help direct more effective screening programmes. In a sister paper (INFD-D-1700468) (14), we conduct a similar analysis for chronic hepatitis C among migrants from endemic countries.

METHODS

The data retrieval and analysis process are described in detail below and in a schematic representation (Figure 1). To estimate the number of CHB cases among migrants in each EU/EEA country, demographic data on the number of foreign-born migrants by country of birth living, in EU/EEA countries were extracted from statistical databases. Country of birth-specific and EU/EEA countryspecific general population Hepatitis B surface antigen (HBsAg) prevalence estimates were derived from a systematic literature search (Part 1).

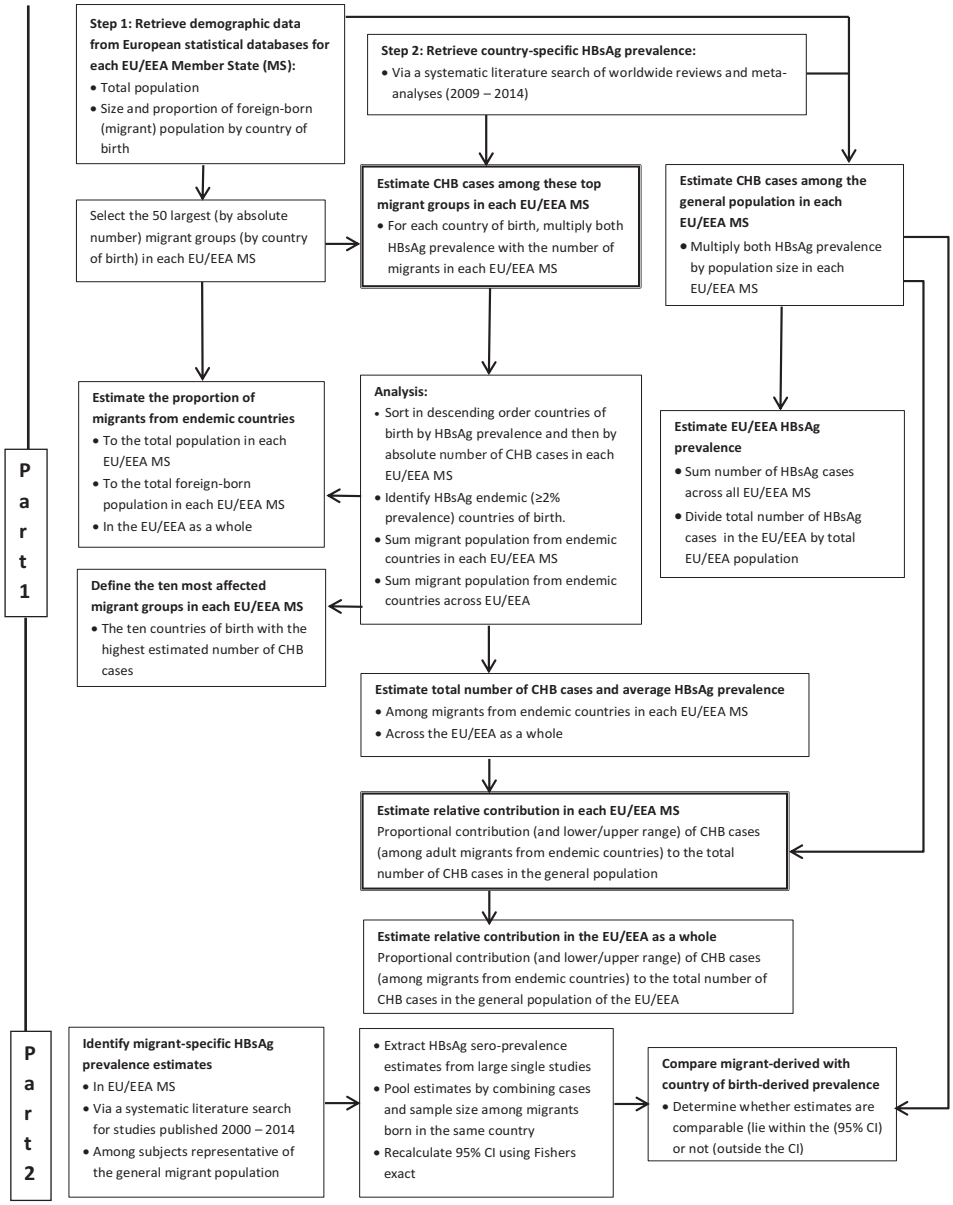

Figure 1. Schematic representation of the methodological process to estimating the burden of chronic hepatitis B among migrants in the EU/EEA

Definitions

Migrant (foreign-born population): includes all persons who were born outside their current country of residence (and listed in the demographic registration databases used in this study). This includes within-EU/EEA migrants, i.e. persons born in another EU/EEA country, as well as those born outside the EU. It does not include undocumented migrants.

Chronic hepatitis B (CHB): refers to a positive hepatitis B surface antigen (HBsAg) test.

Note: According to the WHO and EU (2012) case definition, detection of HBsAg on two occasions at least 6 months apart is classified as CHB. In this study, as in the seroprevalence and screening studies from which prevalence data for this study were extracted, the presence of HBsAg is taken as the standard proxy for chronic infection. The lack of regular screening for HBV and the reduction in incidence of acute HBV infections in most countries justify the assumption that the overwhelming majority of HBsAg positive cases are chronic.

Hepatitis B endemic country: countries with a ≥ 2% HBsAg prevalence in the general population. This follows from the WHO classification of low (<2%), intermediate (2% to 8%) and high (>8%) endemic countries.

To assess the reliability of using country of birth-derived HBsAg prevalence as a proxy for the prevalence among migrants, a systematic literature search was conducted to identify prevalence estimates among migrants in Europe and to compare these with country of birth-derived prevalence (Part 2).

PART 1: THE CONTRIBUTION OF MIGRANTS FROM ENDEMIC COUNTRIES TO THE BURDEN OF CHB IN THE EU/EEA

Demographic data

The size and country of birth of the foreign-born migrant population was obtained for the 31 EU/EEA countries from Eurostat for 2013, if available.(15) Where Eurostat data by country of birth were missing (Croatia, Cyprus, France, Germany, Malta, Portugal and the UK), data from the EU 2011 – Housing and Population Census were used.(16) The most recent demographic data for Greece (2012) and Luxembourg (2010) were only available from the Organisation for Economic Co-operation and Development' (OECD) Stats website. (17) No demographic data were available from the above sources for Lithuania. Data were

thus obtained from the Lithuanian National Statistics Service (2013).(18). The data source is indicated in footnotes in Table 1. For each EU/EEA country, the countries of birth of foreign-born migrants were arranged in descending order of magnitude by the number of migrants. The top 50 countries of birth by size of migrant population were selected for estimating the CHB burden.

Systematic literature search to estimate country- specific HBsAg prevalence

The online databases Medline, Embase, the Cochrane library, Web of Science, Scopus, PubMed publisher and Google Scholar were searched in January 2015 for reviews, systematic reviews and meta-analyses in English about the prevalence of hepatitis B in the general population at national level. The search terms (described in full in Annex 1 of the online supplement) consisted of a combination of disease-related (hepatitis B), outcomerelated (prevalence), population-related (general population, worldwide), and study design-related (reviews) terms. Since the aim was to identify recent reviews, the search was restricted to papers published between 2009 and 2014. The titles and abstracts of retrieved articles were assessed for relevance using exclusion criteria. Key exclusion criteria included studies about hepatitis other than type B; focusing on natural history, clinical features or complications of hepatitis; about medical treatment; focusing on high risk groups e.g. people who inject drugs; and single case studies and cost effectiveness analyses. Full texts of the selected abstracts were retrieved and assessed, decisions to exclude were recorded and a PRISMA flowchart (described in Annex 2 of the online supplement) was prepared.

From included reviews, country-specific HBsAg prevalence estimates and confidence intervals (CI) were extracted into a Microsoft Excel database. Where a country-specific estimate was unavailable, the relevant Global Burden of Disease region estimate was used, if available. If a meta-analysis reported a statistically significant time trend, the estimate from the most recent period was selected. When multiple estimates for a country were available from different reviews, the most robust or relevant review was selected based on the following criteria: sampling method; representativeness of population studied; geographical coverage; sample size; quality of included studies and data collection timeframe. Decisions were made jointly by two reviewers (AF and IV) with the rationale recorded for each decision about a chosen estimate. This rationale, together with the search strategy, the inclusion and exclusion criteria and the PRISMA flowchart are described in annexs 1, 2, 3 and 5 of the online supplement for this article.

Estimating the number of CHB cases among foreign-born migrants from endemic countries in each EU/EEA country

The retrieved HBsAg general population prevalence estimate in the countries of origin were multiplied by the number of migrants from that respective country in each EU/EEA country. The number of migrants born in endemic countries (≥2%) was summed to determine the total and proportional contribution of migrants from intermediate/high hepatitis B endemicity countries to the overall number of migrants residing in the host country. The ten migrant populations originating from intermediate and high endemicity countries with the highest number of HBsAg infected cases in the EU/EEA were determined.

Relative contribution

To estimate the relative contribution of migrants born in endemic countries to the overall number of people infected with CHB in the respective EU host country, the estimated number of infected cases among migrants was divided by the number of infected persons in that country based on the general population prevalence. Given the uncertainty in the size of migrant population and the CHB prevalence estimates in the countries of birth, the range of the relative contribution with a lower and a higher limit was calculated using the Delta method (19).

EU/EEA-level estimates

The population of the EU/EEA was derived by summing up the population of all 31 EU/EEA countries as extracted from demographic sources. To estimate the HBsAg prevalence in the EU/EEA, the number of estimated HBsAg positive cases in all 31 EU/EEA countries was summed up and divided by the total EU/EEA population. To derive the lower and upper prevalence range, the lower and upper estimates of the number of cases across the 31 countries were summed up. To estimate the number of cases among migrants to and within the EU/EEA, the number of cases among migrants from endemic countries (≥2%) across all 31 countries was summed up. This was then divided by the number of cases in the EU/EEA to derive the relative contribution of migrants from endemic countries to the burden of CHB infection in the EU/EEA.

PART 2: SYSTEMATIC LITERATURE SEARCH FOR HBsAg PREVALENCE IN MIGRANT POPULATIONS IN EUROPE

The online databases Medline, Embase, the Cochrane library, Web of Science, Scopus, PubMed publisher and Google Scholar were searched in November 2014 for studies in English that estimate the prevalence of hepatitis B among migrants in any of the 31 EU/EEA countries. The search consisted of a combination of disease-related (hepatitis B), outcome-related (prevalence), population-related (migrants) and geographical area (EU/

EEA countries) terms and was limited to studies published between 2000 and 2014. Only studies about the prevalence in migrants who were considered to be representative of the general migrant population (i.e. not refugees or asylum seekers, hospital patients or other higher risk groups and not lower risk groups like pregnant women or children) were compared with incountry of birth derived prevalence estimates. The full search strategy, inclusion and exclusion criteria and PRISMA flowchart can be found in annexs 3, 4 and 6 of the online supplement.

Country-level HBsAg prevalence estimates among migrants residing in different European countries were extracted from the included studies and entered into Microsoft Excel. Pooled estimates for countries of birth were produced by combining the numbers tested and the number of cases. A 95% CI was re-calculated using the Fisher's exact method. Both pooled and large single study (>25 subjects from a single country of birth) estimates were compared with the in-country estimates extracted in Part 1 to determine whether in-country estimates reflect the prevalence found in migrants. When the point estimate from a study in migrants (Part 2) fell within the CI of the in-country estimate (from Part 1), the estimate was considered to be comparable; when it fell below the lower CI limit, it was considered lower than the in-country prevalence; and when it was higher than the upper CI limit the prevalence in migrants was considered to be higher.

RESULTS

Estimated CHB prevalence and number of infected cases in 31 EU/EEA countries

Chronic hepatitis B (HBsAg) prevalence differs considerably among EU/EEA countries, ranging from 0.1% in Ireland and the Netherlands to 5.5% in Romania. The average prevalence in the general population of the EU/ EEA is estimated at 1.1%, corresponding to an estimated 5.7 million cases (range 4.0 to 7.5 million). These estimates, together with the total number of infected cases, are listed in Table 1. Italy and Romania are the EU/EEA countries with the highest estimated number of CHB cases, both above 1 million.

The distribution of migrants in the EU/EEA based on HBV endemicity in country of birth

The top 50 foreign-born populations in each EU/EEA country included in our analysis make up at least 95% of the total migrant population in 19 of 31 EU/EEA countries and at least 90% in all but three EU/EEA countries (Denmark, Sweden and the UK where it is at least 85%). These migrant populations account for approximately 9.5% of the population in the EU/EEA. The proportion, however, ranges from 0.9% in Romania and 1.3% in Bulgaria to

more than 40% in Luxembourg and 62% in Liechtenstein (Figure 2). Just over half of the EU/EEA migrant population were born in HBV endemic (≥2% prevalence) countries. EU/EEA countries with the highest proportion of migrants from endemic countries among their foreign-born population are Croatia, Estonia and Latvia (>90%), and those with the lowest proportion are Liechtenstein, Luxembourg and Slovakia (<16%) (Figure 2). The foreign-born population and the number and proportion from endemic countries in the EU/EEA and by country are shown in Table 2.

Country-specific HBsAg prevalence estimates

The most comprehensive systematic global review of country-specific prevalence in the general population identified by the systematic literature search was a review by Kowdley et al. published in 2012.(20) This This provided CHB prevalence estimates for 102 countries, based on studies published between 1980 and July 2010 using population-based surveys and studies of groups considered representative of the general population, such as pregnant women, school children, military recruits and healthy controls from cohort studies. Studies in emigrants to the United States, Europe, Australia and elsewhere were also included. Studies in blood donors and in higher risk populations were excluded. The Kowdley et al review used meta-analytic methods to estimate country- and region-specific pooled HBsAg seroprevalence and corresponding 95% CI.(20) Since the Kowdley review did not include a prevalence estimate for the United States, this was taken from the most recent nationally representative survey in 2011.(21) For 11 countries (China, Egypt, Ethiopia, Greece, Italy, Romania, Saudi Arabia, South Korea, Spain, Thailand and Turkey), Kowdley et al (20) reported a statistically significant decrease in prevalence over time and therefore the post-2000 estimate was taken. Estimates from other studies were considered more robust or relevant than this review for 11 countries (Albania, Algeria, Belgium, Cyprus, Finland, Ireland, Libya, Morocco, the Netherlands, Sweden and Tunisia). (9, 11, 22), and the reasons for this are listed in Annex 7 of the online supplement. For the 44 countries and territories where no country estimate was available, the relevant regional estimate calculated by Kowdley et al was used. All country-specific prevalence estimates used can be seen in Annex 8 of the online supplement.

Estimated prevalence and number of CHB infections among migrants

In the EU/EEA overall, between 1 million and 1.9 million migrants born in endemic countries are estimated to have CHB infection, which corresponds to an estimated prevalence of 5.5%. The estimated cumulative number and range of CHB cases among the top 50 migrant populations from intermediate and high endemicity countries in each EU/EEA country is listed in Table 2. The average HBsAg prevalence among migrants from intermediate and high endemicity countries is also available for each EU/EEA country, and ranges from 3% in Estonia, Latvia, Lithuania and Poland to 9% in Portugal.

Table 1. Chronic hepatitis B prevalence and the estimated number of infected cases in the general population of 31 EU/EEA countries

Country	Total Population	HBsAg prevalence			Estimated no. of CHB cases		
		%	Low 95% CI	High 95% CI	Central estimate	Lower estimate	Upper estimate
Austria	8,451,149	0.55	0.34	0.71	46,481	28,734	60,003
Belgium	11,161,642	0.7	0.4	1.2	78,131	44,647	133,940
Bulgaria	7,284,552	4.25	2.80	5.70	309,593	203,967	415,219
Croatia	4,284,889[#]	1.47	0.84	2.10	62,988	35,993	89,983
Cyprus	840,407[#]	0.9	0.3	2	7,564	2,521	16,808
Czech Republic	10,516,125	0.70	0.43	0.98	73,613	45,219	103,058
Denmark	5,602,628	0.55	0.34	0.71	30,814	19,049	39,779
Estonia	1,320,174	0.58	0.42	0.74	7,657	5,545	9,769
Finland	5,426,674	0.2	0.1	0.4	10,853	5,427	21,707
France	64,932,339[#]	0.68	0.44	1.05	441,540	285,702	681,790
Germany	80,219,695[#]	0.6	0.4	0.8	481,318	320,879	641,758
Greece	11,090,000[Δ]	2.33	1.54	3.11	258,397	170,786	344,899
Hungary	9,908,798	1.08	0.04	2.11	107,015	3,964	209,076
Iceland	321,857	0.55	0.34	0.71	1,770	1,094	2,285
Ireland	4,591,087	0.1	0	0.3	4,591	0	13,773
Italy	59,685,227	1.89	1.26	2.52	1,128,051	752,034	1,504,068
Latvia	2,023,825	1.39	1.10	1.67	28,131	22,262	33,798
Liechtenstein	36,838	0.55	0.34	0.71	203	125	262
Lithuania	2,971,905 [μ]	2.03	1.37	2.69	60,330	40,715	79,944
Luxembourg	506,953[∞]	0.55	0.34	0.71	2,788	1,724	3,599
Malta	417,432	0.55	0.34	0.71	2,296	1,419	2,964
Netherlands	16,779,575	0.1	0	0.2	16,780	0	33,559
Norway	5,049,223	0.55	0.34	0.71	27,771	17,167	35,849
Poland	38,533,299	1.44	1.16	1.72	554,880	446,986	662,773
Portugal	10,562,178[#]	1.35	0.66	2.04	142,589	69,710	215,468
Romania	20,020,074	5.49	5.24	5.73	1,099,102	1,049,052	1,147,150
Slovakia	5,410,836	0.70	0.43	0.98	37,876	23,267	53,026
Slovenia	2,058,821	3.29	2.33	4.24	67,735	47,971	87,294
Spain	46,727,890	0.66	0.34	0.97	308,404	158,875	453,261
Sweden	9,555,893	0.2	0.1	0.4	19,112	9,556	38,224
United Kingdom	63,182,180[#]	0.54	0.30	0.60	341,184	189,547	379,093
EU/EEA[β]	509,474,165	1.12	0.79[β]	1.47[β]	5,705,260	4,003,937	7,514,179

*Source is EUROSTAT 2013 unless indicated by the following symbol: [#]ESS 2011 Census; [Δ]OECD 2012; [∞]OECDC 2010; [μ]http:/// www.euras.lt (Lithuanian National Statistics Agency); β For the 31 EU/EEA countries the cumulative HBsAg prevalence and the upper and lower CI were estimated from the sum of the estimated number of CHB cases (central, lower and upper estimate), hence these should be considered as upper and lower prevalence ranges and not CI.

Table 2. Total size and proportion of foreign-born migrant population (from endemic countries) in EU/EEA host countries; estimated number and range of CHB cases among migrants; estimated relative contribution to the total number of cases in the EU/EEA host country

Country	Population of foreign-born migrants			Estimated number of CHB cases (from endemic countries)			Average CHB prevalence among migrants from endemic countries	Estimated relative contribution migrants to the total number of CHB cases in the host country
	Number from top 50 countries	Number from HBV endemic countries	Proportion from HBV endemic countries	Central estimate	Lower estimate	Upper estimate		
Austria	1,298,945	768,773	9.1%	33,456	25,757	41,040	4.4%	72%
Belgium	1,596,848	622,206	5.6%	42,530	32,218	54,309	6.8%	54%
Bulgaria	90,990	62,755	0.9%	2,436	1,860	3,039	3.9%	1%
Croatia	582,271	523,470	12.2%	18,673	11,966	25,376	3.6%	30%
Cyprus	190,568	139,689	16.6%	6,770	5,141	8,445	4.8%	90%
Czech Republic	374,296	234,291	2.2%	12,185	9,637	14,752	5.2%	17%
Denmark	484,139	224,384	4.0%	12,352	9,605	15,152	5.5%	40%
Estonia	197,744	184,642	14.0%	5,432	3,822	7,038	2.9%	71%
Finland	257,044	141,953	2.6%	8,136	6,206	10,067	5.7%	75%
France	6,775,948	3,591,002	5.5%	212,538	131,238	380,923	5.9%	48%
Germany	10,426,860	5,398,700	6.7%	234,792	180,867	288,066	4.3%	49%
Greece	713,471	615,986	5.6%	43,163	36,636	49,346	7.0%	17%
Hungary	411,403	302,781	3.1%	15,286	13,649	16,940	5.0%	14%
Iceland	32,910	7,857	2.4%	421	349	494	5.4%	24%
Ireland	687,462	205,071	4.5%	13,196	10,935	15,574	6.4%	>100%
Italy	5,319,754	3,443,409	5.8%	213,063	174,632	251,539	6.2%	19%
Latvia	278,243	267,617	13.2%	7,866	5,269	10,454	2.9%	28%
Liechtenstein	22,806	2,140	5.8%	97	74	119	4.5%	48%
Lithuania	139,712	121,992	4.1%	3,765	2,469	5,057	3.1%	6%
Luxembourg	189,858	28,085	5.5%	1,450	913	2,019	5.2%	52%
Malta	33,301	9,629	2.3%	637	429	860	6.6%	28%
Netherlands	1,772,756	1,052,695	6.3%	56,650	40,335	73,016	5.4%	>100%
Norway	597,316	277,047	5.5%	17,021	12,125	21,979	6.1%	61%
Poland	659,657	438,446	1.1%	11,679	7,018	16,342	2.7%	2%
Portugal	854,830	475,155	4.5%	42,688	29,595	55,795	9.0%	30%
Romania	166,973	103,740	0.5%	7,531	5,453	9,581	7.3%	1%
Slovakia	155,346	25,170	0.5%	1,073	846	1,301	4.3%	3%
Slovenia	231,276	160,220	7.8%	5,713	3,756	7,663	3.6%	8%
Spain	5,930,170	1,909,343	4.1%	118,316	92,282	148,318	6.2%	38%
Sweden	1,304,130	596,303	6.2%	33,850	23,728	44,011	5.7%	>100%
UK	6,845,805	3,976,870	6.3%	244,409	195,342	294,417	6.1%	72%
EU/EEA	**48,622,832**	**25.911.421**	**5.1%**	**1,427,174**	**1,074,152**	**1,873,032**	**5.5%**	**25%**

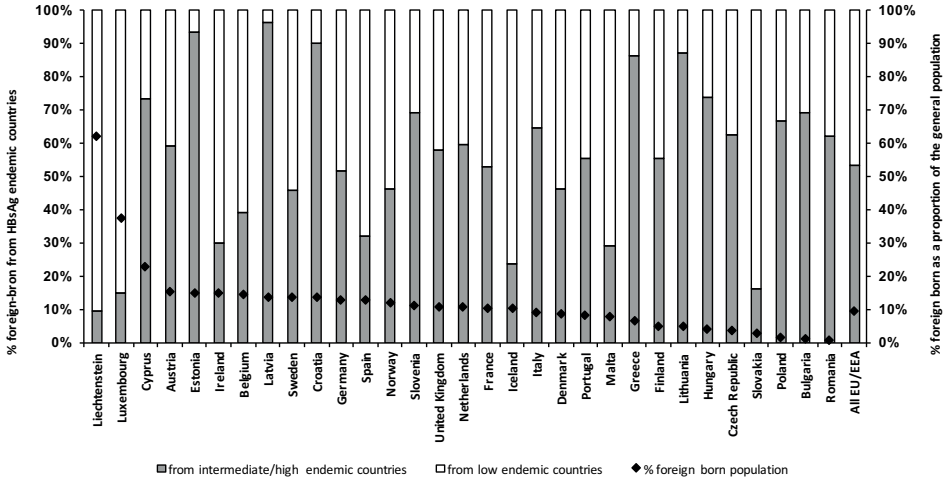

Figure 2. Total (%) of foreign born migrant population in each EU/EEA country and the proportion (of all migrants) originating from HBsAg endemic countries (≥2%)

Migrants originating from China and Romania contribute the largest number of infections, with over 100,000 CHB cases each, followed by migrants from Turkey, Albania and Russia, in descending order, with over 50,000 CHB cases each. Table 3 lists the ten migrant populations with the highest estimated number of CHB cases, adding up to over 680,000 cases and corresponding to 48% of CHB cases among migrants from endemic countries in the EU/EEA. Table 3 lists the EU host countries with the largest populations of migrants born in these countries. Estimates for the 50 migrant groups in each EU/EEA country can be found in Annex 9 of the online supplement.

Migrants from China, Romania and Russia are among the top ten migrant populations with the highest estimated number of CHB cases in 28, 19 and 18 respectively of the 31 EU/EEA countries as listed in Table 4. At least three of the ten migrant populations most affected by CHB in the Czech Republic, Denmark, Finland, Hungary, Iceland, Liechtenstein, Norway, the Netherlands and Sweden were born in South-East or East Asian countries including China, Vietnam, the Philippines and Thailand. People born in Yugoslavia before 1992 or in one of the former Yugoslav Republics since 1992 are represented among three or more of the top ten migrant populations with the highest number of infected cases in Austria, Liechtenstein and Luxembourg as well as in Croatia and Slovenia. Similarly, people born in the Soviet Union before 1991 or in one of the former Soviet Republics since 1991 are represented among three or more of the top ten migrant populations most affected by CHB in Bulgaria, Cyprus, the Czech Republic, Germany, Hungary, Poland, Romania and Slovenia as well as in the Baltic states of Estonia, Latvia and Lithuania (see Annex 9 of the online supplement).

Table 3. The ten migrant groups (from HBsAg endemic countries) with the highest estimated number of CHB cases (rounded) and the main host EU/EEA countries

Migrant country of origin	Total migrant population in Europe	HBsAg prevalence	Cumulative number of CHB cases	Host countries (first 6 with largest populations)*
Romania	2,817,458	5.5	154,679	Italy, Spain, Germany, Hungary, UK, Austria
China	1,012,550	10.2	103,585	UK, Italy, Spain, France, Germany, Netherlands
Turkey	2,266,977	4.3	97,255	Germany, France, Netherlands, Austria, Belgium, UK
Albania	804,570	9.0	72,412	Italy, Greece, Belgium, Austria, Bulgaria
Russia	1,810,197	2.9	52,315	Germany, Latvia, Estonia, Italy, Spain, Lithuania
Vietnam	365,048	12.5	45,557	France, Germany, Czech Republic, UK, Sweden, Norway
Nigeria	336,155	13.3	44,741	UK, Italy, Spain, Ireland, Netherlands, Austria
Kazakhstan	828,526	5.0	41,013	Germany, Latvia, Czech Republic, Poland, Lithuania, Estonia
Algeria	1,482,465	2.6	38544	France, Spain, Belgium, Italy, Ireland
India	1,120,352	3.2	36.188	UK, Italy, Germany, France, Spain, Ireland
Total			**686,289§**	

* if migrant population is at least 1,000; § The sum of CHB cases among the ten migrant groups with the largest number of CHB cases (686,289) corresponds to 48% of the total number of CHB cases among migrants from endemic countries (1,427,174)

Table 4. Countries of birth of foreign-born migrants found amongst the ten migrant groups most affected by chronic hepatitis B in 10 or more of the 31 EU/EEA countries*

Migrant country of birth	Number of EU/EEA countries (of 31)	EU/EEA Countries
China	28	AUT, BEL, BLG, HR, CZ, DK, DE, FIN, FR, EE, HU, IRL, ISL, IT, LIE, LT, LUX, MT, NL, NO, PL, PT, RO, SK, SI, ES, SE, UK
Romania	19	AUT, BEL, BLG, HR, CY, CZ, DK, DE, GRC, HU, IRL, ISL, IT, LUX, MT, PL, PT, SK, ES,
Russia	18	AT, BLG, HR, CY, CZ, DE, FIN, EE, GRC, HU, ISL, LT, LV, MT, PL, RO, SK, SI
Ukraine	14	BLG, HR, CZ, DE, EE, HU, IT, LT, LV, PL, PT, RO, SK, SI
Vietnam	14	BLG, CY, CZ, DK, DE, FIN, FR, HU, ISL, NL, NO, PL, SK, SE
Turkey	12	AUT, BEL, BLG, DK, DE, FIN, FR, GRC, LIE, NL, RO, SE
Moldova	11	BLG, CY, CZ, EE, IRL, IT, LT, LV, PT, RO, SI
Philippines	11	AUT, CY, DK, GRC, IRL, ISL, IT, MT, NO, ES, UK
Afghanistan	10	AUT, BEL, DK, DE, FIN, HU, NL, NO, SK, SE
Bosnia and Herzegovina	10	AUT, HR, DK, DE, LIE, LUX, NO, PL, SI, SE

*selected from the ten largest CHB affected migrant groups from intermediate/high endemicity countries in the EU/EEA countries

In the UK, migrants from India, Pakistan and Bangladesh are among the top ten migrant populations with the highest number of infected cases. Migrants from Maghreb countries such as Algeria and Tunisia are represented in the top ten in France. Across the EU/ EEA, African countries of origin that contribute a large number of estimated cases include Eritrea, Ghana, Nigeria, Senegal, Somalia and South Africa. In Belgium, France, Luxembourg, Malta, Portugal and the UK, four or more of the ten migrant populations most affected by CHB are from African countries.

Relative contribution of migrants from endemic countries to the overall CHB burden in EU/EEA countries

The relative proportion of infected migrants from endemic countries among the overall number of CHB cases in EU/EEA countries is shown in Table 2 and Figure 3. Migrants from intermediate and high endemicity countries contribute more than 90% and, in some instances, up to 100% of the total estimated number of CHB cases in Cyprus, Ireland, the Netherlands and Sweden. Conversely, in Bulgaria, Poland, Romania and Slovakia, migrants contribute less than 4% of the total.

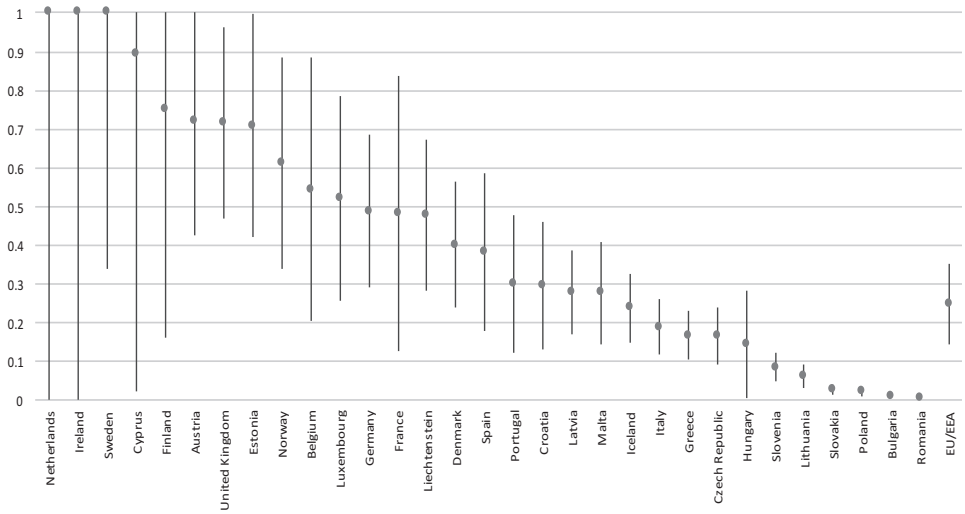

Figure 3. Relative contribution of migrants to the total number of CHB cases per EU/EEA country

Table 5. HBsAg prevalence derived from studies among general migrant populations resident in Europe compared to in-country prevalence estimates derived from worldwide systematic reviews

Country	Migrants				In-country of birth			Comparison
	N tested	Prevalence	95% CI	Reference	Prevalence	95% CI	Reference	
Afghanistan	293	2.1	0.8 – 4.4	26	10.5	5.9 – 15.1	14	Lower
Albania	504[β]	11.7	9.0 – 14.8	34	9.0	8.1 – 9.8	1	Higher
Bangladesh	934	1.3	0.7 – 2.2	(29,30)	4.8	4.0 – 5.6	14	Lower
China[Δ]	1319	9.4	7.9 – 11.1	(30,33)	10.2[α]	9.4 – 11.2	14	Comparable
Dutch Antilles	38	2.6	0.1 – 13.8	27	4.5[*]	2.5 – 6.6	14	Comparable
Egypt	465	1.1	0.4 – 2.5	37	4.2[α]	1.9 – 6.5	14	Lower
Former USSR	675	4.7	3.3 – 6.6	(26, 35)	3.8	2.7 – 4.9	14	Comparable
India	1334	0.1	0 – 0.4	29, 31	3.2	2.9 – 3.6	14	Lower
Iran	153	0.7	0.1 – 2.5	26	3.1	2.7 – 3.5	14	Lower
Iraq	290	0.7	0 – 3.6	26	1.3	0 – 2.9	14	Comparable
Morocco	305	0.3	0 – 1.8	(27, 28)	1.8	1.5 – 5.9	14,16	Lower
Pakistan	3786	1.6	1.2 – 2.1	(29, 30, 31, 32)	4.2	3.6 – 4.8	14	Lower
Somalia	317	7.3	4.6 – 10.7	36	12.4	8.9 – 15.9	14	Lower
Suriname	56	0	0 – 6.4	27	4.5[*]	2.5 – 6.6	14	Lower
Turkey	902	3.7	2.5 – 5.1	(26, 27, 28)	4.3[α]	3.7 – 4.9	14	Comparable
Vietnam	149	10.7	6.3 – 16.9	(30, 26)	12.5	11.5 – 13.5	14	Lower

Notes: [β] age range of participants 10 – 23 years; [Δ] including Hong Kong [α] statistically significant decline over time reported therefore the latest estimate (from year 2000 onwards) selected; [*] regional estimate for Caribbean only

Comparing migrant-derived HBsAg prevalence with country of origin estimates

Sixteen HBsAg prevalence studies in migrants residing in Europe were identified from the literature search for comparison with the in-country estimates derived in Part 1 (Table 5). Prevalence figures for migrants from Suriname and the Dutch Antilles could only be compared with a regional estimate, since in-country data were not available from the review studies in Part 1.

In nine of the remaining 14 studies in migrants, HBsAg prevalence figures were lower than the derived in-country estimate. Prevalence among migrants was comparable with the in-country or region estimate for four migrant populations. HBsAg prevalence among migrants from Albania was higher than the in-country estimate.

DISCUSSION

The number of CHB cases in the general population of the 31 EU/EEA countries is estimated at between 4 million and 7.5 million cases, with a disproportionately high number of these cases found among migrants. Although migrants from endemic countries make up only one in 20 EU/EEA citizens, they account for one in four of all CHB infections. Migrants from ten countries account for 48% of all CHB cases among migrants in the EU/EEA.

The data suggest that the relative contribution of migrants to the overall CHB burden is higher in Western and Northern European countries than in Southern and Eastern European countries. The relative contribution of migrants to the overall burden of CHB is lowest (<4%) in EU/EEA countries with a higher HBsAg prevalence and a lower proportion of migrants such as Romania, Bulgaria, Slovakia and Poland. Conversely, the relative contribution is very high (>100%) in EU/EEA countries with a very low HBsAg prevalence such as Ireland, the Netherlands and Sweden. The estimate of over 100% is a result of the prevalence in the general population of the host country likely to be underestimated (because migrants and other higher risk, harder to reach populations are underrepresented in the samples used to determine this prevalence) or because the prevalence in countries of birth of migrants is an over-estimation of the actual prevalence among migrants.

To assess whether the country of birth prevalence estimates used are over-estimates, we compared these estimates to the prevalence reported in migrant studies in Europe and found evidence indicating an overestimation. Based on the epidemiologic features of HBV, the lower than in-country prevalence among migrants from 9 of 14 countries was surprising, since the infection is often acquired at birth or in early childhood in countries where

HBV is endemic. One explanation could be an age or cohort effect, since the estimates of in-country prevalence include older data from the 1980s and 1990s, while most of the migrant studies in Europe used for comparison were conducted after 2000. A recent study estimating hepatitis B prevalence by region showed a decrease in most regions between 1990 and 2005.(6) This decrease is largely explained by the widespread introduction of antenatal HBV screening together with risk group and infant HBV vaccination programmes (23) and the resulting decline in incidence. The healthy migrant effect, the hypothesis that migrants are often younger and healthier than the general population in their countries of birth, may also be a factor.(24) Study design should also be considered. The figures for prevalence among migrants living in EU/EEA countries tend to be based on data from small-scale, local studies that mostly use convenience sampling, such as screening studies (Table 5). These may under-estimate the true prevalence because people who have already been diagnosed may not participate. Nevertheless, although prevalence among migrants from intermediate and high endemicity countries may not be as high as in the country of birth, the evidence strongly suggests that it is still considerably higher than among the host population in EU/EEA countries and high enough for screening of affected migrant groups to be cost-effective.(11, 25)

This study seeks to inform national screening efforts. The results suggests that an approach focused solely on migrants would have limited impact in most Eastern European countries, specifically Bulgaria, Lithuania, Poland, Romania, Slovakia and Slovenia, where the relative contribution of migrants to the overall national burden of CHB is low (between 1% and 8%) and the proportion of migrants from endemic countries is also low (<5%). In addition, Bulgaria, Lithuania, Romania and Slovenia are HBV-endemic countries with an HBsAg prevalence of >2.0% to 5.5%. A more effective approach would be to screen sub-groups of the general population, i.e. birth cohorts born before antenatal screening, childhood HBV vaccination and the regular screening of blood/blood products were introduced. Screening individuals potentially exposed to HBV through transfusions, transplants and dental or surgical procedures may also help to identify cases.

In contrast, targeted migrant screening approaches would be of value in countries such as Austria, Cyprus, Estonia, Finland, Ireland, the Netherlands, Sweden and UK, where more than 70% of CHB cases are estimated to be among migrants from endemic countries. To optimise cost-effectiveness, screening should target those migrant populations that are most at risk of chronic viral hepatitis infection where the likelihood of detecting cases is higher.

Screening and subsequent contact tracing increases the diagnosis rate and, together with effective linkage to and retention in care and antiviral treatment, are the key to effective secondary prevention. The asymptomatic nature of the disease until its late stages and

the lack of awareness of risk among migrants and often also among health care providers limit early detection. Other barriers to screening include language, health care access and entitlement issues, high work-load among health care staff, and the potential stigma or fear associated with being diagnosed positive.(26, 27) The EU-funded HEPscreen project describes four different screening approaches: (i) outreach screening (e.g. through awareness raising and screening sessions in communities or workplaces); (ii) extension of existing screening programmes (e.g. expanding tuberculosis screening to include other diseases); (iii) opportunistic screening (e.g. offering viral hepatitis screening when patients attend for other health care services); and (iv) invitation-based screening (e.g. using municipal or general practice patient registers). Summaries of screening studies conducted using these different methods, practical guides on how to implement different screening approaches among migrants and resource and logistical considerations are available on the website http://www.hepscreen.eu/ and present a useful resource for public health practitioners.(28)

Undocumented migrants are also an important and vulnerable group. Lack of robust demographic data and the diversity in size and country of birth of undocumented migrants (29) hinder effective planning, resourcing and evaluation of screening interventions for this population. In addition, undocumented migrants face specific access and entitlement challenges when accessing public health services. Promoting voluntary screening for this vulnerable group would have public health benefits, but would require national policies that allow undocumented migrants to receive treatment without adverse consequences.

The systematic approach to estimation of the burden of CHB among migrant populations in the EU/EEA overall and in each of the 31 EU/EEA countries is a strength of this study. The data that underpin these estimates are derived from a common demographic data source (Eurostat 2013) for most countries and from published meta-analytic studies. A potential limitation is that, for some countries, demographic data from earlier years and other sources had to be used. In addition, there are differences in population registration and reporting systems between EU/EEA countries. However, using data from 2013 or earlier has the advantage of limiting the effect of reporting delays with respect to accurate numbers of migrants and their countries of birth.

Using country of birth prevalence data to estimate the CHB burden among migrants may have resulted in a degree of over-estimation for some countries, because of differences in the age structure, risk profile and socioeconomic status between different migrant groups. Migrants sharing the same country of birth but residing in different EU/EEA countries may also differ in terms of risk profile as a result of differences in host country pull factors and reasons for migration. Data allowing a comparison of prevalence figures between the general population in the migrants' countries of birth and from studies among migrants in

Europe were however only available for 14 countries. An additional strength of this study is that, even if the absolute number of estimated CHB cases lies closer to the lower estimate, it identifies which migrant populations would benefit most from targeted screening programs and linkage to care.

CONCLUSIONS

Today, anti-viral treatments for CHB can benefit most patients, offering the prospect of significant public health gains through secondary prevention. Expanded access to screening, linkage to care and treatment, together with the continued implementation of existing primary prevention measures such as vaccinaiton and antenatal screening, are the cornerstones of eliminating viral hepatitis as a global public health threat in the next few decades.

This study confirms that migrant populations are a key risk group for CHB in specific EU/EEA countries. It details the number of CHB cases among migrants by country of birth in each EU/EEA country, identifies the migrant populations that would benefit most from screening and treatment, and highlights which EU/EEA countries would benefit from a migrant-targeted screening approach. The findings in this study about which migrant groups are at highest risk is also useful for developing linguistically-specific and culturally-sensitive screening programmes and raising awareness among physicians so that they offer screening. Efficient and innovative public health approaches to increase access to screening and to screen high-risk populations are needed. Experience from a migrant-specific screening project conducted at the EU/EEA level (28) can help to inform the design of screening programmes that can successfully reach migrant communities. Planners and practitioners can also use the results presented here and those from the HEPscreen project to develop evidencebased screening interventions that target the most affected migrant populations.

Further research is required to inform the development and assessment of effective and cost-effective screening interventions and long-term patient follow up, as well as to improve linkage to and retention in treatment and care among hard to reach risk populations, if we are to realise the vision of a world free of viral hepatitis.

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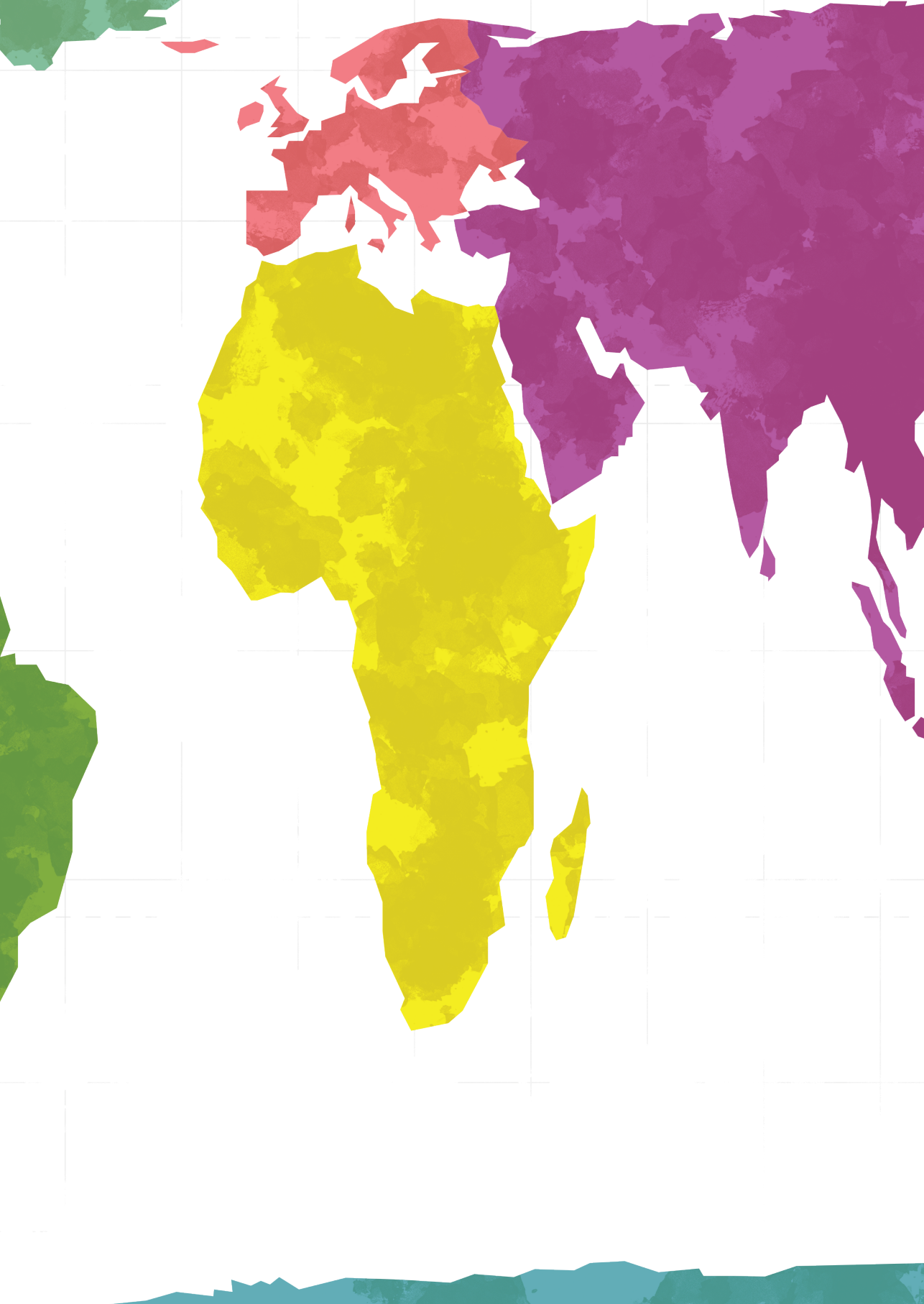

CHAPTER 5

Estimating the scale of chronic hepatitis C virus infection in the EU/EEA: a focus on migrants from anti-HCV endemic countries

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ABSTRACT

Background/aims: Increasing the proportion diagnosed with and on treatment for chronic hepatitis C (CHC) is key to the elimination of hepatitis C in Europe. This study contributes to secondary prevention planning in the European Union/European Economic Area (EU/EEA) by estimating the number of CHC (anti-HCV positive and viraemic) cases among migrants living in the EU/EEA and born in endemic countries, defining the most affected migrant populations, and assessing whether country of birth prevalence is a reliable proxy for migrant prevalence.

Methods: Migrant country of birth and population size extracted from statistical databases and anti-HCV prevalence in countries of birth and in EU/EEA countries derived from a systematic literature search were used to estimate caseload among and most affected migrants. Reliability of country of birth prevalence as a proxy for migrant prevalence was assessed via a systematic literature search.

Results: Approximately 11% of the EU/EEA adult population is foreign-born, 79% of whom were born in endemic (anti-HCV prevalence ≥1%) countries. Anti-HCV/CHC prevalence in migrants from endemic countries residing in the EU/EEA is estimated at 2.3%/1.6%, corresponding to ~580,000 CHC infections or 14% of the CHC disease burden in the EU/EEA.

The highest number of cases is found among migrants from Romania and Russia (50-60,000 cases each) and migrants from Italy, Morocco, Pakistan, Poland and Ukraine (25-35,000 cases each). Ten studies reporting prevalence in migrants in Europe were identified; in seven of these estimates, prevalence was comparable with the country of birth prevalence and in three estimates it was lower.

Discussion: Migrants are disproportionately affected by CHC, account for a considerable number of CHC infections in EU/EEA countries, and are an important population for targeted case finding and treatment. Limited data suggest that country of birth prevalence can be used as a proxy for the prevalence in migrants.

BACKGROUND

Chronic infection with the hepatitis C virus (HCV) is a global public health challenge and a leading cause of liver disease-related morbidity and mortality. The epidemiology remains poorly understood, however, and global, national and risk group-specific anti-HCV and viraemic prevalence estimates vary considerably. Recent studies suggest that between 105 million and 185 million people are anti-HCV positive worldwide and that global anti-HCV prevalence in adults could be as high as 2%.(1, 2) The Global Burden of Disease study estimated that chronic HCV (CHC) infection causes almost half a million deaths annually and is the 25th leading cause of death worldwide.(3)

Chronic HCV infection affects the liver and has a mostly asymptomatic onset, but can lead to cirrhosis and hepatocellular carcinoma (HCC) decades later.(4) The asymptomatic nature of infection and the lack of adequate screening programmes means that the majority of people infected with CHC are unaware of their infection and only around one third of all estimated CHC infections in Europe have been diagnosed.(5-7) Effective antiviral treatment can prevent the development of cirrhosis and HCC and, with newer direct acting antivirals (DAAs) reporting cure rates in more than 90% of cases, (8) the elimination of HCV infection is now possible in Europe.(9) This will require continued primary prevention of new infections in parallel with expansion of secondary prevention through effective screening, linkage to care and treatment.

Primary prevention measures in Europe, including a safe blood supply, improved infection control practices and harm reduction programmes, have led to a significant reduction of HCV transmission in many countries and a mathematical modelling study shows incident cases are declining.(10) Incident data is not systematically collected and reported in most EU/EEEA countries hampering a good understanding of time trends although iatrogenic and nosocomial transmission is reported to be rare in most EU/EEA countries.(11) However, models predict that the peak in the mortality is yet to be reached.(9, 10, 12) An estimated 7.4 million people are anti-HCV positive in the European Union/European Economic area (EU/EEA), although prevalence varies from 0.9% in Western Europe to 3.3% in Eastern Europe.(1, 13) Deaths from viral hepatitis now exceed those from HIV and tuberculosis combined and latest published estimates show that 96,000 people die each year in EU/EEA countries from HBV and HCV-related liver disease.(3) Some populations are disproportionately affected and have a high prevalence of chronic infection. One such population is migrants born in high anti-HCV prevalence countries (10, 14-16), although estimates of the number of cases and the most affected migrant populations in Europe are lacking. This epidemiological study seeks to inform targeted screening, linkage to care and treatment in the EU/EEA by: providing estimates, across and within all 31 EU/EEA countries, of the number of CHC cases

among migrants from countries where anti-HCV prevalence is ≥1%; providing an estimate of the relative contribution of migrants to the overall burden of disease; and comparing the reported in-country of birth prevalence with that found among migrants living in European countries. In a sister paper to this, we conduct a similar analysis for chronic hepatitis B among migrants from endemic countries.

METHODS

The data retrieval and analysis process are described in detail below and in a schematic representation (Figure 1). Demographic data on the size of and countries of birth of migrant populations were extracted from statistical databases. Country of birth-specific and EU/EEA country general population anti-HCV prevalence estimates were derived from a systematic literature search. To assess the reliability of using country of birth-derived prevalence as a proxy for the prevalence among migrants, a systematic literature search was conducted to identify prevalence estimates among migrants in Europe to compare with country of birth-derived prevalence.

Definitions

Migrant: an adult 15 years old or above, born in a country other than the current country of residence. Children are excluded due to the dominance of older age populations in sero-prevalence studies and the higher prevalence reported among adults than among children. (1) The use of the term 'migrant' in this study therefore refers to adult (foreign-born) migrants only. The study accounts for and includes migration from outside the EU/EEA and migration within the EU/EEA, but excludes undocumented migrants.

Anti-HCV prevalence: the common measure of exposure to HCV/endemicity used in seroprevalence studies. Anti-HCV prevalence can include exposed individuals with a resolved infection.

Chronic hepatitis C (CHC): refers to viraemic infection, i.e. anti-HCV and HCV-RNA positivity.

Endemic country: the anti-HCV prevalence in the general adult population is ≥1%. This relatively low threshold was chosen to take into account migrants from countries where prevalence is higher than that of the EU/EEA as a whole.

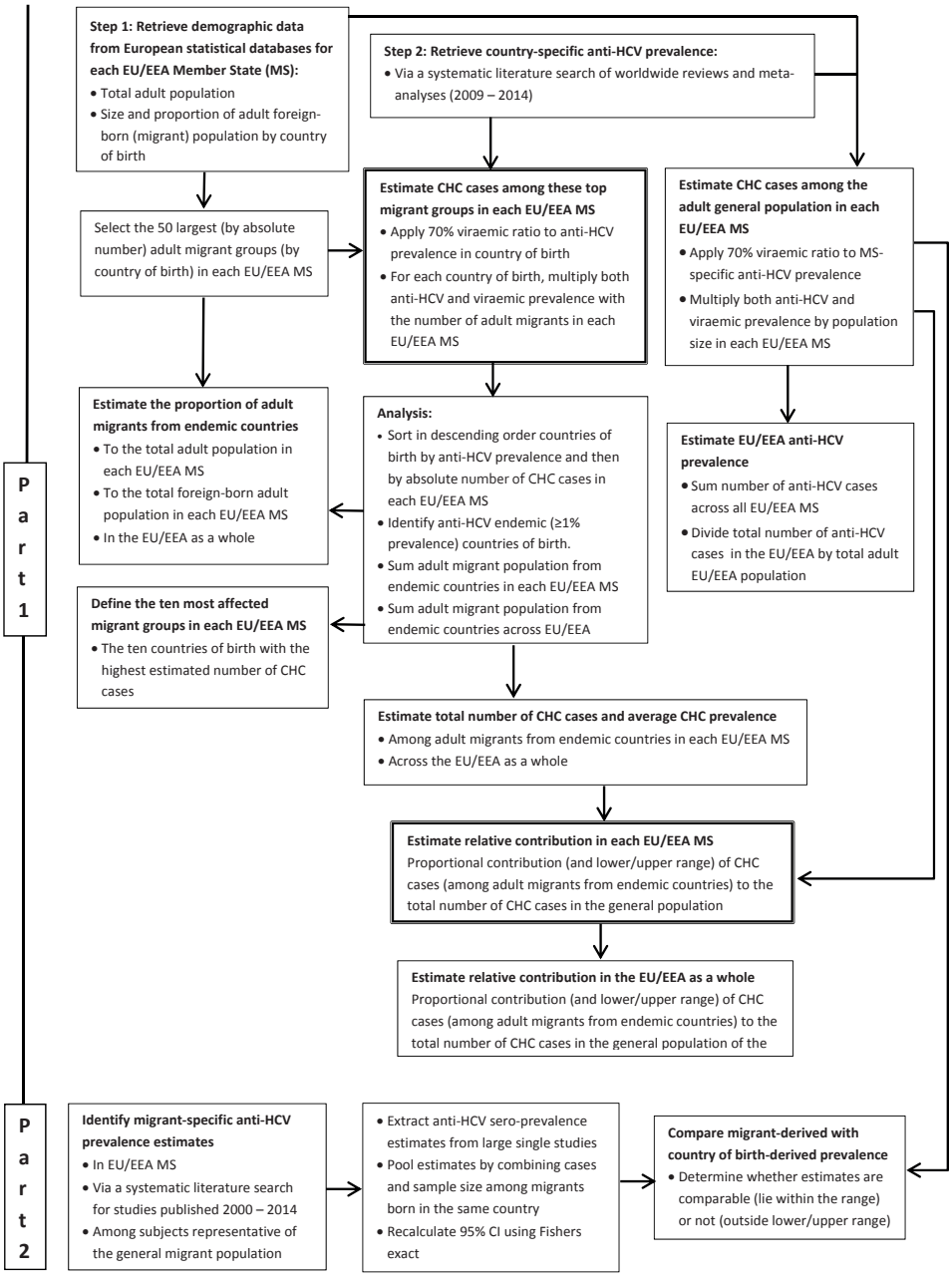

Figure 1. Schematic representation of the methodological process to estimating the burden of chronic hepatitis B among (adult (>15 years) migrants in the EU/EEA

PART 1: THE CONTRIBUTION OF MIGRANTS FROM ENDEMIC COUNTRIES TO THE BURDEN OF CHC IN THE EU/EEA

Demographic data (Step 1)

The size and country of birth of the migrant population was obtained for all 31 EU/EEA countries from Eurostat for 2013, if available (17). Where data were unavailable, either the 'EU 2011 – Housing and Population Census', the most recent demographic data from the Organisation for Economic Co-operation and Development (OECD) Stats website or national statistics were used, in that order.(18-20) The data source is indicated in footnotes in Table 1. For each EU/EEA country, the countries of birth of migrants were sorted into descending order of magnitude of the number of migrants, and the top 50 countries of birth by migrant population size were then selected for estimating the CHC burden.

Country-specific anti-HCV prevalence (Step 2)

The online databases Medline, Embase, the Cochrane library, Web of Science, Scopus, PubMed publisher and Google Scholar were searched in January 2015 for reviews, systematic reviews and meta-analyses in English about the prevalence of hepatitis C in the general population at country level. The search (described in full in Annex 1 of the online supplement) used a combination of disease-related (hepatitis C), outcome-related (prevalence), population-related (general population, worldwide) and study design-related (reviews) terms. Note that the search also included terms related to hepatitis B since we conducted a similar analysis for chronic hepatitis B among migrants from endemic countries (to be published in this journal). Since the aim was to identify recent reviews, the search was restricted to papers published after 2009 to the date of the search. The titles and abstracts, then the full text, of retrieved citations were assessed for relevancy by one reviewer (AF). Key exclusion criteria included studies focused on: hepatitis other than type C; natural history, clinical features or complications of hepatitis; medical treatment; other high risk groups e.g. people who inject drugs (PWID); and single case studies and cost effectiveness analyses. High quality systematic reviews/meta-analyses were selected given the recent publication of robust systematic reviews/meta-analyses of national level prevalence estimates globally.

Country-level anti-HCV prevalence estimates and uncertainty ranges/confidence intervals (CIs) were extracted from the included reviews and entered into a Microsoft Excel database of all countries. Where a country-specific estimate was unavailable, the relevant Global Burden of Disease region estimate was used. If a meta-analysis reported a statistically significant time trend, the estimate from the most recent period was selected. Where multiple estimates for a country were available from different reviews, the most robust was selected based on the assessed risk of selection bias. Risk of selection bias was assessed

based on: sampling method (random favoured over convenience); sampling population (the general population was favoured over more specifically defined (risk) groups); geographical coverage (national favoured over regional; regional favoured over local); sample size (larger studies preferred over smaller one); and data collection timeframe (favouring recency). Decisions were made jointly by two reviewers (AF and IV) based on these criteria (rather than a pre-defined algorithm) with a detailed rationale recorded for each selected estimate. This rationale, together with search strategy, the inclusion/exclusion criteria and a PRISMA flowchart are available in the online supplement.

Estimating the CHC burden among migrants from endemic countries

Anti-HCV prevalence was multiplied by the number of migrants from the top 50 countries of birth of migrants in each EU/EEA country. The countries of birth were then sorted in descending order of magnitude by anti-HCV prevalence to identify all endemic (≥1% anti-HCV prevalence) countries. The total number of migrants born in anti-HCV endemic countries was used to determine both the total and proportional contribution of migrants from these countries to the overall number of migrants residing in each of the 31 EU/EEA countries. To estimate the proportion of CHC (viraemic) cases among the anti-HCV positive migrant population, the worldwide average viraemic proportion of 70% found in a recent global meta-analysis was applied.(1)

Relative contribution

For each EU/EEA country, the estimated number of infected cases among migrants from endemic countries was divided by the total number of infected persons (based on the general population CHC prevalence estimate and the total population) to estimate the relative contribution of migrants from endemic countries to the overall number of people infected with CHC. Given uncertainty in both the size of the migrant population and CHC prevalence estimates in countries of birth, a range in the relative contribution (a lower limit and a higher limit) was also calculated using the Delta method.(21)

PART 2: ANTI-HCV PREVALENCE IN MIGRANT POPULATIONS IN EUROPE

The online databases Medline, Embase, the Cochrane library, Web of Science, Scopus, PubMed publisher and Google Scholar were searched in November 2014 for studies in English that estimate the prevalence of hepatitis C in migrants in any of the 31 EU/EEA countries. The search used a combination of disease-related (hepatitis C), outcome-related (prevalence), population-related (migrants) and geographical area (EU/EEA countries) terms and was limited to studies published between 2000 and 2014. We expected a limited

retrieval from this search and therefore included only selection bias (how representative the study population was of the general population) as a key parameter in the risk of bias assessment. This operationalised through the exclusion of studies sampled from higher risk migrant groups such as refugees/asylum seeker and higher risk (general) populations such as STI clinic attendees, outpatient clinics, international health centres etc. The full search strategy, inclusion/exclusion criteria and PRISMA flowchart are available in the online supplement.

Data from the included studies were entered into Microsoft Excel. Pooled estimates for countries of birth were produced by combining the numbers tested and the number of cases. A 95% CI was re-calculated using the Fisher's exact method. Prevalence estimates pooled from multiple studies or extracted from large single studies (>25 subjects from a single country) were compared with the in-country estimates to determine whether in-country estimates reflect the prevalence found among migrants. When the point prevalence from a study in migrants (Part 2) fell within the CI/uncertainty range of the in-country estimate (from Part 1), this estimate was considered to be comparable; when it fell below the lower CI/uncertainty range, it was considered to be lower than the in-country prevalence; and when it was higher than the upper CI/uncertainty range, it was considered to be higher.

RESULTS

Estimated CHC prevalence and number of infected cases in 31 EU/EEA countries (Table 1)

The anti-HCV prevalence in the general population in the EU/EEA is estimated at 1.4% (range of 0.7-2.2%). However, prevalence estimates range from 0.2% in the Netherlands to 4.4% in Italy and 14 EU/EEA countries are considered endemic by the definition adopted in our study (≥1% anti-HCV prevalence). Table 1 lists the estimated number and range of CHC cases among adults in EU/EEA countries. An estimated 4.2 million (range 2.0-6.6 million) adults in the EU/EEA have CHC infection. Italy has the highest absolute number, with an estimated 1.6 million CHC cases. Other EU/EEA countries with a high absolute number of CHC cases among adults are Romania, with 380,000, and Spain, with 470,000.

Table 1. Demographic data and CHC epidemiology in the general population and among migrants in EU/EEA countries

Country (anti-HCV prevalence; range)	General Adult Population				Migrants from endemic countries						
	Total Population*	Estimated no. of CHC cases			Number	Proportion (of the total population)	Estimated number of CHC cases			CHC prevalence	Relative contribution (and range) to burden of CHC
		Central estimate	Lower estimate	Upper estimate			Central Estimate	Lower Estimate	Upper Estimate		
Austria (0.5%; 0.1-0.7)	7,232,026	25,312	5,062	35,437	883,345	12.2%	11,753	8,243	15,117	1.3%	46% (15% - 77%)
Belgium (0.9%; 0.1-1.2)	9,263,570	58,360	6,484	77,814	1,054,155	11.4%	18,607	9,729	32,764	1.8%	32% (4% - 60%)
Bulgaria (1.1%; 0.3-2.4)	6,294,563	48,468	13,219	105,749	62,941	1.0%	1,366	605	1,836	2.2%	3% (0% - 6%)
Croatia (1.3%; 1.1-1.6)	3,632,461[a,b]	33,055	27,970	40,684	524,609	14.4%	4,901	4,058	6,081	0.9%	15% (10% - 22%)
Cyprus (0.6%; 0.5-0.7)	705,459[a]	2,963	2,469	9,383	128,712	18.2%	2,740	1,821	3,567	2.1%	92% (<0% - >100%)[Δ]
Czech Republic (0.7%; 0.2-0.7)	8,955,829	43,884	12,538	43,884	331,840	3.7%	5,937	2,596	8,219	1.8%	14% (6% – 22%)
Denmark (0.7%; 0.5-0.7)	4,625,032	22,663	16,188	22,663	278,041	6.0%	3,894	2,244	5,194	1.4%	17% (10% - 24%)
Estonia (3.3%; 1.6-4.5)	1,113,355	25,719	12,470	35,071	189,495	17.0%	5,090	1,625	7,033	2.7%	20% (6% - 33%)
Finland (0.7%; 0.6-0.9)	4,535,282	22,223	19,048	28,572	176,980	3.9%	3,383	1,682	4,826	1.9%	15% (7% - 23%)
France (0.7%) (0.5-0.8)	52,901,411[a]	259,217	185,155	296,248	5,714,076	10.8%	88,799	37,816	154,348	1.6%	34% (11% - 58%)
Germany (0.5%; 0.3-0.9)	69,414,404[a]	242,950	145,770	437,311	8,888,710	12.8%	128,809	61,796	193,947	1.4%	53% (11% - 95%)
Greece (1.9%; 0.5-2.6)	9,464,000[b]	125,871	33,124	172,245	588,275	6.2%	12,959	9,854	15,519	2.2%	10% (4% -16%)
Hungary (0.8%; 0.4-2.7)	8,477,933	47,476	23,738	160,233	336,360	4.0%	6,548	4,980	7,889	1.9%	14% (0% - 34%)
Iceland (0.9%; 0.7-1.5)	255,391	1,609	1,251	2,682	18,311	7.2%	206	111	307	1.1%	13% (4% - 21%)
Ireland (1.1%; 0.7-1.6)	3,586,829	27,619	17,575	40,172	321,771	9.0%	5,485	2,934	8,188	1.7%	20% (7% - 32%)
Italy (4.4%; 1.6-7.3)	51,336,889	1,581,176	574,973	2,623,315	4,118,015	8.0%	78,501	52,730	101,393	1.9%	5% (1% - 9%)
Latvia (2.4%; 1.7-3.3)	1,731,509	29,089	20,605	39,998	271,468	15.7%	6,532	2,168	9,209	2.4%	22% (8% - 37%)
Liechtenstein (0.9%; 0.7-1.5)	31,142	196	153	327	14,672	47.1%	172	82	223	1.2%	88% (35% - >100%)[Δ]
Lithuania (2.9%; 0.7-3.0)	2,535,329[d]	51,467	12,423	53,242	127,711	5.0%	2,795	1,046	4,142	2.2%	5% (2%- 9%)
Luxembourg (0.9%; 0.6-0.9)	417,377[c]	2,629	1,753	2,629	104,495	25.0%	1,682	659	2,710	1.6%	64% (24% - >100%)[Δ]
Malta (0.9%; 0.7-1.5)	355,704[a]	2,241	1,743	3,735	17,833	5.0%	295	182	438	1.7%	13% (5% - 21%)
Netherlands (0.2%; 0.1-0.4)	13,901,653	19,462	9,731	38,925	978,698	7.0%	13,262	7,278	18,376	1.4%	68% (10% - >100%)[Δ]
Norway (0.7%; (0.6-0.9)	4,122,334	20,199	17,314	25,971	357,877	8.7%	4,822	2,601	6,907	1.3%	24% (12% - 36%)
Poland (1.1%; 0.6-1.9)	32,736,685	252,072	137,494	435,398	453,723	1.4%	9,633	3,080	12,877	2.1%	4% (1% - 7%)
Portugal (1.8%; 0.5-2.9)	8,989,849[a]	113,272	31,464	182,494	642,212	7.1%	13,505	7,474	24,179	2.1%	12% (1% - 23%)
Romania (3.2%; 2.9-3.6)	16,880,465	378,122	342,673	425,388	102,854	0.6%	2,090	912	2,923	2.0%	1% (0% - 1%)
Slovakia (1.4%; 0.9-2.0)	4,580,260	44,887	28,856	64,124	31,460	0.7%	588	281	782	1.9%	1% (0% - 2%)
Slovenia (1.3%; 1.1-1.6)	1,760,726	16,023	13,558	19,720	208,026	11.8%	2,030	1,607	2,563	1.0%	13% (9% - 17%)
Spain (1.7%; 0.4-2.6)	39,637,891	471,691	110,986	721,410	3,748,924	9.5%	55,164	31,440	75,323	1.5%	12% (3% - 21%)
Sweden (0.6%; 0.5-0.7)	7,944,034	33,365	27,804	38,926	773,085	9.7%	10,579	5,352	14,452	1.4%	32% (17% - 46%)
United Kingdom (0.6%; (0.4-1.2)	52,082,285[a]	218,746	145,830	437,491	4,706,765	9.0%	76,535	45,555	118,608	1.6%	35% (6% -64%)
EU/EEA (1.4%; 0.5-1.5)	429,501,677	4,222,026	1,999,421	6,621,241	36,155,438	8.4%	578,663	312,539	859,941	1.6%	14% (4% - 24%)

*Source is EUROSTAT 2013 unless indicated by the following letter: [a]ESS 2011 Census; [b]OECD 2012/EUROSTAT 2013 age distribution; [c]OECD 2010/EUROSTAT age distribution; [d]http:///www.euras.lt (Lithuanian National Statistics Agency)/EUROSTAT 2013 age distribution. [Δ] The Delta method does not give a reliable confidence interval around the relative contribution as the relative contribution is close to 100% and the distribution of cases in the general population is extremely skewed.

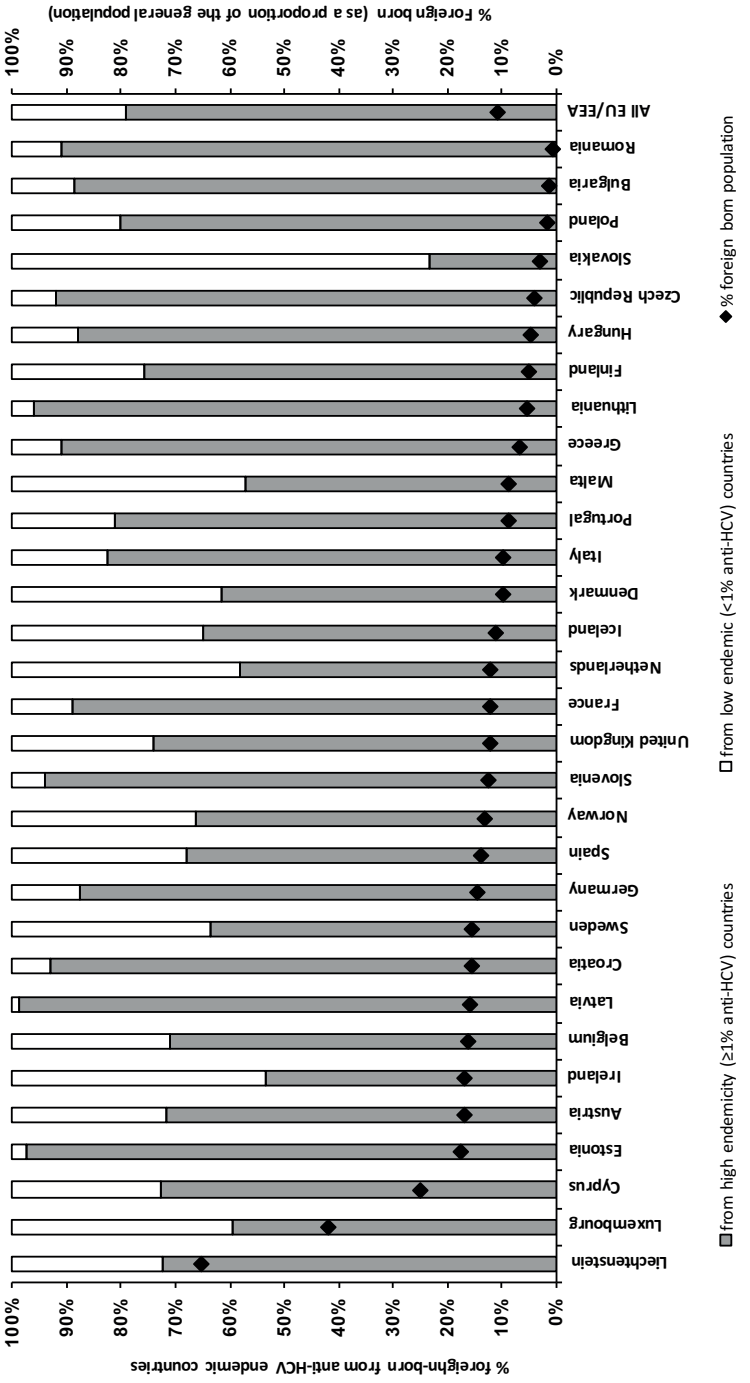

Figure 2. Total (%) migrant population in each EU/EEA country and the proportion born in endemic countries

The distribution of migrants in the EU/EEA based on HCV endemicity in country of birth

The top 50 migrant populations in each EU/EEA country included in the analysis make up at least 95% of the total migrant population in 19 countries and at least 90% in all but three EU/EEA countries (Denmark, Sweden and the United Kingdom, where the proportion is at least 85%). These migrant populations account for approximately 10.7% of the total adult population in the EU/EEA although the proportion in each country varies, ranging from 0.7% in Romania, 1.1% in Bulgaria and 1.7% in Poland to 42.0% in Luxembourg and 65.2% in Liechtenstein (Figure 2).

Nearly 80% of the total migrant population were born in HCV endemic countries. Other than in Slovakia, where 23% of the total migrant population are from endemic countries, over half of all migrants in the other 30 EU/EEA countries were born in countries where the anti-HCV prevalence is ≥1%. In Croatia, Estonia, Latvia, Lithuania, Romania and Slovenia, more than 90% of all migrants are from endemic countries (Figure 2). The number and proportion of all migrants that from endemic countries, at country level and in the EU/EEA as a whole are shown in Table 1.

Country-specific anti-HCV prevalence estimates

The most comprehensive review with country-specific estimates of anti-HCV prevalence identified by the search was published in 2014 by Gower et al.(1) This review includes studies published after the year 2000 and provides estimates for 87 countries and for each of the 21 Global Burden of Disease regions. The country-level estimates from Gower do not have 95% CIs but a lower and upper uncertainty range; the lower range is based on studies among populations considered representative of 'healthy adults' (such as blood donors), but the methodology applied to derive the upper limit is unclear. For nine countries, Gower's regional or in-country estimate was replaced with estimates from other systematic reviews deemed more robust according to the criteria described in the methods. (2, 22-26) The 224 country-level prevalence estimates and the source, together with an overview of decision rationale where an estimate other than Gower was available, are listed in the online supplement.

Estimated prevalence and number of CHC infections among migrants

Across the EU/EEA, the overall anti-HCV prevalence among migrants from endemic countries is estimated at 2.3%, which corresponds to a CHC prevalence of 1.6% and an estimated 580,000 CHC infections (Table 2). The estimated prevalence of CHC infection among migrants from endemic countries ranges from 0.9% in Croatia to 2.4% in Estonia. Table 2 lists the ten migrant populations with the highest estimated number of CHC cases

and the host EU/EEA countries with the largest populations of migrants born in these countries. Based on cumulative analysis of the CHC burden among the different migrant populations from endemic countries to or within the EU, migrants from Romania, Russia, Italy and Poland contribute most, in descending order, to the overall number of CHC cases. An estimated 50,000-60,000 CHC cases are found among migrants from Romania and from Russia.

Table 2. The ten migrant groups (adults from endemic countries) accounting for the highest number of CHC cases

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

rounded to nearest 1,000; * if migrant population is at least 1,000

Some countries of birth of migrants are common across EU/EEA countries. Adult migrants from Russia, a high CHC prevalence country (2.9%), are represented among the top ten migrant populations in 25 of 31 EU/EEA countries. Migrants from Romania and Italy are among the top ten migrant groups in 20 EU/EEA countries. Although small in number, migrants from Egypt are among the top ten CHC-infected migrant populations in 16 of 31 EU/EEA countries due the very high anti-HCV prevalence (15.7%) in Egypt. In Estonia, Lithuania and Latvia, the top ten migrant populations with the highest number of infected cases are all from countries of the former Soviet Union. This is also the case in five to six of the top ten migrant populations with the highest number of infected cases in Bulgaria, the Czech Republic and Poland. People born either in Yugoslavia before 1992 or in one of

the countries that emerged from the fall of Yugoslavia since 1992are represented in six of the top ten migrant populations with the largest of number of CHC cases in Croatia and Slovenia and three of the top ten in Austria. Migrants from the Algeria, Morocco and Tunisia are represented among the ten most CHC-affected migrant populations in France. EU/EEA countries with three to five African countries represented among the top ten CHC-affected migrant groups include Belgium, France, Luxembourg, Portugal and the UK. Prevalence, population size and number and range of CHC infections among, for all 50 countries of birth of migrants in each EU/EEA country can be found in the online supplement.

Relative contribution of migrants to the CHC burden in EU/EEA countries

The relative proportion (and range) of infected migrants from endemic countries within the overall CHC burden in EU/EEA countries is shown in Table 1 and Figure 3. The relative contribution is low (<4%) in Bulgaria, Poland, Romania and Slovakia and much higher (64%-92%) in Cyprus, Liechtenstein, Luxembourg and the Netherlands.

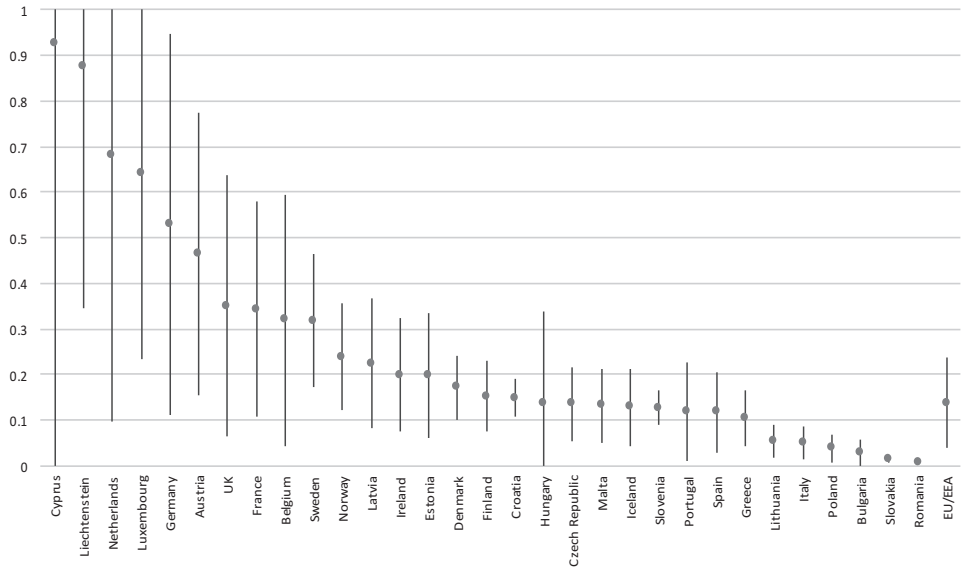

Figure 3. Estimated relative contribution (and range) of migrants to the total number of CHC cases

Comparing migrant-derived anti-HCV prevalence with country of birth estimates

The literature search identified thirteen anti-HCV prevalence estimates from studies in migrants in the EU/EEA for comparison with the in-country estimates derived in Part 1. Two of the thirteen estimates, from studies among migrants from the former Dutch Antilles and Suriname, were higher than the comparator regional prevalence.(1) One estimate, from a study among migrants from the former Soviet Union, could not be compared with in-country anti-HCV prevalence since this nation state is now dissolved. Of the remaining ten estimates, seven were comparable with the in-country estimate and three, among migrants from Egypt, Pakistan and Turkey, were lower than the in-country prevalence (Egypt: 2.4% in migrants vs. 15.7% in-country; Pakistan: 2.8% in migrants vs. 5.5% in-country; and Turkey: 0.2% in migrants vs. 1.0% in-country), although for Turkey the two confidence intervals overlap. See Table 3 for details.

Table 3. Comparing migrant study-derived prevalence to country of birth-derived prevalence

Country of birth	Migrants			In-country		Comparison
	N. tested	Prevalence (95% CI)	Reference	Prevalence (95% CI)	Reference	
Afghanistan	293	1.0 (0.2 – 3.0)	(32)	1.1 (0.6 – 1.9)	(1)	Comparable
Bangladesh	934	0.4 (0.1 – 1.1)	(52, 53)	1.3 (0.2 – 2.2)	(1)	Comparable
Dutch Antilles	38	2.6 (0.1 – 13.8)	(15, 45)	0.8[$] (0.2 – 1.3)	(1)	Higher
Egypt	465	2.4 (1.2 – 4.2)	(54)	15.7 (13.9 – 17.5)	(25)	Lower
Former USSR	65	3.1 (0.4 – 10.7)	(32)	3.3* (1.6 – 4.5)	(1)	Comparable
India	1334	0.4 (0.2 – 1.0)	(52, 53)	0.8 (0.4 – 1.0)	(1)	Comparable
Iran	153	0.7 (0 – 3.6)	(32)	0.5 (0.2 – 1*)	(1)	Comparable
Iraq	290	0.3 (0 – 1.9)	(32)	3.2 (0.3 – 3.2*)	(1)	Comparable
Morocco	331	0.9 (0.2 – 2.6)	(15, 45)	1.6 (0.6 – 1.9*)	(1)	Comparable
Pakistan	3562	2.8 (2.3 – 3.4)	(30, 52, 53)	5.5 (4.4 – 5.5)	(26)	Lower
Suriname	225	2.4 (0.5 – 7.0)	(15, 45)	0.8[$] (0.2 – 1.3)	(1)	Higher
Turkey	965	0.2 (0 – 0.8)	(15, 45, 46)	1.0 (0.7 – 1.1)	(22)	Lower
Vietnam	126	1.6 (0.2 – 5.6)	(32)	1.0 (0.8-1.8)	(1)	Comparable

*Regional estimate from GBD Eastern European region; [$] Caribbean GBD Regional estimate

DISCUSSION

This is the first study we know of that attempts to systematically estimate the overall number of CHC cases among migrants, as well as the relative contribution of cases among migrants to the overall burden of CHC in EU/EEA countries. Migrants from endemic countries account for one in 12 EU/EEA adult citizens and for one in seven of all CHC cases in the EU/EEA. As the contribution of migrants to the overall burden of CHC varies between EU/EEA countries, effective approaches to secondary prevention will, therefore, also differ. Screening programmes targeting migrant populations will be most effective in EU/EEA countries such as Austria, France, Germany, the Netherlands and the UK where migrants account for a large proportion of the disease burden (32%-92%, see Figure 3) and a small proportion of the total population (7%-15%, see Figure 2).

In contrast, in countries where HCV prevalence is high in the general population and the contribution of migrants is low, it may be more cost-effective to implement population-based screening. (27) (28) Examples of such countries include Bulgaria, Poland, Romania and Slovakia where less than 4% of the CHC burden is attributable to migrants from endemic countries. The differences in general population prevalence between EU/EEA countries, together with the contribution of migrants moving within the EU/EEA from high to low prevalence countries, suggests that there may also be value in allocating EU health funding to scale up and systematise screening and treatment efforts in EU/EEA countries with a high general population prevalence, to strengthen efforts to reduce cross-border health threats and to improve overall population health in the EU. A recent modelling study estimated that only around a third of all CHC cases across Europe have been diagnosed and that there are wide differences in both the proportion diagnosed and the proportion on treatment comparing EU/EEA countries.(6) There is however no data on the estimated proportion of migrants from endemic countries that are diagnosed. The data reported, as well as the strategies and interventions suggested, in this study can contribute to increasing the proportion of cases of CHC diagnosed and on treatment.

Previous studies of hepatitis B/C screening implemented among migrant populations describe different models. These include: outreach offering awareness raising and/or on-site screening by public health teams in social, civic or cultural locations familiar to the target community (29-31); invitation-based screening where municipal, population or patient registries are used to send postal invitations to attend screening to people born in higher prevalence countries (32, 33); opportunistic offering of screening to patients with country of birth-related risk factors who attend health care services for other health issues (34, 35); and adding viral hepatitis screening to an existing screening programme, such as for tuberculosis, that targets people from high prevalence countries (36). Each of these

models differs in terms of logistical and resource requirements, uptake and case yield, but few studies have compared the characteristics and effectiveness of different models (37). The characteristics of screening programmes that have demonstrated success in uptake and yield include: involvement of the community in planning and raising awareness; provision of screening in suitable and accessible locations for the target community; provision of language support, for example, translated materials and interpreters; planning and provision for people without health insurance coverage; cultural sensitivity about and efforts to reduce or eliminate stigma; and availability of follow-up and care in the community. Retention within a follow-up care and treatment pathway is crucial to ensure that the public health benefits of screening are realised (38). A summary of migrant-specific screening programmes, an appraisal of factors contributing to success, and a range of other scientific and practical resources are available as part of the HEPscreen Toolkit, produced by the EU-funded HEPscreen project, which focused on screening for chronic viral hepatitis among migrants (39).

In four countries, (Cyprus, Lichtenstein, Luxembourg and the Netherlands) the upper range of the estimated relative contribution of migrants as a proportion of the total number of estimated cases was found to be over 100%. This reflects unmeasured correlation between the input parameters (prevalence in countries of birth and the size of the migrant population) for the Delta method as well as the strong skew in the distribution of cases in the general population in these countries. It is also possible that the prevalence in the general population in these EU/EEA countries is under-estimated, due to unrepresentative sampling or low participation of risk populations who are harder to reach, such as PWID and ethnic minorities as well as migrants. Under-representation of migrants and ethnic minorities is a widely recognised phenomenon in clinical trial and health survey research, (40, 41) although literature specifically focused on sero-prevalence sampling and uptake is very limited. (23) In addition, it is possible that estimates based on prevalence in countries of birth results in over-estimation of the prevalence among migrants. For example, it is probable that no longer living in a high prevalence country would reduce the risk of transmission of HCV, especially since much of the transmission in higher prevalence countries is nosocomial (42) and most EU/EEA countries have successfully controlled nosocomial transmission through health care infection control procedures. Over-estimation may also be due to the characteristics of migrants to the EU/EEA, who may be younger and healthier, and so less likely to have experienced hospitalisation or serious medical intervention and more likely to have benefited from improved primary prevention in the last two decades. Migrants to the EU may also be from higher socio-economic groups in their countries of birth and able to afford better, safer health care (43). We sought to test out this theory of over-estimation

and found that, for just three of the ten countries of birth for which we retrieved estimates for, (15, 29, 30, 44-47) the prevalence in migrants was lower than the reported in-country prevalence.

Despite the systematic nature of data retrieval, there are some data limitations. Detailed demographic data was available from Eurostat for only 21 EU/EEA countries. There is also heterogeneity in the parameters and methods used by the different demographic databases and in the way that demographic data on migration is collected and reported by EU/EEA countries. From other literature, we know that countries such as Germany, France and the Netherlands require municipal registration upon arrival in a new area and collect country of birth data as part of registration. Other countries, like the UK, rely on population census data to systematically collect population size and origin.(48) However, there is very limited information in the literature on the methods used by each database or on the heterogeneity of demographic data collection methods across the EU/EEA. Despite these differences, the demographic data used in this study are derived from databases that in turn derive data from national statistical institutes. We believe it to be the best and most reputable available. These analyses do not include undocumented migrants, partly because the size and origin of this population is very dynamic, but mostly because of the imprecision and unreliability of the data.(49) The use of systematic reviews and meta-analyses for the country of birth prevalence input has reduced the reliance on less reliable single study estimates, and whilst we critically appraised the quality of the systematic reviews and meta-analyses, which all applied quality criteria to select studies, we did not directly assess the quality of the estimates included in these reviews. A further note of caution relates to the studies retrieved on prevalence in migrants, as just ten countries of birth were represented in the estimates and few studies had the specific aim of estimating the prevalence in migrants. The use of convenience sampling in many of these studies increases the chance of selection bias and, specifically, that people already diagnosed may not present for screening.

CONCLUSIONS

Advances in antiviral treatment open up the possibility of eliminating hepatitis C infection in Europe, but achieving this will require countries to scale up and better target screening, linkage to care and treatment. This study provides strategic, timely and detailed epidemiological intelligence for EU/EEA countries on the hepatitis C burden among migrant populations, a key population group affected by this infection in Europe. It also provides prevalence estimates for 224 countries and territories, which should serve as a useful resource for other countries and regions wishing to understand the relative contribution of migrants to the burden of hepatitis C. This intelligence, together with the

learning from previous migrant-specific screening projects in the EU/EEA (39), can help to inform the design of screening programmes to reach migrant populations most affected by chronic hepatitis C infection. A targeted approach in higher risk populations makes more effective use of health care resources and contributes to reducing health inequalities. The World Health Organisation's Global Strategy for Viral Hepatitis (50) and the European Action Plan (51) both share the ambitious goal of elimination of viral hepatitis by 2030. If this goal is to be realised, it will be essential to dramatically increase the proportion of people who are diagnosed, aware of their infection and on treatment. Future research can contribute by focussing on improving the evidence base on effective strategies to reach and retain migrant and other risk populations in screening and treatment and on cost-effectiveness across the treatment cascade.

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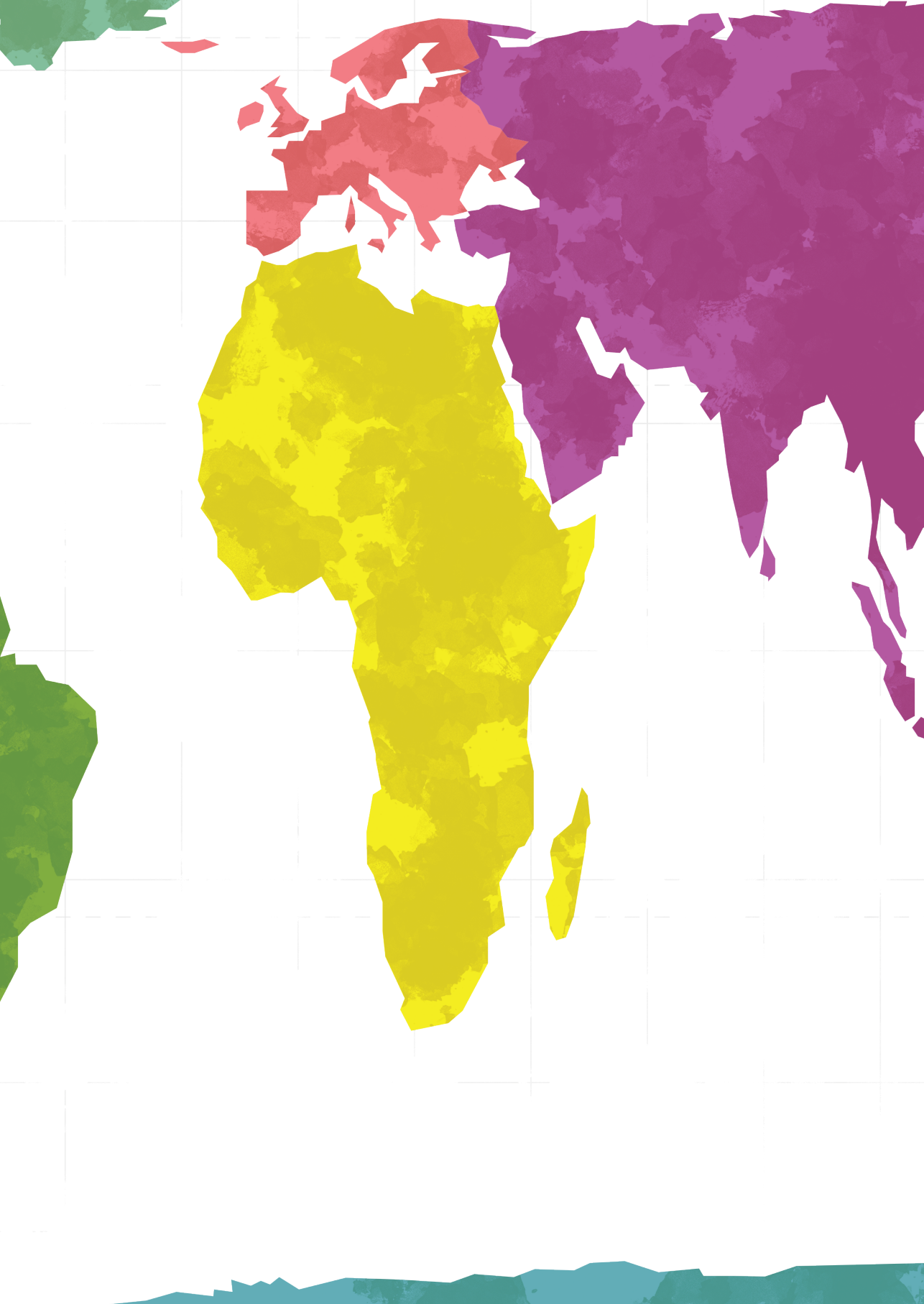
PART II

SCREENING AND LINKAGE TO CARE FOR CHRONIC HEPATITIS B/C AMONG MIGRANTS: RESULTS OF THE HEPSCREEN PROJECT



CHAPTER 6

Models of chronic hepatitis B and C screening among migrants in Hungary, Spain and the UK: implementation, outcomes and costs

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ABSTRACT

Background: Migrants born in endemic countries are a key risk group for chronic hepatitis B and C virus (HBV/HCV) infection in many EU countries. In the EU-funded HEPscreen project (2011-2014) we compared costs and outcomes of six different screening models targeting migrants in the UK, Spain and Hungary.

Methods: Two outreach screening models (one in communities, one in workplaces), an opportunistic and an invitation-based model in primary care, and two extension models (adding hepatitis B/C to university-based tuberculosis screening and antenatal screening) were implemented. Outcome data collected included: screening uptake, cascade of care retention, HBsAg and anti-HCV prevalence and costs.

Results: Five of the six screening models were completed, screening 1203 people. Uptake varied from 33% in workplace outreach screening to 78% in opportunistic screening. The invitation-based model ceased prematurely due to low uptake (2.3%). The multi-stage screening pathway in the community outreach led to attrition of 49% of participants. Overall, the highest HBsAg prevalence (12.9%) was detected among South-East Asian migrants. Overall, the highest anti-HCV prevalence was found in migrants from Central (10.3%) and South (8.3%) Asia, and Eastern Europe (5.3%). Costs per person screened ranged from €48 (tuberculosis screening extension model) to €111 (community outreach model).

Conclusions: Migrants can be effectively reached via screening in health care and community settings. Uptake and cost per person screened in community-based outreach screening may be improved by offering testing at the first point of contact. To maximise impact and improve cost favourability, chronic viral hepatitis screening should prioritise migrants born in intermediate to high endemic countries.

INTRODUCTION

Advances in treatment for chronic infection with the hepatitis B (HBV) and hepatitis C (HCV) viruses, especially the cure of chronic HCV infection with interferon-free, virtually side effect-free regimens, have increased the scope for secondary prevention of liver disease-related morbidity and mortality.(1-3) The World Health Organisation (WHO) recently agreed the ambitious goal of the elimination of chronic hepatitis B (CHB) and C (CHC) as a health threat in Europe by 2030.(4) The journey to elimination is set out in the action plan for the health system response in the European region.(5) Alongside the continuation (and expansion for some countries) of primary prevention measures to halt transmission, the scale up of screening and treatment for people with chronic viral hepatitis is crucial for elimination. (6-11)

In Europe, migrants from countries where HBV/HCV is endemic are an important risk group for CHB and CHC infection.(12-15) Two recent studies, funded by the European Centre for Disease Prevention and Control (ECDC), estimated that 14% of the burden of CHC (viraemic) and 25% of the burden of CHB in the EU/EEA is attributable to migrants from endemic countries.(16-18) These studies also highlight the differences across the EU in prevalence in the general population and in demographic characteristics related to migration. Migrants from endemic countries account for a much larger proportion of estimated cases of chronic viral hepatitis in low CHB/CHC prevalence countries in Northern and Western Europe than in higher prevalence countries in the Eastern and Southern part of Europe. Migration flows are dynamically driven by economic circumstances, conflict, geography, linguistic affinity and immigration policy, although countries in Northern and Western Europe have tended to experience much higher net migration from endemic countries (from within and outside the EU).(19)

Health planners and service providers in countries experiencing high net migration (where migrants are disproportionately affected and account for a large proportion of CHB/CHC cases) can make use of scientific work on how to engage, reach, screen and retain at risk migrants in a cascade of care for chronic viral hepatitis. Various models of screening among migrants have been described in literature. These include: outreach offering awareness raising and/or on-site screening in social, civic or cultural locations accessible for the target community (20-24); invitation-based using municipal or patient registries (25-27); opportunistic screening of migrant patients who attend health care services for other health issues (28-30); and adding viral hepatitis screening to an existing migrant-specific screening programme, such as for tuberculosis (TB).(31)

In addition to evidence on effectiveness, public health decision makers increasingly demand economic assessments in order to make rational, sustainable and equitable decisions about the use of scarce health care resources. Most cost-effectiveness studies of the secondary prevention of chronic viral hepatitis either begin with a cohort of diagnosed patients (32) or make assumptions about the costs and characteristics (uptake of screening, retention in a cascade of care) of hypothetical opportunistic or invitation-based case finding.(33-36) In a systematic review, Geue et al (37) conclude that most cost-effectiveness studies neglect to include costs associated with actual screening efforts, such as recruiting patients from (harder to reach) populations.(36) Yet screening intervention costs were found to account for 43% of the variation in costs per QALY in a study modelling cost outcomes of HCV case finding and treatment among migrants from South Asia.(35) Few cost-effectiveness analyses include model parameters based on 'real world' experience of screening strategies.(38) Fewer still are studies that seek to compare the relative effectiveness and costs across different models of screening among migrants. One study from the US compared five models of HBV screening including three unique models (a community outreach, a community clinic and a partnership model) and two hybrid models (incorporating elements of the unique models) to determine effectiveness and cost-effectiveness (39). There are no studies that compare the costs and outcomes of different models of screening among migrants that include both HBV and HCV.

We report on the planning, implementation, effectiveness and costs of six migrant HBV/HCV screening models carried out between October 2011 and October 2014 in Hungary, Spain and the United Kingdom (UK) (England and Scotland). We report key outcomes including uptake of screening, cost per person screened, cost per case identified and prevalence in order to inform policy making and research on chronic viral hepatitis.

METHODS

We aimed to plan, implement and evaluate the six models of screening described below. In each model, local data were used to select the target migrant communities for HBV/HCV screening. Our study is part of HEPscreen (40), co-funded by the Health Programme of the European Union in 2011-2014.

Implementation of screening models

Workplace-based outreach model in Grampian

From August to November 2013, this model combined awareness-raising with confidential on-site blood-borne virus (BBV) (HBV, HCV and HIV) screening in six food processing businesses employing a significant proportion of migrants (64% of the workforce on

average, range of 32%-85%). One of three models of awareness-raising was used. In the simplest model, posters and written briefs were available in English and other employees' languages (Bulgarian, Latvian, Lithuanian-Russian, Polish and Portuguese) regarding times/locations of screening sessions and the rationale for testing. In the second model, in addition to the above, a Public Health doctor provided a verbal briefing to employees at lunch. In the third model, information materials were used together with staff briefings given by team managers, following discussion with the Public Health doctor. Companies chose a drop-in screening and released employees from shifts, an appointment system or a combination, whichever was least disruptive to the business. To avoid stigmatisation, screening was offered to all 1,465 (935 migrants and 530 UK-born) employees of these six businesses. Everyone with a chronic HBV/HCV infection was given their results by the study-specific liver nurse. A joint target to screen 500 people was set for this and the University-based TB extension described below. This pilot and the TB extension pilot both operated a centralised regional system with co-ordinated referrals between primary and secondary care.

Community-based outreach model in Barcelona

Between December 2012 and July 2014, the local Public Health Agency in Barcelona, Spain developed a community outreach model where community health workers (CHWs) organised educational sessions about viral hepatitis (symptoms, transmission, prevention, treatment and prognosis) for migrants from Latin America and Central/Eastern Europe in a range of social, civic and cultural locations. These regions of origin were selected because they account for the largest migrant populations in Spain, excluding Western European-born migrants. After the educational session, participants were offered an appointment with a physician at an international health centre, where a questionnaire on socio-demographic variables and HBV/HCV risk factors was completed. Testing was completed at a third appointment and results provided in a fourth. A 10-journey metro card was given to educational session participants to financially compensate for health centre visits. In both Barcelona pilots, an agreement was in place to provide health care coverage if HBsAg/anti-HCV infection was detected in a study participant without legal access to the health care system (due to undocumented status or social vulnerability). This model set a target to invite 450 migrants to educational sessions.

Opportunistic screening in primary care and an international health centre in Barcelona

An opportunistic approach was developed in Barcelona whereby migrants from Latin America and Central/Eastern Europe who visited an international health centre or a primary care centre between October 2012 and July 2014 were offered a return appointment for HBV/

HCV screening. The two health centres are located in an area with a large (>40%) migrant population. Patients consenting to the offer of screening completed a questionnaire and underwent testing at a second appointment. Results were given in a third visit. This model set a target to offer screening to 300 migrants.

TB screening extension model in Grampian, Scotland

Existing new entrant TB screening for students arriving from countries of high TB prevalence was extended in the academic year 2012/2013 to include an offer of confidential on-site BBV screening in Aberdeen and Robert Gordon Universities. At one university, a brief presentation and written BBV information was provided by a TB nurse at the welcome session for foreign students. Students completed a questionnaire, and those from high TB prevalence were sent an email invitation for TB screening. The second university publicised TB screening to all students by email and at general welcome sessions, allowing students to self-select. For those accepting the offer at either university, a Mantoux skin test was performed for TB screening and viral hepatitis screening information was provided. Students returned two days later for the Mantoux reading and those with a negative response were offered BBV screening after a pre-test discussion with a nurse. BBV screening is part of routine TB follow-up care for those with a positive Mantoux reading and BBV results are not reported here. Translation was not provided since students were expected to have a good command of English. Everyone with a chronic HBV/HCV infection was given results via email or telephone by the study-specific liver nurse.

Antenatal extension model in Budapest/Pest Country

From April 2013 and to March 2014, antenatal infectious disease screening was extended to include HCV for first and second generation migrant pregnant women. Subjects were provided with pre-test information about viral hepatitis and the study and offered HCV screening at a later antenatal visit with a Health Visitor. As well as Hungarian, information was available in Arabic, English, Chinese, Romanian, Russian, Serbian, Vietnamese and Turkish. Women who agreed to HCV screening signed an informed consent declaration and completed a questionnaire. The blood sample was taken at a later appointment with an obstetrician/gynaecologist. Results were given by the same obstetrician/gynaecologist. A screening target of 500 pregnant women was set.

Invitation-based model in primary care in London

From January to September 2014, patient registries from two London GP practices were used for postal invitations to adults (aged 18 and over) of Black African, South Asian or Turkish ethnicity without a known CHB/CHC infection. This model was designed as a randomised control trial where half of the target population received an invitation to make

an appointment for HBV/HCV testing and the other half for BBV (HBV, HCV and HIV) testing. The pilot set a target of 500 people to be invited. Invitations included information about viral hepatitis (and HIV, if applicable) and the study. The invitation and information were translated into Turkish for invitees from the Turkish community. Results were to be given by the GP.

Ethical approval

Each study site followed locally specific medical ethical regulations. In Grampian, specific ethical research approval was not required since the pilot was planned as a service improvement. In Barcelona, the study protocol was licensed by the Research Ethics Committee of the Hospital del Mar in September 2012. In London, the RCT protocol was licensed under consent number ETT/TUKEB 150/2013 (7157/2013/EKU) by a Research Ethics Committee in April 2013 and by the University Research & Development Department in September 2013. In Budapest, the study protocol was licensed by the national ethical committee under the consent number ETT/TUKEB 150/2013 (7157/2013/EKU).

Definitions

A first generation migrant (FGM) was defined by birth outside the current country of residence. A second generation migrant (SGM) was defined by at least one parent born outside the current country of residence.

Laboratory testing methods

CHB infection was suspected in the presence of HBsAg and confirmed by the presence of HBV DNA. CHC infection was suspected in the presence of anti-HCV and confirmed by the presence of HCV RNA.

In Grampian, both dry blood spot (DBS) and venous sampling were used. HBV testing was performed using the Biokit Bioelisa anti-HBc followed by Beckman Coulter Access HBsAg for reactive samples with further neutralisation test confirmation; viral load testing was completed with ABBOTT Realtime HBV Assay. HCV testing was performed using Bio-Rad Access HCV Ab Plus with reactive samples re-tested with Ortho HCV 3.0 assay. HCV viral load was determined with ARTUS HCV QS-RGQ on a QIAsymphony platform. In Barcelona, HBsAg and anti-HCV were detected by ELISA and HBV DNA/HCV RNA confirmed (in specialist care) via PCR. In Hungary, all serum samples were tested for HBsAg and anti-HCV using an ELISA. Every reactive serum sample was re-tested using an ELISA, and repeatedly reactive samples were confirmed using an ELISA (for HBsAg) and an INNO-LIA HCV Score kit (for anti-HCV). HCV RNA was determined by nested-RT-PCR. In London, an ELISA was used to detect HBsAg and anti-HCV with HBV DNA/HCV RNA further confirmed with PCR.

Cost data collection

To coordinate cost data collection, a data sheet listing activities, time spent on these activities and costs was agreed among the different sites. Each site then entered the observed hours of work and salaries for different staff involved in the planning, implementation and running of the screening model. Consumable costs (e.g. blood tests, leaflets) were then added to obtain total cost for each model. A (hypothetical) routine implementation cost was then estimated for each model by excluding the start-up/planning costs and assuming the same uptake and prevalence. Purchasing Power Parities (PPP) were extracted from the Organisation for Economic Cooperation and Development (OECD) and used to convert local cost data into 2013 US$.(41) US$ costs were converted into 2013 Euros.

Data analysis

Anonymised data from all sites were aggregated and analysed in Microsoft Excel to compare costs and outcomes. Cascade of care indicators included: total number of migrants exposed to some aspect of pre-test information and/or offered screening; total number of migrants screened; uptake (the proportion of migrants offered screening that were actually screened); total number (and proportion of those screened) found HBsAg and/or anti-HCV (and HBV DNA/HCV RNA) positive (and number of newly diagnosed infections); total number of (combined) HBsAg or anti-HCV positive people who reached secondary care; total number with an indication for treatment (according to local treatment guidelines); and total number who started treatment. Cost data included: total cost of each screening model in the pilot phase and in (hypothetical) routine implementation; cost per person screened; cost per HBsAg case detected; cost per anti-HCV case detected; and cost per (combined) HBsAg or anti-HCV case identified. In Hungary, we report cascade of care and cost data only for anti-HCV, since the innovation tested was the extension of routine antenatal HBsAg screening to include anti-HCV. HBsAg and anti-HCV prevalence was measured by the number of people with positive serology divided by number screened (n/N) by country of birth (if N screened is >10 per country). Countries were grouped into Global Burden of Disease (GBD) regions (42) and the regional HBsAg and anti-HCV prevalence calculated. Country and region-level 95% CIs were calculated using Fisher's Exact method.

RESULTS

All screening models except the invitation-based model in primary care were implemented and completed. In the invitation-based model, 560 invitation letters from two GP practices were sent out but uptake of testing was unexpectedly low (2.3%) and the trial was discontinued prematurely.

Overall uptake and prevalence

In total 2531 migrants were given the opportunity to participate in the five screening models, 2374 of whom received pre-test information. The five pilots screened 1203 people (48% of the total target population), 94% (N=1133) of whom were FGM born outside Western Europe or North America. Around two thirds of those screened were female. Excluding the antenatal data decreases the proportion female to 58%. Excluding the HBsAg cases diagnosed through the antenatal model (since HBsAg screening is routine), 14 cases of HBsAg and 18 cases of anti-HCV cases were identified of which 10 and 15 (respectively) were new diagnoses. Eight anti-HCV cases were RNA positive, two were negative, and eight were lost to follow up and RNA testing was not performed. Table 1 summarises the uptake and cascade of care data. Prevalence among FGM across the five pilots was 2.7% for HBsAg and 1.6% for anti-HCV. The community outreach model and the opportunistic screening model reached socially vulnerable migrants including (respectively): 37 (21.6%) and 28 (12.0%) undocumented migrants; 21 (12.3%) and 9 (3.9%) people without access to the health care system; and 97 (56.7%) and 92 (39.3%) people who were unemployed.

Prevalence demographics

HBsAg prevalence was highest among migrants from East/South East Asia (12.7%) (Table 2, Figure 1). A high prevalence was also found among migrants from South and Central Asia (7.7% and 6.9%, respectively), Sub-Saharan Africa (3.3%), and Central Europe (2.7%). Anti-HCV prevalence was highest among migrants born in Central and South Asia (10.3% and 8.3%, respectively), followed by Eastern Europe (5.3%). Prevalence among migrants from Latin America/the Caribbean was low (HBsAg: 0.6%; anti-HCV: 0.3%).

Cascade of care (Table 1)

In both the workplace-based outreach and the TB extension model, screening was successfully completed in everyone consenting to screening, and all diagnosed cases successfully reached secondary care for treatment assessment. Treatment was indicated in none (of eight) HBsAg cases and in five (of seven) anti-HCV cases, with all five CHC (viraemic) cases successfully starting treatment. There was however some attrition across the cascade of care in the other models. In the community outreach model, 337 people attended 45 education sessions, 316 of whom agreed to participate and 210 of these attended the GP appointment. HBV/HCV screening was completed in 171. Just one of the nine HBsAg/anti-HCV cases identified by this model successfully reached secondary care. Treatment was indicated in this one case of CHC (viraemic) infection. In the opportunistic screening model, 247 of the target sample of 300 people consented. Screening was completed in 234 people. Just one (of four) anti-HCV case and two (of three) HBsAg cases successfully reached secondary care. Treatment was not indicated in both CHB cases. In Hungary, 331 women

consented to screening although 51 samples were lost to follow up due to unfamiliar laboratory arrangements or insufficient blood taken. The one case of CHC successfully reached secondary care, and treatment was indicated.

Table 1. Screening and treatment cascade across the five pilot models

	Screening model					
	Workplace outreach (Grampian)	**Community Outreach (Barcelona)**	**Opportunistic (Barcelona)**	**TB extension (Grampian)**	**Antenatal extension◊ (Budapest)**	**Total**
Number of migrants offered screening	935Δ	450	300	455	401	2531
Number of migrants screened	305#	171	234	156	280	1146
Uptake	33%	38%	80%	34%	69%	45%
Number HBsAg positive (% of screened)	4 (1.3%)	3 (1.8%)	3 (1.3%)	4 (2.6%)	N/A	14 (1.2%)
Number new HBsAg positive	4	2	2	2	N/A	10
Number anti-HCV positive (% of screened)	7 (2.1%)	6 (3.5%)	4 (1.7%)	0 (0%)	1 (0.4%)	18 (1.6%)
Number new anti-HCV positive	7	4	3	0	1	15
Number HCV-RNA positive	5	1*	1*	n/a	1	8
Number new HCV-RNA positive	5	1	1	n/a	1	8
Number HBsAg or anti-HCV positive (% of screened)	11 (3.6%)	9 (5.3%)	7 (3.0%)	4 (2.6%)	1 (0.4%)	32 (2.8%)

◊ Anti-HCV screening reported only ΔExcludes 530 UK-born employees. #Excludes 57 UK-born employees that were screened.
*The remaining anti-HCV cases were lost to follow up

Table 2. Number positive (n), number screened (N) and prevalence (95% CI) for HBsAg and anti-HCV by country of birth[#Δ]: first generation migrants (across all models)

Country/GBD Region	HBsAg			Anti-HCV		
	n	N	Prevalence (95% CI)	n	N	Prevalence (95% CI)
Ghana	1	12	8.3 (5.6 - 13.6)	0	12	0.0 (0.0 - 5.6)
Nigeria	3	95	3.2 (2.8 - 3.9)	0	95	0.0 (0.0 - 0.7)
Other Sub-Saharan African countries*	0	13	0.0 (0.0 - 5.2)	0	13	0.0 (0.0 - 50.0)
Sub-Saharan Africa Total	**4**	**120**	**3.3 (3.1 - 3.9)**	**0**	**120**	**0.0 (0.0 - 0.6)**
*N<10 each from Cameroon, Kenya, South Africa, Sudan, Tanzania and Uganda						
South Asia* Total	**1**	**13**	**7.7 (5.2 - 12.6)**	**1**	**12**	**8.3 (5.6 - 13.6)**
*N<10 each from Afghanistan, India and Pakistan						
Georgia	1	16	6.3 (4.2 - 10.3)	3	16	18.8 (16.4 - 22.5)
Other Central Asian countries*	1	13	7.7 (5.2 - 12.6)	0	13	0.0 (0.0 - 5.2)
Central Asia Total	**2**	**29**	**6.9 (5.7 - 9.1)**	**3**	**29**	**10.3 (9.1 - 12.5)**
*N<10 each from Armenia, Azerbaijan, Kazakhstan, Mongolia, Uzbekistan						
China (incl. Taiwan)	4	42	9.5 (8.7 - 11.0)	0	40	0.0 (0.0 - 1.8)
Viet Nam	4	20	20.0 (18.1 - 23.0)	0	19	0.0 (0.0 - 3.6)
Other East/South East Asian countries*	1	9	11.1 (7.4 - 18.0)	0	9	0.0 (0.0 - 7.4)
East/South East Asia Total	**9**	**71**	**12.7 (12.2 - 13.6)**	**0**	**68**	**0.0 (0.0 - 1.0)**
*N<10 each from Indonesia, Malaysia, Philippines, Thailand						
North Africa/Middle East* Total	**0**	**7**	**0.0 (0.0 - 9.4)**	**0**	**6**	**0.0 (0.0 - 10.9)**
*N<10 each from Egypt, Kuwait, Libya, Syria and Turkey						
Bolivia	1	174	0.6 (0.4 - 1.0)	0	174	0.0 (0.0 - 0.4)
Colombia	0	31	0.0 (0.0 - 2.2)	0	31	0.0 (0.0 - 2.2)
Dominican Republic	0	13	0.0 (0.0 - 5.2)	0	13	0.0 (0.0 - 5.2)
Ecuador	1	49	2.0 (1.4 - 3.4)	0	49	0.0 (0.0 - 1.4)
Peru	0	14	0.0 (0.0 - 4.8)	1	14	7.1 (4.8 - 11.7)
Other Latin American/Caribbean countries*	0	47	0.0 (0.0 - 1.5)	0	17	0.0 (0.0 - 4.0)
Total Latin America/Caribbean	**2**	**328**	**0.6 (0.5 - 0.8)**	**1**	**328**	**0.3 (0.2 - 0.5)**
*N<10 each from Argentina, Brazil, Chile, Cuba, El Salvador, Honduras, Mexico, Nicaragua, Paraguay, Uruguay and Venezuela						

Table 2. (continued)

Country/GBD Region	HBsAg			Anti-HCV		
	n	N	Prevalence (95% CI)	n	N	Prevalence (95% CI)
Poland	3	163	1.8 (1.6 - 2.2)	0	162	0.0 (0.0 - 0.4)
Romania	7	210	3.3 (3.2 - 3.6)	1	189	0.5 (0.4 - 0.9)
Slovakia	0	14	0.0 (0.0 - 4.8)	0	12	0.0 (0.0 - 5.6)
Other Central European countries*	1	27	3.7 (2.5 - 6.1)	2	17	8.0 (6.6 - 10.6)
Central Europe Total	**10**	**407**	**2.5 (2.4 - 2.6)**	**3**	**380**	**0.8 (0.7 – 1.0)**
*N<10 each from Albania, Bulgaria, Croatia, Czech Republic, Hungary, Serbia and Slovenia						
Latvia	0	54	0.0 (0.0 - 1.3)	6	54	11.1 (10.4 - 12.3)
Lithuania	1	84	1.2 (0.8 - 2.0)	1	84	1.2 (0.8 - 2.0)
Russian Federation	1	19	5.3 (3.6 - 8.7)	2	17	11.8 (9.7 - 15.4)
Ukraine	1	34	2.9 (2.0 - 4.9)	1	31	3.2 (2.2 - 5.4)
Other Eastern European countries*	0	4	0.0 (0.0 - 15.9)	0	4	0.0 (0.0 - 15.9)
Eastern Europe Total	**3**	**195**	**1.5 (1.4 - 1.9)**	**10**	**190**	**5.3 (5.1 - 5.6)**
*N<10 each from Estonia and Moldova						
Total$^{\Delta}$	**31**	**1170**	**2.6 (2.6 - 2.7)**	**18**	**1133**	**1.6 (1.6 - 1.7)**

Countries were grouped into Global Burden of Disease (GBD) supra-regions.(25) #If N<10 at the country of birth level, the data were suppressed into regions. $^{\Delta}$Excluding migrants from GBD regions of Western Europe and North America.

Cost comparison

Costs per person screened in the pilot phase ranged from €58 in the TB screening extension model to €193 in the community outreach model (Table 3). Costs per HBsAg case detected ranged from €2,254 in the TB extension model to €10,976 in the community outreach model. Costs per anti-HCV case detected ranged from €4,158 in the workplace-based outreach model to €40,405 in the antenatal extension model. Costs per (combined) HBsAg or anti-HCV case detected ranged from €2,254 in the TB extension model to €40,405 in the antenatal extension model. Costs per person screened if the models were to (hypothetically) continue as routine implementation (without the set up/planning costs) were estimated to range from €48 in the TB extension model to €111 in the community outreach model (Table 3).

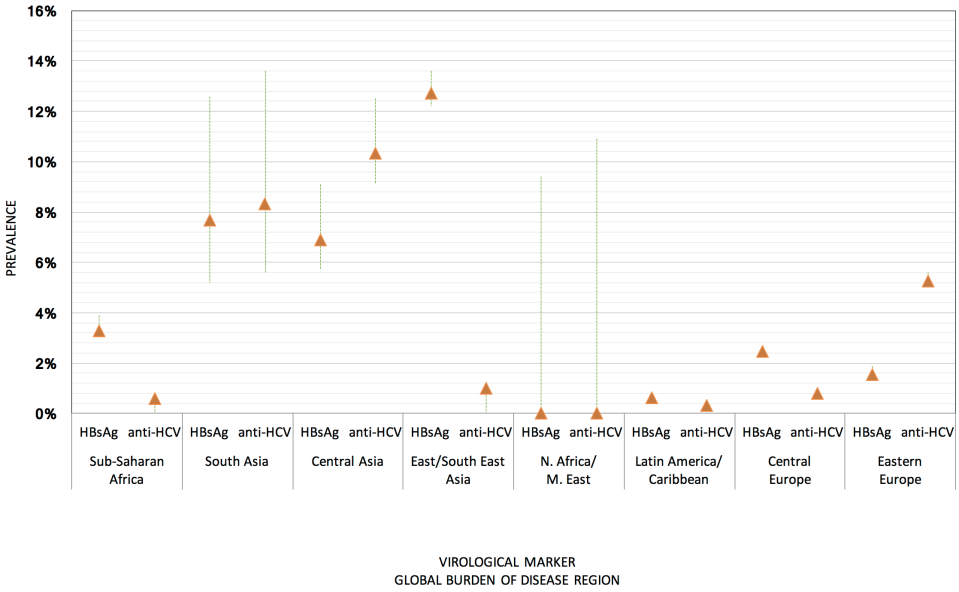

Figure1. GBD Regional HBsAg or anti-HCV prevalence and 95%CI

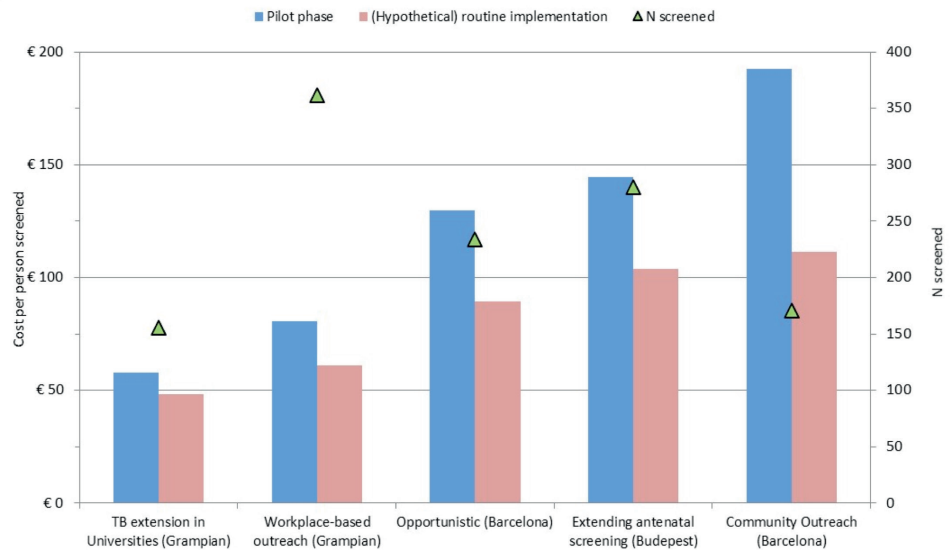

Figure 2. Cost per person screened and number screened during pilot and (hypothetical) routine implementation phases

DISCUSSION

This is the first study to plan, implement and compare costs and outcomes from different models of HBV and HCV screening among migrants. Our study does not permit conclusions on the cost-effectiveness of the different screening models, as final health outcomes were not incorporated. However, our study can significantly contribute to future cost-effectiveness studies through the provision of data to recalibrate key model parameters, specifically: data on the actual costs (across the cascade of care) for various models of screening, in both a pilot phase and as (hypothetical) routine implementation; uptake of screening; and the measured HBsAg/anti-HCV prevalence in 1133 FGM. The scope of intervention costs included here are in line with similar studies.(39, 43, 44)

Prevalence

Prevalence in the target population is a key consideration in weighing the potential population health benefits and harms of screening.(45) It is also a key parameter in cost-effectiveness assessment.(36, 38) This study was not designed as a sero-prevalence study and the subjects included may not be representative of the general (migrant) population. We are therefore cautious in general (migrant) population extrapolation. Our results along with other studies in migrants (24, 39, 46, 47) and countries of birth (48) suggest an intermediate/high HBsAg prevalence among people born in East/South East Asia. The high anti-HCV prevalence among migrants from Eastern/Central Europe and from Central/South Asia found reflects that reported in countries of birth.(49) However, the case yield from offering screening among migrants from low prevalence areas, for example Latin America, appears to be low. These findings reinforce the evidence to specifically target screening for people born in HBV/HCV intermediate to high endemic countries.

Anti-HCV prevalence in the extended antenatal model was 0.4%, despite more than half of subjects being born in Romania where the anti-HCV prevalence is estimated to be 3.2%. (49) This finding is possibly explained by the relatively young age (for CHC infection (50)) of participants (median age of 29) and by living in low HCV prevalence country (Hungary) for most of their lives. This low prevalence, the high cost per case together with findings from another study (51) suggest there is limited value in including HCV in antenatal screening. University-based TB screening extended to include BBV detected 2.6% HBsAg prevalence, suggesting that this model could be an effective way of identifying cases among migrant students. No cases of HCV were found, probably explained by the relatively young age (mean of 28 years) of this student population.

Table 3. Cost data from five screening models

	Workplace-based outreach (Grampian)		Community Outreach (Barcelona)		Opportunistic (Barcelona)		TB extension (Grampian)		Antenatal extension (Budapest/Pest County)	
Cost Categories	**Pilot**	**Routine**	**Pilot**	**Routine**	**Pilot**	**Routine**	**Pilot**	**Routine**	**Pilot**	**Routine**
Staff costs:										
Planning	€2,861	€60	€2,007	€0	€1,472	€0	€1,421	€60	€10,964	€0
Implementation	€1,446	€618	€3,218	€1,586	€711	€213	€201	€0	€7,576	€790
Running	€8,211	€8,211	€15,531	€5,371	€10,746	€3,297	€2,567	€2,627	€9,112	€17,146
Consumables:										
Communication	€298	€298	€188	€188	€0	€0	€180	€180	€725	€725
Translation/interpretation	€5,294	€1,951	€93	€0	€30	€0	€0	€0	€1,632	€0
Lab tests	€10,996	€10,996	€11,889	€11,889	€17,406	€17,406	€4,648	€4,648	€10,395	€10,395
Total Cost*	**€29,106**	**€22,133**	**€32,927**	**€19,034**	**€30,335**	**€20,916**	**€9,016**	**€7,515**	**€40,405**	**€29,056**
Drop in costs (%) from pilot to routine		24%		42%		31%		17%		28%
Number of people screened	362	362	171	171	234	234	156	156	280	280
Cost per person screened	€80	€61	€193	€111	€130	€89	€58	€48	€144	€104
Cost per HBsAg case detected	€7,277	€5,533	€10,976	€6,345	€10,112	€6,972	€2,254	€1,879	N/A	N/A
Cost per new HBsAg case detected	€7,277	€5,533	€16,464	€9,517	€15,168	€10,458	€4,508	€3,758	N/A	N/A
Cost per anti-HCV case detected	€4,158	€3,162	€5,488	€3,172	€7,584	€5,229	n/a	n/a	€40,405	€29,056
Cost per new anti-HCV case detected	€4,158	€3,162	€8,232	€4,759	€10,112	€6,972	n/a	n/a	€40,405	€29,056
Cost per HBsAg or anti-HCV case detected	€2,646	€2,012	€3,659	€2,115	€4,334	€2,988	€2,254	€1,879	€40,405#	€29,056#
Cost per new HBsAg or anti-HCV case detected	€2,646	€2,012	€5,488	€3,172	€6,067	€4,183	€4,508	€3,758	€40,405#	€29,056#

*Due to rounding, the total cost listed may not be the exact sum of the different cost categories. #Anti-HCV screening only (see methods).

Screening uptake

Screening uptake is an important parameter in assessing cost-effectiveness, which is why we endeavoured to measure it in our study. Screening uptake is however difficult to compare between models and is arguably most accurate in models that offer screening on a one-to-one basis, since the target population offered and accepting testing is easier to define than in outreach models where, for instance, an entire workforce, anyone attending a civic or social centre or an entire local population (24) could be considered part of the target population. Indeed, no studies of outreach screening among migrants report screening uptake.(21, 24, 39, 52-54)

In our study, models with a larger target population reported a lower screening uptake. Furthermore, a higher screening uptake was observed in models offering screening in health care by health care workers i.e. opportunistically in primary care (78% uptake) and antenatal screening by health visitors (69% uptake). Brady et al (in a study during 2012-2014) also found a higher screening uptake in opportunistic models, 32% among patients in internal medicine clinics and 20% via electronic patient record prompted testing in primary care (compared to 10% in an invitation-based model).(44) The higher uptake of screening reported in individually-focused models raising awareness and offering testing in confidential, one-to-one clinical encounters suggests that these models could be more conducive to a higher acceptance of the offer of testing.(47) However, our findings do not support the inclusion of 100% screening uptake in opportunistic screening in primary care as assumed in a cost-effectiveness study by Wong et al (36), although the 70% included in Hutton et al seems realistic.(34)

The relatively low screening uptake in the workplace-based outreach (33%) and the TB extension model (34%) could be due to an inability to take up screening among students/workers (due to shift work or study priorities). Time pressures/priorities for individuals reached at work and in educational settings are important explanations, as priorities may be different than for individuals approached in health care services. The TB extension model was offered in two universities and screening uptake was higher (42% compared to 28%) where the offer of TB screening was targeted to students born in high prevalence countries. The relatively low screening uptake in the community outreach model (38%) is partly explained by the number of steps (and potential for attrition between appointments) in the screening pathway as well as other factors such as low local language skills (especially among migrants from Central and Eastern Europe) and being female carers with significant family responsibilities (according to a local analysis, data not shown).

Retention in the treatment cascade

The success of referral to secondary care was highest in the TB extension and workplace outreach models where a specialist liver nurse and a centralised regional system with co-ordinated referrals were in place. Partnership between primary and secondary care services has been shown elsewhere to be successful in other outreach screening models.(21, 23, 24) Loss to follow up in the community outreach model and the opportunistic model can partly be explained by a complex referral pathway as well as by participant characteristics: labour mobility or socio-economic vulnerability (e.g. undocumented status, unemployment). Our experience suggests that appointing case workers (such as health or social workers) for socially vulnerable, linguistically marginalised migrants with evidence of chronic viral hepatitis may improve retention in a cascade of care. Offering testing at the first point of contact (and simplifying the testing cascade) may also improve uptake and retention. We found translation provision (via for instance migrant-language proficient CHWs in the community outreach or the use of telephone interpretation in the workplace-based outreach) overcame language barriers and seemed to partially improve retention. Other studies have found that language barriers are perceived to be a principal barrier in onward care and that immigration status is associated with not receiving viral hepatitis treatment. (55-57) Whilst none of the ten HBsAg cases that reached secondary care were eligible for treatment according to existing clinical guidelines, the monitoring of liver function and disease progression/activation in HBsAg patients is recommended.(24, 58, 59)

Cost data

Our cost data findings can be compared with one US-based study. In this study, Rein et al compared five screening models (in 2008) and whilst the costs per person screened were broadly in the same range ($40-280 US$ compared to $49-239 in our study (US$ data available from the corresponding author)), costs per HBsAg case identified were generally much lower (at $609-$4,657 compared with $2,885-$12,942 in our study).(39) Rein et al also found that integrating screening into existing clinical care (the community clinic model) was the least costly model but reached the fewest people. It also found that the community outreach model was the most costly but reached the highest number of people. We did not see the same linear relationship between costs per person screened and number of people screened (Figure 2), although it is unlikely that our study would have since all five models set a target for the number of people to be screened over a fixed time period.

No studies reporting costs per HCV case identified by a recent systematic review focus on migrants.(60) In a randomised trial of three models of HCV screening among people born during 1945-1965, Brady et al found costs per person screened of US$ $19-25 and costs per

HCV case identified of US$ $4,230-7,005.(44) Aside from the antenatal extension model, the cost per anti-HCV case is broadly comparable with the routine implementation costs in our study.

Future research should focus on three priority areas. More studies of combined HBV/HCV screening focused on migrants born in endemic countries that report on and investigate four key indicators: uptake; costs per person screened/cost per case identified; prevalence by country/region of birth; and retention across the treatment cascade. Future screening studies should also evaluate enabling factors and barriers in securing a high uptake and in successful referral/retention.(47) Finally, cost-effectiveness studies should base model parameters on 'real world' measures of screening uptake and costs such as those reported here and elsewhere.(39, 60)

CONCLUSIONS

Results from the workplace-based outreach show that there is support among employers to run (health) screening interventions on-site during work time, that this model of screening is acceptable to the target population and that migrant workers (here workers born in higher prevalence countries in Eastern/Central Europe) are a key population for HCV case finding (2.3% anti-HCV prevalence). Experience from the two primary care-based models suggests that offering HBV/HCV screening in clinical encounters leads to a high screening uptake although it does not reach people who are not engaged with health care. Conversely, the community outreach model successfully reached at-risk migrants who were not yet integrated into the health care system. Short-term migrants, whether for work or study, may not remain in the country long enough for screening to be judged cost-effective from the host country perspective. However, taking a global health view, diagnosis may lead to future treatment and support informed lifestyle choices that aim to decrease the risk of disease complications and onward transmission. Finally, to maximise the population health impact, minimise costs and maximise the effective use of resources, HBV/HCV screening should focus on migrants born in endemic countries.

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competing interests. The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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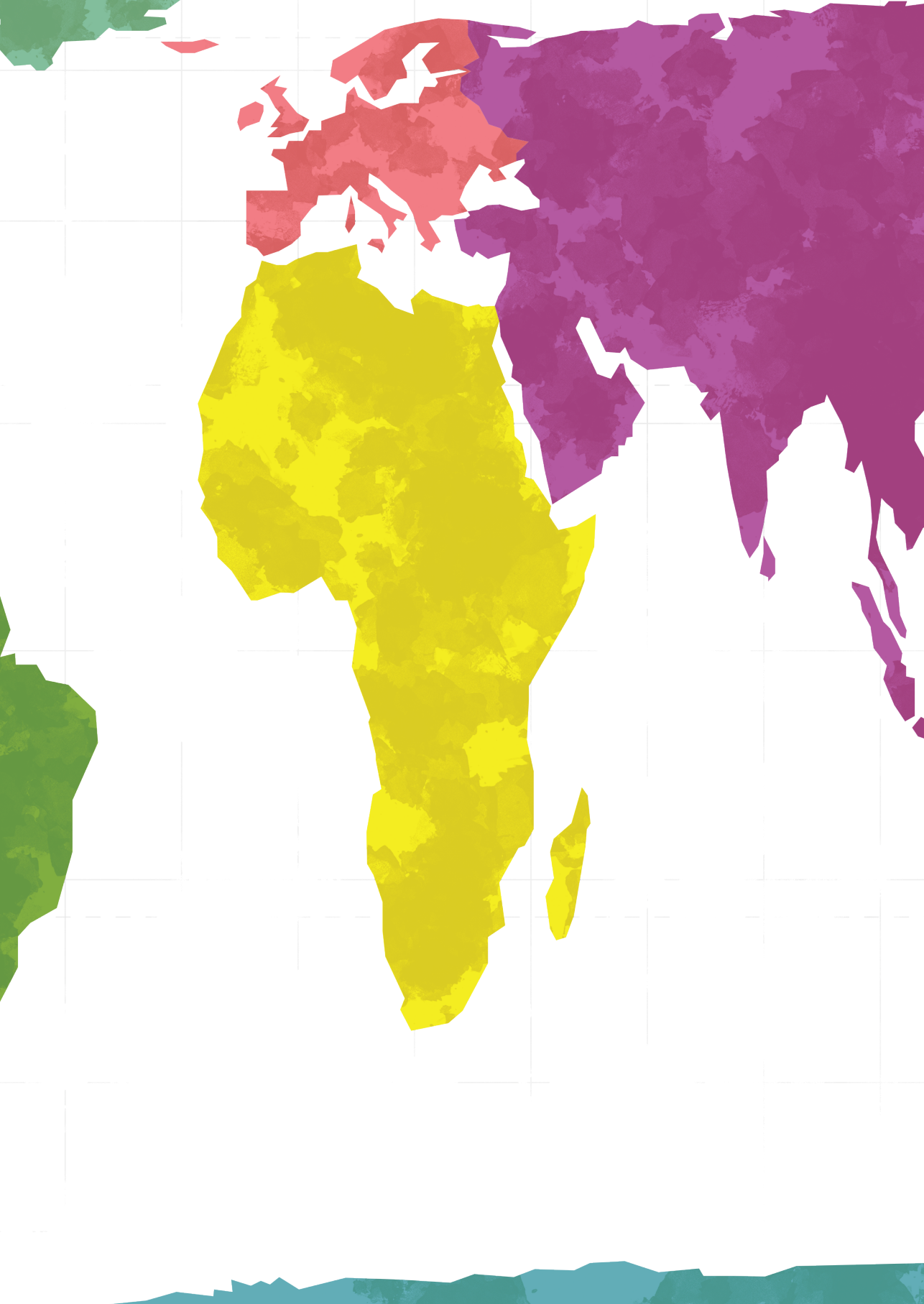

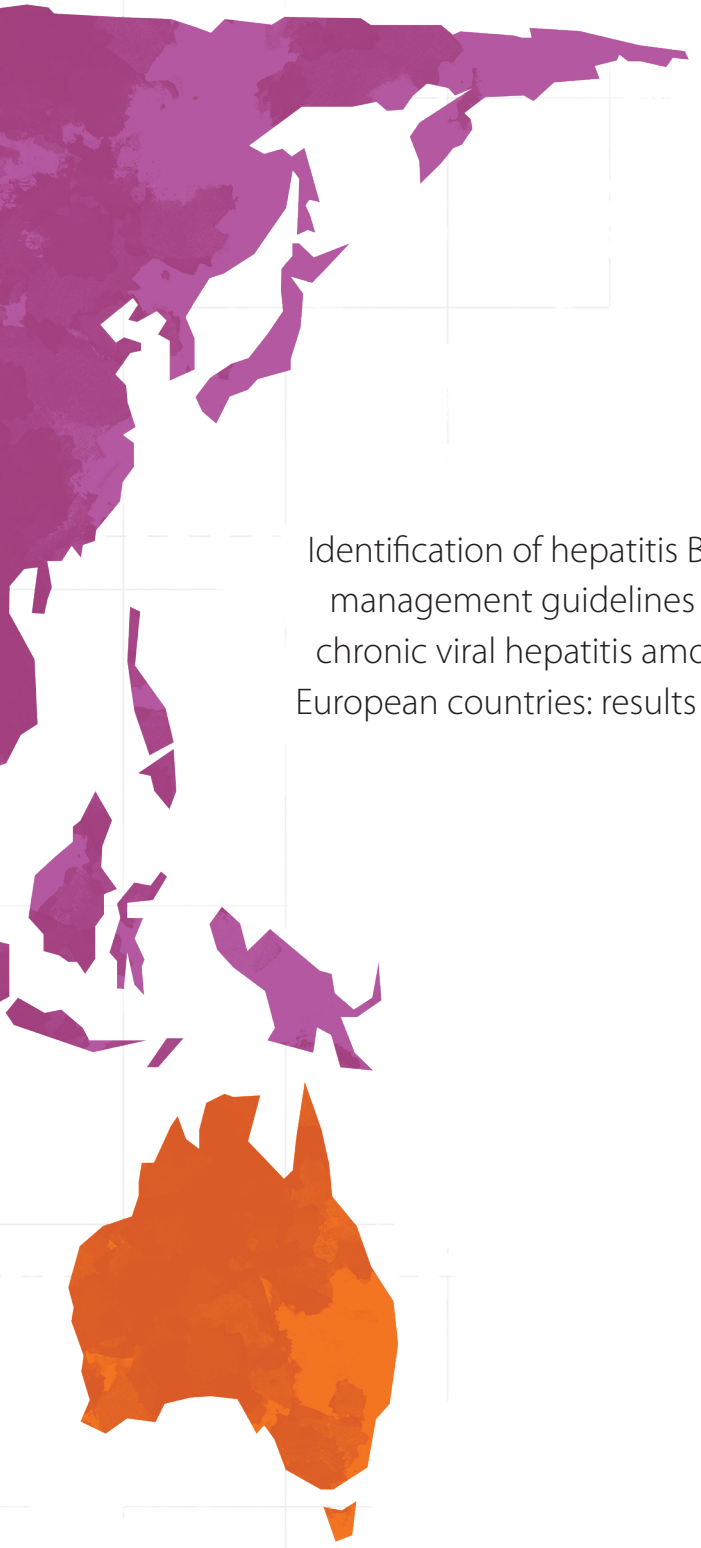

CHAPTER 7

Identification of hepatitis B and C screening and patient management guidelines and availability of training for chronic viral hepatitis among health professionals in six European countries: results of a semi-quantitative survey

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ABSTRACT

Background: As part of the EU funded project 'HEPScreen', the aim of this study is to identify hepatitis B and C screening and patient management guidelines, to assess the awareness of these among health professionals (HPs) and to explore the availability of hepatitis B/C training programmes for HPS in Germany, Italy, the Netherlands, the UK, Spain and Hungary.

Methods: A comprehensive literature search through the main scientific databases was performed to retrieve guidelines, following which an online survey was developed and sent to HPs in six areas of health care, including public health, to verify whether HPs are aware of these guidelines, to retrieve additional guidelines and to find out whether specific professional training is available.

Results: Twelve national guidelines were identified through the literature search. Of the 268 respondents, 80% were aware of hepatitis B guidelines and 73% were aware of hepatitis C guidelines in their country. The national guidelines identified through the literature search were mentioned by 1/3 of HP in the UK and Germany, 13% of HPs in the Netherlands, 14% in Italy and 4% in Spain. An additional 41 hepatitis B/C related guidance documents were retrieved through the online survey: 15 in the UK, seven in Hungary, six in Italy, five in the Netherlands, four in Germany and four in Spain. Availability of training programmes to improve skills and knowledge in viral hepatitis was most often reported in the Netherlands, with 82% indicating availability and just 10% indicating no availability, and least commonly in Italy, with 42% indicating yes but 40% indicating no. Availability was also reported by the majority in the UK, Hungary and Spain, while in Germany the majority selected unsure.

Conclusions: Results suggest that the scientific databases are not the most important information source of best clinical practice for many HPs. Implementation of best practices requires that guidelines are specifically designed and actively promoted among those who are to follow them. Training can disseminate these best practice recommendations and raise awareness of guidelines. It is therefore encouraging that diverse training about hepatitis B/C is available to the different professional groups.

BACKGROUND

Chronic hepatitis B and C are leading causes of liver cancer and are both important public health issues in Europe. In the European Union (EU), some segments of the population, such as migrants from areas where HBV or HCV are endemic and people who inject drugs (PWID), are disproportionately affected by these diseases (1–4). The prevalence in the general population varies from 0.4 to 5.2% for anti-HCV and from 0.1 to 5.6% for HBsAg (5). However, also due to the largely silent nature of these infections, reliable epidemiological data in Europe are lacking both on HBV and HCV (6, 7) and it has been estimated that up to 90% of infected individuals are undiagnosed (8). Therefore, despite the existence of effective antiviral treatment that slows disease progression and prevents the development of cirrhosis and liver cancer, many patients who might benefit from treatment remain undetected (9, 10). Studies also allude to ineffective counselling and referral of diagnosed patients, as well as to the failure of chronically infected patients to reach secondary care, leading to eligible viral hepatitis patients being under-treated (11–16).

Informing health professionals (HPs) of evidence-based recommendations on the prevention of hepatitis B and C, the targeted screening of at-risk individuals, and the diagnostics and clinical management of patients with chronic viral hepatitis, is crucial to obtain the best possible health outcomes. The provision of comprehensive high quality guidelines, as well as advanced training programmes to improve the skills and knowledge of HPs on viral hepatitis management, are ways to achieve this purpose. Numerous studies, however, demonstrate little familiarity or low compliance of HPs with guidelines summarising the best available evidence in their specialties (17–21). National and European hepatitis B and C management guidelines exist, however little is known about the extent to which HPs who are to actually implement them are aware of their existence. Similarly, little is known about the availability of in-service training on chronic viral hepatitis prevention, diagnosis, management and treatment.

This study, conducted as part of EU HEPscreen, a project co-funded by the EU Health Programme (www.hepscreen.eu), has four specific aims. First, to provide an overview of published hepatitis B and C clinical practice guidelines available in Europe and in particular in six EU countries with large migrant communities and representation of migrant health and patient platform, i.e. the UK, Germany, the Netherlands, Hungary, Italy and Spain. Second, to assess the awareness of guidelines among HPs working in these six countries in six fields: public health, antenatal care, primary care, care for asylum seekers/refugees, sexual health, and gastroenterology/hepatology. Third, to measure the availability of viral hepatitis specific training programmes for HPs in these fields. Finally, to investigate HPs' opinion on the existence of barriers such as limited guidance available to primary health

care professionals about onward referral, counselling and patient management of hepatitis B/C patients and low training uptake among professionals as explanations of why hepatitis B/C cases do not reach specialized care for further investigation and treatment.

METHODS

First, a comprehensive literature search was conducted to retrieve published national and European hepatitis B and C clinical guidelines. A modified version of the "PICO" method (22) was applied, using a search syntax comprising of four categories: (1) Population: "general population" OR migrants OR "sex workers" OR "Intravenous drug users" OR IDUs; (2) Disease: "hepatitis B" OR "hepatitis C"; (3) Intervention: screening OR counselling OR referral OR treatment OR therapies OR "clinical management"; (4) Setting: Germany OR Hungary OR Italy OR Spain OR the Netherlands OR the UK OR Europe. These four categories were combined with "AND" to build the final syntax. MEDLINE, EMBASE and the Cochrane Library databases were searched. In addition, websites of the National Institute for Health and Clinical Excellence, the Scottish Intercollegiate Guidelines Network, the Italian National Guidelines System, the European Association for the Study of the Liver (EASL), the European Centre for Disease Prevention and Control (ECDC), the Robert-Koch-Institute, the World Health Organization, the World Hepatitis Alliance, the European Liver Patients Association and the Italian Liver Patient Association, were searched. The literature search encompassed guidelines published between January 2000 to March 2012 in English, Spanish, Italian, Dutch, Hungarian or German and it was conducted between November 2011 and February 2012. Titles, abstracts and full-texts of relevant documents were screened by two reviewers, independently. Disagreements about eligibility were resolved through discussion. A list of all guidelines retrieved was developed and categorised by country and type of hepatitis.

To identify further professional guidelines missed by the literature search and to assess awareness about existing guidelines among different groups of HPs involved in screening for or caring for chronic viral hepatitis, six semi-quantitative online surveys were developed. The surveys were sent to HPs in their respective field i.e. to public health professionals (PHPs); to general practitioners (GPs); to sexual health service providers (SHS) and/or genitourinary medicine (GUM) specialists; to antenatal care (ANC) providers; to asylum seeker care (ASC) providers and to specialists (SP) in the field of gastroenterology/hepatology and infectious diseases. Each survey was pilot tested, translated into the national language of the respective study countries, uploaded into the open source online software package LimeSurvey, and sent by e-mail to HPs in the six areas, who were identified by board membership of clinical associations, professional networks, ECDC focal points, scientific literature and other means. Rather than to reach a large representative sample of practising clinicians, the aim

in each professional group was to reach 5– 10 HPs deemed able to reflect on the practice within their specialism in general. Data were collected between July and September 2012. Respondents agreed to participate by answering the questionnaire.

We measured whether official national guidelines were available, both general guidelines (the question was included in all six surveys), with a request to provide the title and publisher in a text field in case of a positive response, and guidelines specifically developed for professionals in their field. We also asked public health specialists whether specific guidelines for migrants from endemic areas exist. The responses were exported into SPSS 19.2 and a descriptive analysis was performed to evaluate which hepatitis B/C guidelines are known to HPs, how many professionals mentioned the main guidelines identified through the literature search and how many additional guidelines were retrieved. In all surveys, except the survey aimed at public health professionals, a question about the provision of hepatitis B/C-related training for HPs in their respective medical specialties was also included. The identification of general hepatitis guidelines by respondents was analysed in connection with their opinion on the existence of professional training to improve knowledge and skills about viral hepatitis. Finally, all professional groups were asked to indicate on a five-point Likert scale, from "strongly agree" to "strongly disagree", to which extent they agree that the given statements are explanations of why hepatitis B/C cases do not reach specialized health care for further management: i) There is limited guidance available to primary health care professionals about onward referral, counselling and patient management of hepatitis B/C patients; ii) Although training on viral hepatitis management is available for health care providers, uptake is generally low among professionals. The study complied with the Helsinki Declaration (23).

RESULTS

Literature search results: clinical practice guidelines

The literature search retrieved eight international guidelines: two from EASL (24, 25); two from the Association for the Study of Liver Diseases (26, 27); the "European Guideline for the Management of Hepatitis B and C Virus Infections" by the International Union against Sexually Transmitted Infections (28); the "Best Practice in the Treatment of Chronic Hepatitis B" published by the European Viral Hepatitis Educational Initiative (29); and two National Institute of Health Consensus Statements on the management of hepatitis C and B from the US (30, 31). Twelve major national guidelines were retrieved: six in the UK (32–37), two in Italy (38, 39), two in Germany (40, 41) and two in the Netherlands (42, 43).

Since the date of the search (March 2012), several guidelines have been revised, mostly due to treatment advances. In such cases, the updated guidelines are cited as references.

Survey results

We received a total of 268 responses to the survey, not evenly distributed across the six professional groups or across the six countries (Table 1).

Table 1. Number of health professionals completing the questionnaire by country and by survey

Survey (% of health professionals for each survey by country)	Country						Total
	UK	DE	NL	HU	IT	ES	
Public health	9 (20%)	13 (29%)	7 (16%)	2 (4%)	8 (18%)	6 (13%)	45 (100%)
Antenatal care	8 (10%)	33 (40%)	6 (7%)	4 (5%)	23 (28%)	8 (10%)	82 (100%)
GP	8 (21%)	4 (11%)	9 (24%)	1 (3%)	14 (37%)	2 (5%)	38 (100%)
Care for asylum seekers	4 (22%)	3 (17%)	4 (22%)	3 (17%)	3 (17%)	1 (6%)	18 (100%)
SHS	9 (35%)	4 (15%)	7 (27%)	3 (11%)	1 (4%)	2 (8%)	26 (100%)
Specialist care	9 (15%)	7 (12%)	22 (37%)	8 (14%)	9 (15%)	4 (7%)	59 (100%)
Total	47 (18%)	64 (24%)	55 (21%)	21 (8%)	58 (22%)	23 (9%)	268 (100%)

Identification of HBV and HCV guidelines through the online survey

National or international guidelines already identified through the literature search were mentioned by one third of respondents in the UK and Germany, and only by a minority of HPs in Italy (14%) and the Netherlands (13%) and by just 4% in Spain. An additional 41 hepatitis B/C-related national guidance documents were identified by HPs through the online survey: 15 in the UK, seven in Hungary, six in Italy, five in the Netherlands, four in Germany and four in Spain. Table S1 online compiles all hepatitis B/C related guidelines and guidance documents retrieved through the literature search and/or identified by HPs.

National general HBV and HCV screening and management guidelines

The existence of official national general hepatitis B or C screening and patient management guidelines in the study countries, was reported by 61% and 56%, respectively (Table 2). Among these, only about 40% provided the title and publisher of the guideline. Around two thirds to three quarters of HPs in the Netherlands and in Hungary reported availability

of general guidelines compared to just over half in the UK and Italy. Conversely, the majority of HPs in Spain and, for hepatitis C guidelines, in Germany, reported uncertainty or that no general guideline is available.

Table 2. Health professionals reporting the existence of national general hepatitis B and C guidelines in their country

Hepatitis B guidelines	**UK (n = 47)**	**DE (n = 64)**	**NL (n = 55)**	**HU (n = 21)**	**IT (n = 58)**	**ES (n = 23)**	**Total (n = 268)**
Proportion of health professionals reporting the existence	57%	56%	78%	67%	57%	43%	61%
Provided name and publisher[a]	41%	31%	44%	36%	45%	50%	40%
Hepatitis C guidelines	**UK (n = 47)**	**DE (n = 64)**	**NL (n = 55)**	**HU (n = 21)**	**IT (n = 58)**	**ES (n = 23)**	**Total (n = 268)**
Proportion of health professionals reporting the existence	60%	47%	67%	67%	57%	39%	56%
Provided name and publisher[b]	39%	37%	51%	29%	45%	44%	42%

a Percent of the respondents who reported the existence of general hepatitis B guidelines; b Percent of the respondents who reported the existence of general hepatitis C guidelines

Professional group-specific national HBV and HCV guidelines

Overall 80% (n = 215) of respondents are aware of hepatitis B guidelines and 73% (n = 196) of hepatitis C guidelines in their country. Among the 45 PHPs, around two thirds mentioned the existence of general Hepatitis B and hepatitis C guidelines. Among the 38 GPs, 29% mentioned specific HBV guidelines for GPs and 21% the existence of HCV guidelines for GPs. Interestingly, among PHPs, 47% mentioned the existence of HBV guidelines specifically for GPs and 40% the existence of GP-specific HCV guidelines. Of the 82 ANC experts, 52% mentioned HBV and 26% HCV guidelines for antenatal services. Among the 59 secondary care specialists, 61% mentioned HBV guidelines and 56% mentioned HCV guidelines. None of the 18 ASC experts identified the existence of HBV/HCV guidelines for the care of asylum seekers. Just 22% (for HBV) and 13% (for HCV) of PHPs reported the existence of specific guidelines for migrants from endemic areas. Detailed results are displayed in Table 3.

Table 3. Health professionals identifying hepatitis general or specific guidelines by professional group and by country

HBV GUIDELINES	**UK**	**DE**	**NL**	**IT**	**ES**	**HU**	**Total**
General Hepatitis B guidelines (Public health professionals)	56%	77%	71%	50%	67%	100%	67%
Antenatal care experts	50%	33%	67%	44%	13%	50%	39%
General Practitioners	38%	50%	78%	71%	100%	100%	66%
Asylum seekers Experts	100%	100%	50%	100%	0%	100%	83%
SHS Experts	56%	75%	86%	100%	0%	67%	65%
Specialists	67%	100%	86%	56%	75%	50%	75%
GP guidelines (Public health professionals)	67%	31%	100%	25%	33%	0%	47%
General Practitioners	13%	0%	78%	21%	0%	0%	29%
Antenatal guidelines (Public health professionals)	78%	8%	71%	25%	67%	50%	44%
Antenatal care Experts	75%	40%	67%	39%	88%	100%	52%
Asylum seekers guidelines (Public health professionals)	33%	0%	14%	13%	0%	0%	11%
Asylum seekers Experts	0%	0%	0%	0%	0%	0%	0%
Specialists guidelines (Public health professionals)	78%	38%	57%	25%	33%	50%	47%
Specialists	44%	43%	86%	33%	75%	50%	61%
Migrant care guidelines (Public health professionals)	33%	0%	14%	25%	67%	0%	22%
HCV GUIDELINES	**UK**	**DE**	**NL**	**IT**	**ES**	**HU**	**Total**
General HCV guidelines (Public health professionals)	56%	77%	57%	50%	67%	100%	64%
Antenatal care experts	38%	18%	67%	44%	25%	25%	32%
General Practitioners	38%	50%	67%	71%	50%	100%	61%
Asylum seekers Experts	100%	100%	50%	100%	0%	100%	83%
SHS Experts	67%	75%	71%	100%	0%	67%	65%
Specialists	78%	86%	73%	56%	50%	63%	70%
GP guidelines (Public health professionals)	67%	23%	57%	38%	33%	0%	40%
General Practitioners	0%	0%	56%	21%	0%	0%	21%
Antenatal guidelines (Public health professionals)	33%	0%	14%	25%	0%	0%	13%
Antenatal care experts	25%	13%	0%	35%	75%	25%	26%
Asylum seekers guidelines (Public health professionals)	11%	0%	0%	13%	0%	0%	4%
Asylum seekers Experts	0%	0%	0%	0%	0%	0%	0%
Specialists guidelines (Public health professionals)	56%	23%	29%	25%	0%	0%	27%
Specialists	44%	43%	73%	44%	50%	50%	56%
Migrant care guidelines (Public health professionals)	33%	0%	0%	13%	33%	0%	13%

Reported availability of hepatitis B/C training for health care professionals

Table 4 shows the reported availability of training in the six countries. Among secondary care specialists, availability of training was reported by 84% (although only by 44% in Italy), among GPs by two thirds (although only by half of them in Germany and Spain and by 40% in the UK) and by 55% among SHS experts. Most HPs working in antenatal care indicated that training is not available or selected unsure. The majority opinion among those providing care to asylum seeker is that training is not available for professionals in their field.

Table 4. Availability of training to improve knowledge and skills in viral hepatitis in the six countries

UK	**GP (n = 10)**	**Antenatal (n = 8)**	**Asylum (n = 4)**	**SHS (n = 10)**	**Specialist (n = 10)**
Yes	40%	50%	25%	70%	100%
No	10%	13%	75%	0%	0%
Unsure	50%	38%	0%	30%	0%
DE	**GP (n = 4)**	**Antenatal (n = 36)**	**Asylum (n = 3)**	**SHS (n = 5)**	**Specialist (n = 9)**
Yes	50%	11%	67%	60%	67%
No	0%	25%	33%	0%	0%
Unsure	50%	64%	0%	40%	33%
NL	**GP (n = 9)**	**Antenatal (n = 6)**	**Asylum (n = 4)**	**SHS (n = 8)**	**Specialist (n = 22)**
Yes	89%	33%	75%	63%	100%
No	0%	50%	25%	13%	0%
Unsure	11%	17%	0%	25%	0%
HU	**GP (n = 1)**	**Antenatal (n = 4)**	**Asylum (n = 3)**	**SHS (n = 3)**	**Specialist (n = 10)**
Yes	100%	50%	33%	0%	80%
No	0%	25%	33%	100%	0%
Unsure	0%	25%	33%	0%	20%
IT	**GP (n = 14)**	**Antenatal (n = 25)**	**Asylum (n = 3)**	**SHS (n = 1)**	**Specialist (n = 9)**
Yes	79%	28%	0%	0%	44%
No	7%	52%	100%	100%	33%
Unsure	14%	20%	0%	0%	22%
ES	**GP (n = 2)**	**Antenatal (n = 8)**	**Asylum (n = 1)**	**SHS (n = 2)**	**Specialist (n = 4)**
Yes	50%	75%	0%	50%	100%
No	50%	25%	100%	0%	0%
Unsure	0%	0%	0%	50%	0%

Guidelines and Training

Availability of general national guidelines was most commonly mentioned by HPs who reported the existence of professional training (Table 5). Over two thirds of those who indicated that professional training is available also indicated the existence of general guidelines for hepatitis B (69%) and hepatitis C (64%), whereas among those who indicated that training is not available, just 47% for HBV and 42% for HCV reported the existence of general national guidelines. Surprisingly, in Hungary, general hepatitis B guidelines were identified more often by HPs reporting a lack of, or uncertainty about, available training for professionals.

Perceived barriers to inadequate referral of hepatitis B/C cases

Limited guidance available to primary health care professionals about onward referral, counselling and patient management of hepatitis B/C patients was perceived as a reason of why hepatitis B/C patients do not reach specialized health care for further investigation and treatment according to nearly half of the respondents in Italy (43% answered they "agree" or "strongly agree"), around a third of respondents in Spain, a quarter in the UK and in Germany and a fifth in the Netherlands, but not in Hungary (Table 6). Low training uptake among professionals as a possible explanation was reported by more than half of the respondents in Italy (54% agreed or strongly agreed with such a statement), by 38% of those in the UK, a third in the Netherlands, along with a sixth in Germany in Hungary and 9% in Spain (Table 6).

Table 5. Identification of general guidelines by health professionals in relation to the perceived availability of training

		UK	DE	NL	HU	IT	ES	Total
Health professionals reporting that training **is** available for professionals	Health professionals mentioning hepatitis B guidelines	15/25 (60%)	14/17 (82%)	34/40 (85%)	7/12 (58%)	13/22 (59%)	5/12 (42%)	88/128 (69%)
	Health professionals mentioning hepatitis C guidelines	15/25 (60%)	12/17 (71%)	29/40 (73%)	8/12 (67%)	13/22 (59%)	5/12 (42%)	82/128 (64%)
Health professionals reporting that training **is not** available for professionals or who were unsure	Health professionals mentioning hepatitis B guidelines	7/13 (54%)	12/34 (35%)	4/8 (50%)	5/7 (71%)	16/28 (57%)	1/5 (20%)	45/95 (47%)
	Health professionals mentioning hepatitis C guidelines	8/13 (62%)	8/34 (24%)	4/8 (50%)	4/7 (57%)	16/28 (57%)	0/5 (0%)	40/95 (42%)

Note: Public health professionals' responses were not taken into consideration, since the question on the availability of training was not asked in the survey aimed at public health professionals

Table 6. Health professionals' opinion on the existence of barriers as explanations of why hepatitis B/C cases do not reach specialized health care (e.g. hepatologists) for further investigation and treatment. Results are presented by country

		UK (n = 47)	DE (n = 64)	NL (n = 55)	HU (n = 21)	IT (n = 58)	ES (n = 23)
There is limited guidance available to primary health care professionals about onward referral, counselling and patient management of hepatitis B/C patients.	Strongly disagree	11%	8%	2%	33%	7%	17%
	Disagree	32%	31%	58%	29%	34%	39%
	Neither agree or disagree	30%	38%	18%	33%	16%	13%
	Agree	21%	20%	18%	5%	40%	30%
	Strongly agree	6%	3%	4%	0%	3%	0%
Although training on viral hepatitis management is available for health care providers, uptake is generally low among professionals.	Strongly disagree	2%	8%	2%	29%	3%	13%
	Disagree	23%	31%	9%	24%	21%	43%
	Neither agree or disagree	36%	45%	56%	33%	22%	35%
	Agree	34%	16%	31%	10%	52%	9%
	Strongly Agree	4%	0%	2%	5%	2%	0%

DISCUSSION

It has been estimated that in Europe only a minority of hepatitis B or C cases are diagnosed, and that less than 20% of infected individuals receive treatment (44). The reasons for the low treatment rate include on one hand the largely silent nature of the disease, described accordingly as "the silent epidemic", which often prevents patients to seek care until the disease has progressed to end-stage liver disease or hepatocellular carcinoma. On the other hand, patients' lack of knowledge about the disease, language difficulties, lack of social support and lack of understanding of the healthcare system contribute to the exclusion from health care of migrants from endemic areas, despite current evidence showing that they account for one of the largest HBV- or HCV infected group in Europe (45). Legal, administrative, financial barriers and the stigmatization of certain at-risk groups, such as sex workers or PWID, also represent major obstacles to an effective clinical management of this condition (46, 47). Models show that, with treatment at current levels, mortality related to HCV is expected to rise and to peak around 2030 (48). Cohen et al. recently introduced the concept of "under-treatment" to refer to the disparity between the number of chronically infected individuals and the number of patients receiving treatment (12). In order for chronic viral hepatitis-related morbidity and mortality to stop to rise in Europe, large increases in early detection and treatment of patients are urgently needed.

Our study set out to measure availability and awareness of two important means through which evidence-based recommendations can influence clinical practice and HPs' action towards effective clinical management, i.e. guidelines and training. Availability of general hepatitis guidelines was most commonly reported by HPs for whom professional training is also available in their country. Encouragingly, we identified a total of 53 national hepatitis B or C guidelines and guidance documents, with examples across the six countries. However, just twelve of these were retrieved via the literature search. For Hungary, the search failed to retrieve any guidelines published in English, however seven guidelines, all in Hungarian, were retrieved via the online survey. Moreover, in accordance with prior studies (17–21), few HPs themselves identified guidelines published in the scientific literature. These findings suggest that the scientific databases are not the most important information source of best clinical practice for many HPs. Interestingly, more public health officials identified specific guidelines for GPs than GPs themselves. Limited guidance available was perceived as a reason for inadequate referral of patients according to sizeable proportions of HPs in all countries, with the exception of Hungary. More comprehensive guidelines, tailored to the needs of specific professional groups like GPs, sexual health or maternity services, may be an alternative to increase awareness and improve implementation of recommendations.

Our findings also indicate that there is either scarcity or complete lack of guidance for HPs about screening practices and disease management of migrants and asylum seekers from endemic areas.

Results on the availability of specific hepatitis B/C training programmes suggest that, for many professionals, in the Netherlands, the UK, Hungary and Spain training is available. However there are differences between professional groups within countries. Results in the UK suggest that training is lacking or unknown for GPs and professionals in health care for asylum seekers. In Germany, training is similarly neither widespread nor well known across all professional groups. In Hungary, training is not widely available, especially for professionals working in the area of sexual health. In Italy, a lack of availability was reported by over half of the antenatal care providers and by all respondents to the asylum seeker and SHS survey; training seems to be more available to GPs. The low numbers of respondents among some professional groups in Hungary and Spain limit the generalizability of findings, although in Spain, training seems to be available for antenatal care providers and specialists.

That training is most commonly available to secondary care specialists is perhaps not surprising; what is more surprising is that less than half in Italy and only two thirds of specialists in Germany reported the availability of training. Given the role of the specialists and the rapidly advancing knowledge of viral hepatitis, especially the new treatment options for hepatitis C, this finding is particularly concerning. Results suggest that, except for Spain, training for antenatal care providers is rather limited, but especially so in Germany, Netherlands and Italy. The implications of this could be sub-optimal care and ineffective referral of pregnant women testing positive, as well as a lack of contact tracing. It would be particularly interesting to know how this lack of training has an impact on the care of hepatitis B positive pregnant women. Low training uptake as a possible explanation of why hepatitis B/C cases do not reach specialized health care was reported by relevant proportions of HPs in Italy, in the UK, and in the Netherlands.

The findings from our study highlighted that the awareness of screening and patient management guidelines and in-service training courses among HPs are presently insufficient. Improving results, as supported by key stakeholders (49), would imply a strong involvement of national health authorities with the implementation of specific national action plans, an effective disease surveillance to develop effective policies and the establishment of specialized centres. In this respect, the undeniable success of the experiences developed in Scotland and in France provide a working model for other countries to follow. Among the strategic actions of the Hepatitis C Action Plan for Scotland (50), a document was produced (51), with the aim to support NHS Boards build action plans for facilitating, delivering and evaluating workforce education development for staff. Complements this a workbook (52),

published to provide staff with a structured approach to assessing, demonstrating and developing their ability to carry out their role in delivering Hepatitis C services. Scaling up HPs training and evaluating the compliance to clinical practice guidelines were also objectives of the French National Plan for hepatitis B and C 2009–2012, following which the management of hepatitis B and C was set as a priority topic in continuing medical education (53). Subsequently, guidelines for the management of patients with hepatitis B and C were developed (54), with recommendations aimed at HPs and the other key stakeholders.

CONCLUSIONS

Our results suggest that not only are there few examples of guidelines for the professional groups most able to implement the recommendations, but also that there is low awareness of those that do exist among primary care professionals most often representing patients' first points of contact. Without short, precise and feasible guidelines, there are likely to be wide inconsistencies in screening, referral and patient management. Results from our survey also suggest that scientific databases are not the most important information source of best clinical practice for many HPs. Implementation of best practices at both national and European level requires not only the availability of high quality guidelines tailored to the needs of the different professional groups, but also that their existence is actively promoted among those who are to follow them, especially when we consider that availability of research evidence alone does not necessarily coincide with the adoption of recommended practices by physicians. The availability of relevant summaries within guidelines, as well as target dissemination to less experienced clinicians, along with the provision of clear and concise information to patients, are possible solutions to enhance guidelines implementation among clinicians. Given the growing interest in knowledge translation and research dissemination, our findings could prompt key decision making bodies to improve physicians' awareness, agreement, adoption and adherence to clinical practice guidelines, for example through professional associations and training. Our results show that knowledge and availability of hepatitis B/C training could also be improved. Further studies assessing the impact of existing training and guidelines on the care, health literacy and onward referral of patients would be very valuable.

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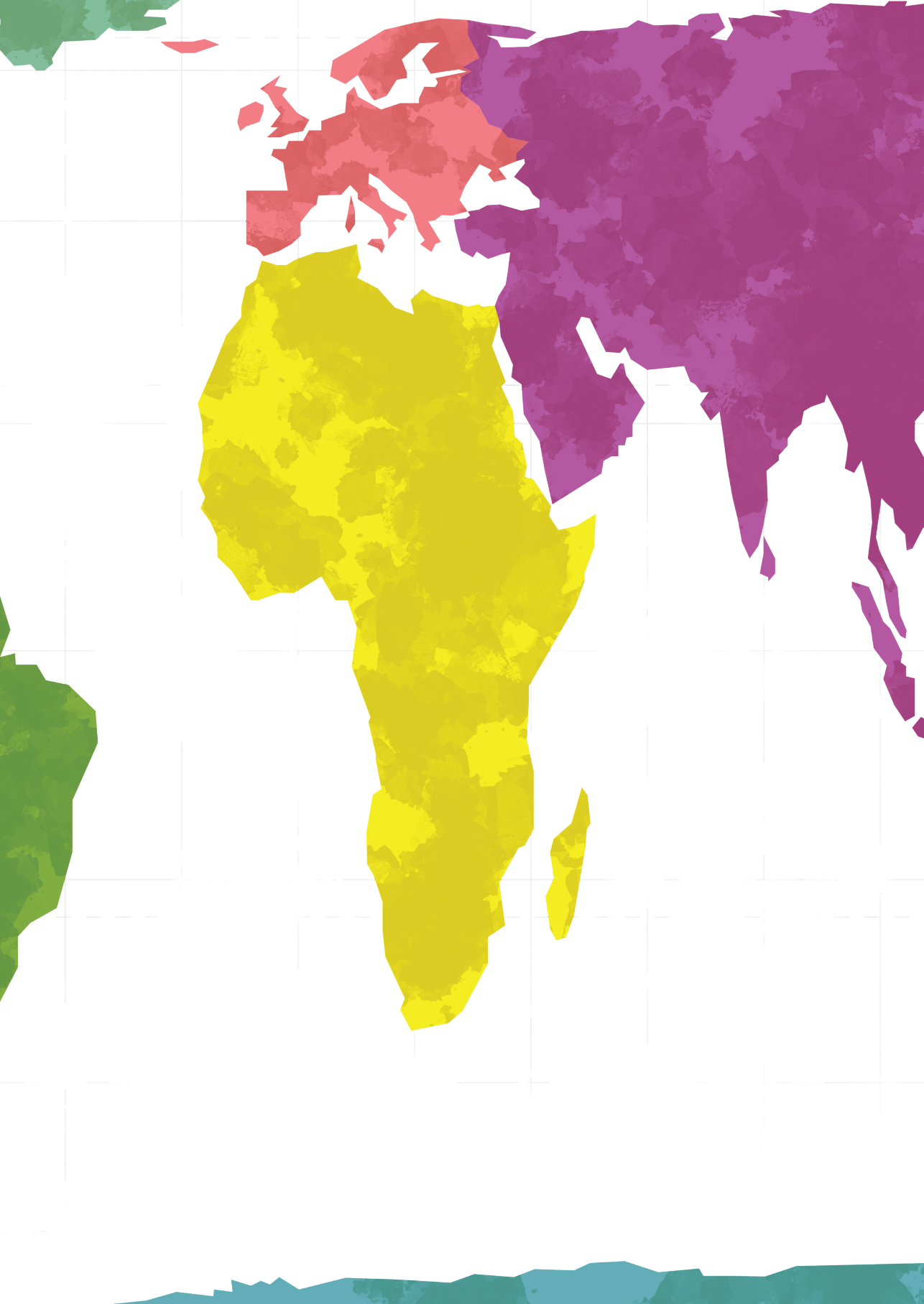

CHAPTER 8

Language support for linguistic minority chronic hepatitis B/C patients: an exploratory study of availability and clinicians' perceptions of language barriers in six European countries

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ABSTRACT

Background: Language support for linguistic minorities can improve patient safety, clinical outcomes and the quality of health care. Most chronic hepatitis B/C infections in Europe are detected among people born in endemic countries mostly in Africa, Asia and Central/Eastern Europe, groups that may experience language barriers when accessing health care services in their host countries. We investigated availability of interpreters and translated materials for linguistic minority hepatitis B/C patients. We also investigated clinicians' agreement that language barriers are explanations of three scenarios: the low screening uptake of hepatitis B/C screening, the lack of screening in primary care, and why cases do not reach specialist care.

Methods: An online survey was developed, translated and sent to experts in five health care services involved in screening or treating viral hepatitis in six European countries: Germany, Hungary, Italy, the Netherlands, Spain and the United Kingdom (UK). The five areas of health care were: general practice/family medicine, antenatal care, health care for asylum seekers, sexual health and specialist secondary care. We measured availability using a three-point ordinal scale ('very common', 'variable or not routine' and 'rarely or never'). We measured agreement using a five-point Likert scale.

Results: We received 238 responses (23% response rate, N = 1026) from representatives in each health care field in each country. Interpreters are common in the UK, the Netherlands and Spain but variable or rare in Germany, Hungary and Italy. Translated materials are rarely/never available in Hungary, Italy and Spain but commonly or variably available in the Netherlands, Germany and the UK. Differing levels of agreement that language barriers explain the three scenarios are seen across the countries. Professionals in countries with most infrequent availability (Hungary and Italy) disagree strongest that language barriers are explanations.

Conclusions: Our findings show pronounced differences between countries in availability of interpreters, differences that mirror socio-cultural value systems of 'difference-sensitive' and 'difference-blindness'. Improved language support is needed given the complex natural history of hepatitis B/C, the recognised barriers to screening and care, and the large undiagnosed burden among (potentially) linguistic minority migrant groups.

BACKGROUND

Most chronic viral hepatitis infections in Europe are detected among migrants born in countries with a medium to high prevalence of hepatitis B and/or C (1). This includes most of Africa and Asia, Central/Eastern Europe and the countries of the former Soviet Union (2, 3). Chronic viral hepatitis B (CHB) and C (CHC) infections have a complex natural history and could require lifelong clinical monitoring and antiviral treatment (4). People chronically infected with hepatitis B or C can also remain infectious to others and should modify or avoid certain behaviours that have a high risk of transmission (5). These features underline the need to provide patients with information and advice about the implications of a diagnosis such as referral to specialist secondary care, diagnostic tests required, the availability of antiviral treatment, how to prevent onward transmission, contact tracing and HBV vaccination. However, research suggests that many diagnosed patients do not reach secondary care for clinical monitoring and antiviral treatment (6, 7), that language barriers are perceived to be the primary barrier to health care for viral hepatitis (8), and that immigration status is associated with not receiving treatment (9). The asymptomatic nature as well as a lack of screening and suboptimal referral strategies means that more than 60% of people infected are unaware of their infection, undiagnosed and not in treatment (1, 10, 11). Effective antiviral treatment for both chronic hepatitis B/C that can prevent the development of cirrhosis and hepatocellular carcinoma, and with newer direct acting anti-virals (DAAs) reporting cure rates in up to 90% of cases of chronic hepatitis C, (12) the elimination of chronic viral hepatitis a possibility in Europe (13). This will require the continued primary prevention of new infections alongside the expansion of secondary prevention through screening and treatment.

Language barriers between linguistic minority migrants (migrants who face language barriers because they do not speak the local language) and health care professionals are reported to increase inequalities in health care via adverse effects on accessibility, quality of care, patient satisfaction, patient safety and patient health outcomes (14). A systematic review of medical interpreter services in the United States (US) showed negative health outcomes as well as poor knowledge and understanding of diagnoses, treatment and implications of the disease, among patients who needed but did not have access to interpreter services, which resulted in inaccurate medical history-taking and missed/incorrect diagnoses (15). Conversely, interpreters have been demonstrated to have a positive impact both on clinical outcomes and in reducing inequalities (16). Thus, interpreters are deemed to be of benefit from both the perspectives of social justice and of evidence-based clinical medicine. Studies that examine good practice in health care for migrants recommend the provision of interpreters and/or translated materials to overcome language barriers as a means to improve patients safety, the quality of health care, medical ethical practice and patient

outcomes (16, 17). Good practice studies of viral hepatitis screening programmes among at-risk migrant populations also provide translated materials and/or interpreters to improve screening uptake, to reach more vulnerable sub-populations (those with very limited local language skills) and to raise awareness in communities at risk (18–21).

There is a distinct lack of disease-specific research however, and much of the literature about language barriers is focused on the countries of the English speaking world (the United States (US), Canada, the UK and Australia) where language proficiency is defined as limited English proficiency. We use 'linguistic minority' as a more appropriate term for our research in the European Union (EU), specifically in Germany, Hungary, Italy, the Netherlands, Spain and the United Kingdom (UK) These six European countries are the locations of the academic and clinical teams participating in the HEPscreen project from which this study arose (http://www.hepscreen.eu). They also differ considerably in their history and experience of migration as well as the health system response to diversity. The proportion of the adult population defined as foreign-born varies from 4.6% in Hungary and 9.5% in Italy to more than 10% in the Netherlands (11.5%), the UK (12.6%), Spain (13.2%) and Germany (13.6%) (22, 23). The UK, the Netherlands and Spain have been described as having a 'difference-based' or communitarian approach to migration and diversity, by recognising difference, actively adapting services to diversity and providing tailored (as opposed to mainstream) health care services (24). The 'difference-blind' or 'republication' systems of Germany, Italy and Hungary assume all citizens should be treated equally through the provision of mainstream (as opposed to separatist) services that are passive to diversity and operate with expectations of assimilation by migrants (25). The six study countries also vary in regard to the financing available for health care. For instance, Germany and the Netherlands spend around five times the amount (per capita) on health care than Hungary (4753.9 USD and 5456.5 USD (respectively) vs. 991.3 USD in 2012) (26).

It is likely that these differences in experience of migration, of socio-cultural value system response to diversity and in health care financing will affect the availability of language support services in the six study countries. In this exploratory study, we investigated the availability of language support services (interpreters and translated written materials about the virus/disease) for linguistic minority chronic viral hepatitis patients. We also investigated health care professionals' agreement that language barriers are explanations of the lack of hepatitis B/C screening among people born in medium/ high prevalence countries in primary care, the low uptake of screening among these patients and why people diagnosed with a chronic infection do not reach specialist care. This study is part of HEPscreen ((http://www.hepscreen.eu)), an EU Health Programme-funded project generally focused on screening for chronic viral hepatitis among migrants in Europe and specifically focused on these six countries.

METHODS

We developed an online survey and sent it to a large convenience sample (n = 1026) of expert clinicians involved in screening or care for viral hepatitis in six EU countries: Germany, Hungary, Italy, the Netherlands, Spain and the UK (England, Wales and Scotland). Recipients were identified via a comprehensive snowballing method via stakeholder consultation within our HEPscreen project consortium, and membership of professional networks or clinical associations involved in five areas of health care: general practice/family medicine, antenatal care, health care for asylum seekers, sexual health services, and specialist secondary care. The aim was to reach knowledgeable experts able to reflect on the circumstances in their profession and country rather than use a representative sampling framework among individual clinicians. We took a health system approach, looking across countries rather than within specific health care services.

The survey measured availability of written and oral language support services (translated materials and telephone or face-to-face interpreters) using closed questions and a three-point ordinal scale: 'very common', 'variable or not routinely' and 'rarely or never' (unsure was also available). We also measured clinicians' perception, using three closed questions and a five-point Likert scale of agreement, of how far language barriers explain three scenarios: the low uptake of screening for hepatitis B/C among migrants born in medium/high prevalence countries; the lack of screening by primary care services among migrants with country of birth-related risk factors; and why people diagnosed with a chronic infection do not reach specialist care for further investigation and antiviral treatment. These three scenarios respectively reflect patient-related, health care service-related and health care system-related issues. The questions reported here are specific sections of a larger survey aimed at understanding screening, referral, treatment and clinical management of hepatitis B/C patients in the six countries. Findings from other sections will be and are reported elsewhere (27).

The survey was pre-tested five times in English in three of the study countries, each with a professional from each of the five professions/health care sectors: from general practice (in Italy), an antenatal care (in Germany), health care for asylum seekers (in Italy), sexual health (in the Netherlands), and specialists in hepatology/gastroenterology (in the Netherlands)). The method used to pre-test was influenced by cognitive interviewing techniques which allow for every detail, no matter how trivial, to be captured by asking subjects to 'think out loud' about the question and answer options. Interviewers can gauge how well the subject has interpreted and understood each aspect of the survey. These techniques also allow for ambiguous or unfamiliar terms and questions to be identified (28). Feedback from each interview was discussed within the research team and a consensus was reached on

each proposed amendment or addition. Several minor changes were made to each survey following pre-testing. Please see the Additional files available online for the final version of the survey.

A professional translation company was used to translate the survey into the languages of the study countries. To ensure the versions provided were understandable, accurate and professional, a native speaker (and fluent English speaker) from the HEPscreen project consortium checked each language translation.

The survey was sent via email in July 2012. Two further reminders were sent and the survey finally closed in September 2012. The reminder schedule conformed to the deadlines set out within our EU Health Programme milestone framework (achievement of which was a condition of our funding). Data were anonymised, extracted and a descriptive analysis was performed using SPSS 19.02. We calculated proportions at the country level for both questions about language support availability and about agreement with language barriers as explanations. To account for different numbers of respondents across each of the five health services, we calculated a weighted average by summing the proportions in each response category in each survey and dividing by five.

RESULTS

We received a total of 238 responses from 1026 recipients (23% response rate). The distribution across the six countries was: 17 in Spain, 21 in Hungary, 42 in the UK, 49 in the Netherlands, 52 in Italy and 57 in Germany. The total included representatives from each of the five areas of health care in all six countries, 81% of whom have a clinical role/are involved in the care of patients. The health care professions/areas of expertise of the 238 respondents were as follows: 87 (37%) from antenatal care, 64 (27%) specialists in gastroenterology/ hepatology or infectious diseases (in secondary care), 40 (17%) from general practice/family medicine, 29 (12%) from sexual health/genito-urinary medicine, and 18 (8%) from health care for asylum seekers and refugees.

Availability of language support

Of all six study countries, translated materials in languages other than the national language were most commonly available in the Netherlands and Germany where just over one third (35 and 37%) indicated very common. However, a large proportion (44 and 36% respectively) indicated they were variably available (Table 1). Translated materials were least commonly available in Italy, where 80% of respondents indicated 'rarely or never' along with the majority in Hungary (61%) and Spain (60%). Half in the UK (51%) indicated translated materials were

variably or not routinely available, with the other half of respondents distributed in all of the other response categories. Interpreters are also very commonly available in the Netherlands (60%), and in the UK, where over half (54%) indicated very common and no-one indicated rarely or never (also Table 1). In contrast, interpreters are rarely or never available for over half in Italy (56%) and nearly half (45%) in Germany, along with over a third in Hungary. Interpreters in Spain seem to be more common than translated materials, which is a general trend seen in our data except for in Germany where translated materials appear to be more commonly available.

Table 1. Availability of translated materials (TM) and interpreters (I) in the six countries

	DE (n = 57)		HU (n = 21)		IT (n = 52)		NL (n = 49)		ES (n = 17)		UK (n = 42)	
	TM	I	TM	I	TM	I	TM	I	TM	I	TM	I
Very common	35%	10%	6%	14%	5%	2%	37%	60%	15%	25%	20%	54%
Variable or not routinely	36%	23%	16%	40%	13%	38%	44%	24%	20%	50%	51%	36%
Rarely or never	17%	45%	61%	36%	80%	56%	14%	10%	60%	23%	13%	0%
Unsure	12%	22%	17%	11%	2%	4%	6%	6%	5%	3%	17%	11%

Abbreviations: DE Germany, HU Hungary, IT Italy, NL the Netherlands, ES Spain, UK United Kingdom

Language barriers as explanations

In the UK, over half agree or strongly agree that language barriers explain all three scenarios (screening uptake, screening offer and referral), and only a minority (between 7 and 15%) expressed disagreement (Table 2). Strongest agreement in the UK emerges about the role of language barriers in referral, where nearly three quarters (73%) strongly agree that these explain why cases do not reach secondary care. A similar pattern emerges in Germany, where three quarters of respondents agree/ strongly agree that language barriers are explanations. Most agreement (over 75%) in Germany is seen for the notion of language barriers as explanations of the lack of screening by primary care services. A less conclusive pattern is found in the Netherlands, where, although between 40 and 55% agree that language barriers are explanations of all three scenarios, a large proportion are neutral and a significant minority disagree/strongly disagree that language barriers explain the low uptake of screening (33%) and why infected patients do not reach secondary care (19%). An interestingly divergent pattern is seen in Hungary, especially in response to language barriers as explanations of low uptake and of why cases do not reach secondary care. Whilst nearly half in Hungary disagree/strongly disagree that language barriers explain the low uptake of

screening, over a third agree/strongly agree that they do explain the low screening uptake. Similarly, nearly half (44%) agree/ strongly agree that language barriers explain why cases of chronic viral hepatitis do not reach specialist care, one third in Hungary disagree/strongly disagree with this notion. There is agreement (77%) that language barriers explain why screening is not offered by primary care services in Hungary. A similarly divergent view is seen in Italy; 80% agree that language barriers explain the lack of screening in primary care, no such strong consensus emerges regarding the other two issues. Although around half agree/strongly agree that language barriers explain a low screening uptake and why cases do not reach secondary care, a significant minority disagree, especially so about the lack of screening offer (26%). In Spain, there is also some diversity in opinion although around two thirds (68%) agree that language barriers are explanations of the lack of screening in primary care and why hepatitis B/C cases do not reach secondary care. Variety in perception of language barriers as explanations of low screening uptake is seen, with 40% in agreement/ strong agreement and 33% in disagreement/strong disagreement.

Table 2. Scale of agreement that language barriers explain three scenarios

Scenario	Response option	DE (n = 31)	HU (n = 18)	IT (n = 35)	NL (n = 49)	ES (n = 15)	UK (n = 39)
Language barriers explain the low uptake of screening by people with country of birth-related risk factors	Strongly disagree	3%	18%	0%	2%	13%	3%
	Disagree	10%	35%	26%	31%	20%	13%
	Neutral	23%	12%	26%	22%	27%	23%
	Agree	52%	24%	31%	39%	33%	54%
	Strongly Agree	13%	12%	17%	6%	7%	8%
A lack of translated materials/ interpreters explains the lack of screening in primary care	Strongly disagree	0%	6%	0%	0%	0%	0%
	Disagree	7%	6%	6%	14%	13%	15%
	Neutral	16%	12%	14%	45%	27%	33%
	Agree	68%	59%	63%	37%	53%	44%
	Strongly Agree	10%	18%	17%	4%	7%	8%
Language barriers explain why hepatitis B/C cases do not reach specialist secondary care	Strongly disagree	4%	22%	0%	0%	0%	0%
	Disagree	13%	11%	15%	19%	18%	7%
	Neutral	17%	22%	35%	26%	18%	20%
	Agree	58%	33%	39%	41%	46%	63%
	Strongly Agree	8%	11%	12%	15%	18%	10%

DISCUSSION

European countries have differing historical experiences of migration, with the six countries in our study illustrative both of these differences and of the availability services to overcome barriers to health care, in this instance language barriers. Our first aim was to understand availability of language support (translated materials and interpreters) in health care services most involved in screening and/or treating chronic hepatitis B/C among at risk migrant communities. Results suggest that translated materials are rarely or never available in Hungary, Italy and Spain but more commonly or variably available in the Netherlands, Germany and the UK. Our results suggest that interpreters are quite commonly available in the UK, the Netherlands and Spain but more variably or rarely available in Germany, Hungary and Italy. Our second research aim was to investigate how far professionals agree that language barriers explain three scenarios: the low uptake of screening among people with country of birth-related risk factors; the lack of screening in primary care among these risk groups; and why cases of chronic viral hepatitis do not reach specialist care for clinical management and treatment. Three interesting results emerge from this second research question: one, that opinion about the role of language barriers in the three scenarios is not identical in each country; two, that differences of opinion within one country about each scenario exist; and three, that professionals in countries with the most infrequent availability (Hungary and Italy) disagree most that language barriers are explanations.

Our findings both mirror and contrast with those from other studies about language support in health services in these six study countries and about barriers to screening and referral for chronic viral hepatitis internationally. In an analysis of migrant health policies, the provision of interpreters was found to be detailed in policy goals in the UK, the Netherlands and Spain although actual implementation of policy was considered patchy (26), which is what we see in our results for these three countries. A summary study in Germany similarly found that the use of interpreters in health care is not well established and that availability is the exception not the rule (29), again in line with the variable or not routine availability reported by 36% of respondents here. Other studies from the Netherlands seem to suggest a less frequent availability of support services than we see reported in our study; studies found poor information exchange between migrant patients and health care professionals, an underreporting of poor Dutch proficiency in medical records, that family members are used as interpreters and that professional interpreter services are hardly used in hospital settings (30, 31).

In the UK, the Netherlands and Germany, migration from the former Empire (in the case of the UK) and from the Mediterranean region (in the Netherlands and Germany) has been an historic trend since the 1950s, although war, conflict and economic crisis in the Eastern

Mediterranean region has led to an influx of migrants presenting new challenges to health care systems. In contrast, migration to Spain and Italy is a relatively new phenomenon and it is only in the last two decades that these countries have experienced migration in large numbers from, for example, 2.5% in 2001 in Spain to 13.2% in 2012 (32). Migration to Hungary is still relatively uncommon with just 4.6% of the population foreign-born in 2012 (23). Given these differences in the population of migrants, disagreement about the role that language barriers play in screening and referral could be explained by how likely it is that professionals encounter linguistic minority patients in their services. Disagreement about their role a could reflect a perception that people with country of birth-related risk factors are not linguistic minorities (due to speaking the same/similar languages) and/or can speak the national language to a good enough standard not to require support.

The results could also reflect underlying socio-cultural value systems that migrants should assimilate and adapt by learning the national language. Indeed, interpreters are reported to be less common in the three 'difference-blind' systems in our study, namely Germany (10%), Hungary (14%) and Italy (2%) compared to the 'difference-based' systems of the UK (54%), the Netherlands (60%) and Spain (25%). Agreement that language barriers exist is however most strong in Germany, suggesting that clinicians may not subscribe to the socio-cultural value system of assimilation over adaptation. Agreement in the Netherlands is surprisingly low across the three scenarios, which could be explained either by the common availability of interpreters we see in the results from our first aim (and therefore removal of language barriers) or by the socio-political shift from multiculturialist 'difference-based' policies to inter-culturalist policies that favour individual responsibility and encourage migrants to learn Dutch (24). A recent study from the Netherlands offers some support for this notion and found that whilst it is hospital policy to make (hospital-funded) interpreters available, nursing service heads rarely reference the policy, and health care providers indicated that it is the responsibility of patients to overcome language barriers by bringing an interpreter to appointments (30). Similarly, public funding for interpreters in health care was recently withdrawn (33).

Disagreement about the role of language barriers in the three scenarios could also reflect a perception of prioritisation i.e. that language barriers are not as important explanations when compared to other factors such as health care provider knowledge, awareness of country of birth as a risk factor, or a lack of time in health care appointments (34). A study from the US found that hepatitis C testing is rarely performed in primary care among patients presenting with infection risk factors, although the list in the study did not include birth in an endemic country, itself an indication of the lack of awareness about this important risk group (35). Another study in the US found frequent reports of communication barriers between physicians and CHC patients, including stigmatisation, assumptions of sexual

promiscuity or injecting drug use as the source of infection, a lack of disease-related explanation or post-test counselling, and an unwillingness to refer (36). The finding that stigmatisation and assumptions are made about patients infected with viral hepatitis, about people with the additional barrier of language, increases the likelihood of these patients receiving poor quality health care. A study in Australia about barriers faced by migrants in accessing health care for viral hepatitis infection found that language barriers was the 'chief barrier' for 45% of patients with a migrant background (8). Studies from the UK, the Netherlands and Italy show that a large proportion of chronic viral hepatitis patients do not reach secondary care (6, 9, 37, 38) and that immigration is negatively associated with being on treatment (39, 40). These studies suggest multiple explanations for why screening isn't offered to or taken up by at-risk migrant groups as well as why diagnosed patients do not reach specialist care. However, to realise the public health gains possible due to improved treatment regimens, screening and referral needs to be scaled up (41).

A strength of this study is the inclusion of study countries that reflect different models and value systems in health care delivery. Previous multi-country research among expert clinicians and policy makers about the provision of hepatitis B/C screening and treatment services for at risk populations has only been conducted in English (42, 43). The translation of our survey into the national languages of our study countries is a concerted effort to overcome language barriers, an important strength given the focus of the study on language barriers themselves. A further strength is the inclusion of experts across the patient pathway, from primary to secondary care as well as specific services for refugees and asylum seekers. It is notoriously challenging to yield high response rates to non-incentivised online surveys among busy, practising clinicians. We reached 238 knowledgeable experts in five areas of health care in the six countries and, although the overall response rate is low (23%), the results in all six countries are broadly in line with the scarce disease-specific, migrant population-specific and European-focused research available to compare and contrast our findings with.

CONCLUSIONS

Our findings show pronounced differences between countries in the availability of interpreters, differences that mirror the underlying socio-cultural value systems of 'difference-sensitive' and 'difference-blindness' that have been described in literature. Results also suggest varying or service-/professional-specific availability of interpreters and/or translated written materials for chronic viral hepatitis. This is despite the complexity of the disease, the recognised barriers to screening and care, and the large undiagnosed burden among (potentially) linguistic minority migrant groups. This finding is mirrored in the view

among many clinicians in the six study countries that language barriers are important explanations of low screening uptake, a lack of screening by primary care, and why diagnosed hepatitis B/C patients do not reach secondary care. Europe is behind the curve of viral hepatitis-related mortality and getting ahead requires expanding and improving access to screening among at-risk populations, especially among people with country of birth-related risk factors. Evidence shows that interpreters and translated materials can improve acceptance of screening, patient knowledge and understanding, and, most importantly, clinical outcomes. To overcome language barriers, it is important that existing and future screening programmes provide language support for linguistic minority patients at risk of or diagnosed with chronic viral hepatitis.

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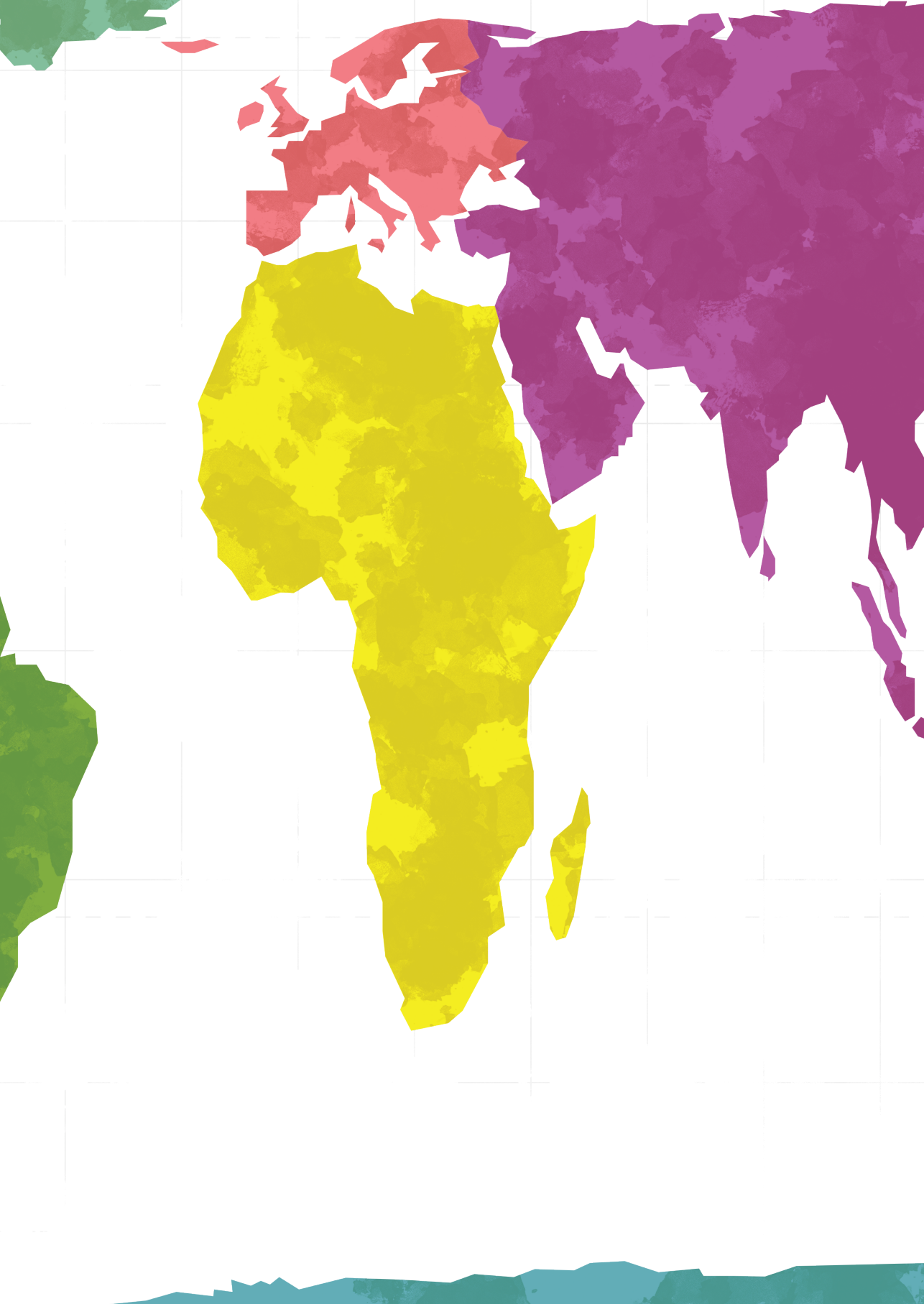

CHAPTER 9

Pre-test information before chronic hepatitis B/C screening among migrants - balancing informed choice and securing uptake: a mixed methods exploratory study

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ABSTRACT

Objective: Explore and develop the concept of pre-test information before HBV/HCV screening among at-risk migrants.

Methods: Systematic literature review/content analysis to identify pre-test information objectives and topics. An online survey among health care providers (HCPs) to acquiesce consensus on the importance of a) each objective and b) each topic across three domains (securing informed choice, reducing stigma and fear, and if/when time is limited).

Results: The content analysis identified six pre-test information objectives. These were ranked by the 43 respondents to the survey in the following order of importance: raising knowledge/awareness, securing informed choice, improving acceptance, preparing for a positive result, reducing stigma/fear and normalising testing. Ten pre-test information topics were consolidated from the content analysis. The five most important topics across the three domains were: reasons for testing, health benefits offered by treatment, implications of a positive test result for the individual, modes of transmission and confidentiality of test results.

Conclusion: HCPs see it as their role to increase screening uptake, to encourage people to undergo screening.

Practice Implications: We developed a 'pre-test information checklist' (included as a supplementary annex) to enable HCPs to provide pre-test information that can secure informed choice, reduce stigma and fear, and be delivered if/when time for a discussion is limited.

INTRODUCTION

If left untreated, chronic hepatitis B (CHB) and C (CHC) infections slowly attack the liver and can cause serious liver disease including cirrhosis and hepatocellular carcinoma (HCC). Advances in antiviral treatment have improved the scope for secondary prevention through suppression of viral replication, prevention of disease progression and, in the case of CHC, cure within 12 weeks using often side-effect free, interferon-free direct acting antivirals (DAAs).(1-3) As many people who are chronically infected are asymptomatic, unaware of their status and have not yet reached the advanced stages of the disease, attributable morbidity and mortality in high-income countries are predicted to at least double in the next two decades.(4, 5) Asymptomatic CHB/CHC cases are unlikely to be spontaneously diagnosed by presenting to health care services for testing.(6) To reduce the burden of CHB/CHC associated morbidity and mortality and to expand access to treatment, screening among certain populations is recommended by clinical and public health guidelines in most high-income countries and by the World Health Organisation.(7-10) These populations include the baby boomer birth cohort born 1945-1965 (for HCV), migrants born in intermediate/high prevalence countries, men who have sex with men (MSM), and people who inject(ed) drugs (PWID).

Screening programmes should demonstrate that the benefits outweigh the harms at a population level.(11) People offered screening should also be made aware of these benefits and harms, via the provision of unbiased information, and to choose, free from coercion, whether they wish to participate in screening.(12) The information exchange between people offered screening and health care professionals is also described as pre-test information. This information should be of sufficient relevancy and quality to make an informed choice. The notion of informed choice in screening reflects the desire to respect individual autonomy and is based on three principal considerations: first, that it is unethical to provide medical interventions to people who are unaware of the consequences; second, that an informed choice can lead to improved health outcomes; and finally, the threat of litigation due to misunderstandings about the consequences of screening.(13) Much of the literature describing these concepts and their application in practice is focused on non-communicable diseases like cancers (mostly in screening for breast, colorectal and lung) or antenatal screening for chromosomal or genetic abnormalities where the decision to undergo screening or not has largely individual implications. Unlike non-communicable disease screening, the infectious nature of viral hepatitis means that the decision to (not) undergo screening has a wider community health impact due to the risk of onward transmission and the potential for contact tracing and vaccination (for HBV).

The field of pre-test information before screening for chronic infectious disease such as HBV/HCV is much less well defined and researched than the field of screening for cancers or of screening in pregnancy. Specifically for HBV/HCV, there is a lack of clarity about the aims and content of pre-test information and a lack of studies that investigate what is actually provided by health care professionals (HCPs) offering screening. Studies that investigate pre-test information provision relating to chronic hepatitis B/C across Europe are virtually non-existent, in part due the methodological and resource challenges posed by the research question.

Our study takes place within the European context and we are specifically interested in screening among migrants born in HBV/HCV endemic countries. Migrants to Europe from intermediate/high HBV/HCV prevalence countries account for around 11% of the EU/EEA populations but are estimated to account for around a quarter of CHB infections and around 15% of all CHC infections.(14) Migrants from high endemic countries are therefore disproportionately affected by chronic viral hepatitis and a key population for HBV/HCV screening and linkage to care.(15) Perinatal HBV transmission and nosocomial/iatrogenic HCV transmission (in health care services with inadequate infection control practices) are responsible for the majority of HBV/HCV acquired in higher prevalence low- and middle-income countries (LMIC).(16) These risk factors are 'generalised' and largely affect the general population.(17) In contrast in many low prevalence industrialised countries, incident cases of HBV/HCV are largely reported among behavioural risk groups specifically PWID, MSM or sex workers.(18-20) Strongly associating HBV/HCV infection with these risk factors when offering screening to people unlikely to have been exposed due to individual behaviour per se, can be stigmatising, lead to feelings of discrimination, undermine trust in HCPs, and limit screening uptake.(21-27)

The literature on HBV/HCV screening among migrants is scarce but we can identify four main ways of offering screening: 1) *outreach-based* offering awareness-raising and/or screening in community, social or civic locations (28-32); 2) *invitation-based* using municipal or patient registry data to select and invite at-risk migrants for HBV/HCV screening in health care services (33, 34); 3) *opportunistically* offering screening to at-risk migrants attending health care services for other issues (35-37); and 4) *extending an existing migrant-focused screening programme* to include viral hepatitis.(35, 38) These four different models also provide different ways of awareness-raising and exchanging information between HCPs and people (migrants) offered screening.

This exploratory study seeks to add knowledge and understanding to the concept of pre-test information before HBV/HCV screening via three main research aims: 1) to define the topic contents of pre-test information included in guidelines/good practice studies;

2) to explore perceptions among HCPs about the objectives of pre-test information; and 3) to understand what are the 'desirable' and what are the 'feasible' aspects of pre-test information. We were interested in the HCP perspective and built on the work conducted by Gilbert et al but with a focus on at-risk migrants and in Europe.(39) Using the findings of this study, and others that provide some background (40-42), we developed a practical pre-test information checklist to enable and support HCPs providing HBV/HCV screening among migrants from endemic countries. Our study takes places as part of HEPscreen, an EU Health Programme-funded project (during 2011-2014) focused on screening for chronic viral hepatitis among migrants in Europe.(43)

METHODS

We utilise systematic literature review, content analysis and a DELPHI-inspired survey technique in this mixed methods exploratory study. Data were gathered mostly from the six European countries included in the HEPscreen project, namely Italy, Spain, Germany, Hungary, the Netherlands and the United Kingdom (UK) although European and international guidelines and studies were included in the literature review described below.

Literature review and content analysis

To address the first research aim, a systematic literature search of MEDLINE, EMBASE and Cochrane Library databases was conducted in 2012 to identify guidelines and studies published (in the main European languages e.g. English, Spanish, French, Italian or German and in Dutch and Hungarian i.e. languages of our specific study countries) about screening for hepatitis B/C infections. We also trawled the reference lists of included studies, grey literature and professional/clinical association websites for additional literature not retrieved via the database search. The search has been previously described.(40) We assessed the relevancy of retrievals specifically for this study using pre-defined inclusion/exclusion criteria. A content analysis of documents included on the basis of full text was conducted to develop a comprehensive list of a) recommended topics for inclusion in pre-test information for people offered HBV/HCV screening and b) the objectives/aims of providing pre-test information.

Survey

We sought to generate in-depth elaboration (on pre-test information objectives) and gather consensus (on the desirability and feasibility of pre-test information) using a semi-qualitative survey among a small number of expert respondents to a previous survey disseminated as part of HEPscreen.(41, 44) The survey methodology was influenced by work on informed choice and uptake of screening (13, 45, 46).

To explore the operationalisation of the tension between screening uptake and informed choice we asked survey recipients to rate on a five-point ordinal scale the importance of six pre-test information objectives derived from literature: 1) securing informed choice; 2) normalising testing; 3) promoting uptake; 4) reducing stigma and fear; 5) raising knowledge and awareness; and 6) preparing for a positive result. To develop a consensus on and distil a list of the most important pre-test information topics, we explored the importance/implications of each of the topics identified in the literature search in three domains: 1) securing informed choice; 2) reducing stigma and fear; and 3) when/if HCPs time for pre-test information is constrained. The importance of discussing each topic on securing informed choice was measured with a five point ordinal scale (very unimportant to very important). The impact of discussing a topic on reducing stigma and fear was measured by a three point ordinal scale (increases stigma/fear, neutral and decreases stigma and fear). The prioritisation of the topic if/when time is limited was measured by a five point ordinal scale (not a priority to essential). The three domains (informed choice, stigma and fear, and if/when time is limited) were conceptualised as a means to understand how pre-test information can be both 'desirable' and 'feasible'.

The survey was pilot tested with an infectious disease doctor at the Rotterdam-Rijnmond Municipal Public Health Service (where the corresponding author is based), revised and uploaded into Survey Monkey. An invitation with a unique link to the survey was sent by email to 253 expert respondents to a previously described survey as part of the HEPscreen project.(40, 41, 44) The initial sample was identified by snowballing methodology and by membership of professional networks, clinical associations or other means. The aim was not to develop a representative sampling frame, but rather to reach a small number of knowledgeable experts across five primary and secondary health care services involved in the screening, clinical management and treatment of chronic viral hepatitis. The five areas of health care were: antenatal services (due to antenatal HBV screening), general practice/family medicine, sexual health services, services for asylum seekers, and secondary care specialists in hepatology, gastroenterology or infectious diseases. We aimed to reach experts able to understand and articulate at the level of their health care profession or in their health care service. Our study took place in 2014 across six EU/EEA countries: Hungary, Germany, Italy, the Netherlands, Spain and the United Kingdom.

Survey Data Analysis

Data was exported from Survey Monkey into SPSS 19.0.2 for descriptive statistical analysis. Differences between countries and expert groups were explored. Likert scale responses were measured by using the central tendency (mode and median). For the measurement of central tendency the median score was favoured as compared to the mean, because

when reflecting a convergence of opinion the data can be skewed. The mode was used to identify the point(s) of polarisation/clustering. Proportions were used to determine level of consensus and to rank the list of topics in each of the three domains (informed choice, if/when time is limited and on stigma and fear).

RESULTS

Literature search and content analysis: pre-test information topics

The content analysis of retrievals from the previously described search (40) yielded ten pre-test information topics: general information about viral hepatitis; reasons for testing; routes of transmission/risk factors; the test itself; confidentiality of results; implications of a positive test for the individual including onward referral; impact of a positive test on his/her family/close contacts; health benefits of treatment; support groups available to people diagnosed with chronic hepatitis B/C infections; and implications of a negative test result.

Survey: Respondents

We received 46 responses from 253 recipients, equal to a response rate of 18.2%. The respondents included experts from all six different countries: 15 from the Netherlands, 11 from the UK, nine from Italy, six from Germany, four from Hungary and one from Spain. They also included representatives from all five different areas of health care (nine experts in antenatal care, five from general practice/family medicine, 10 from sexual health services, 5 from asylum seeker health care and 17 specialists in hepatology/gastroenterology/infectious diseases). We did not analyse differences between groups of health care providers given the small numbers. Three respondents were excluded from the analysis due to invalid/missing data. Data analysis was performed on the remaining 43 respondents.

Survey: Rating the importance of pre-test information objectives

On an importance scale of one to five (from very unimportant to very important), the median score and the mode for all six objectives were both four (important), implying that, on average, each objective was perceived as being important. 'Securing informed choice' was rated as important/very important by 40 out of 43 respondents (93%) and as unimportant by one (2.3%). 'Improving acceptance' and 'raising knowledge and awareness' were rated as important/very important by 88.4% and by none as unimportant. 'Preparing for a positive result' was rated as important/very important by 33 respondents (76.7%). Although 'normalising testing' was perceived as the least important objective, the overall perception (using the mean and the median) was 'important'. Using these data, the objectives can

be ranked in order of importance as follows: (1) improving awareness and knowledge, (2) securing informed choice, (3) improving acceptance, (4) preparing for a positive result, (5) reducing stigma and fear, and (6) normalising testing (Figure 1).

Survey: Rating the importance of pre-test information topics for securing informed choice

In this question, participants were provided the list of ten topics (as described above) and asked to rate the importance of discussing each topic before the offer of screening if the main aim (of information) is securing informed choice. On an importance scale of 1 to 5 (from very unimportant to very important), the average median score for nine topics was 4 (important), except for 'the test itself', which had a median score of 3 (neutral). Thus, on average, discussion of all topics was perceived as important in securing informed choice, except for 'the test itself', opinion on which was neutral. Based on the proportion of respondents that indicated very important/important in securing informed choice (Figure 2), the topics were ranked (Table 1).

There was a strong degree of consensus (>75% agreement towards important/very important) between respondents on seven topics: 'implications of a positive test result for the individual', 'reasons for testing', 'modes of transmission', 'health benefits offered by treatment', 'implications of a positive test result for family/close contacts', 'general information about viral hepatitis', and 'confidentiality of test results' (Figure 2). From these results, we infer a consensus on these topics being the priority topics (considered very important/important) in securing informed choice. The remaining three topics were considered less important.

Survey: Prioritisation of topics if/when time for pre-test information is limited

Participants were asked to prioritise each of the 10 topics (on a five point scale: 1 = not a priority and 5 = essential) if/when time for pre-test information was limited. Five out of the ten topics ('reasons for testing', 'modes of transmission', 'confidentiality of test results', 'implications of a positive test result for the individual' and 'health benefits offered by treatment') had a median score and a mode of 4 (high priority), except for 'reasons for testing', which had a mode of 5 (essential). The remaining five topics ('general information about viral hepatitis, 'the test itself', 'implications of a positive test result for his/her family/close contacts', 'implications of a negative test result' and 'organisations and social support available to patient') had a median score of 3 (medium priority). Also the mode of these topics were 3 (medium priority), except for 'general information about viral hepatitis', which

had two modes being 3 (medium priority) and 4 (high priority). Each topic was ranked (Table 1) based on the proportion of respondents indicating high priority/essential (Figure 3).

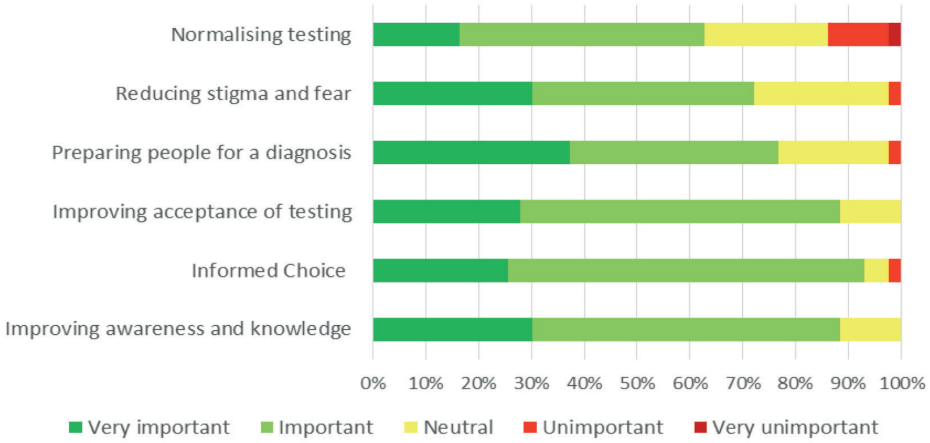

Figure 1. Rating of the importance of each pre-test information objective

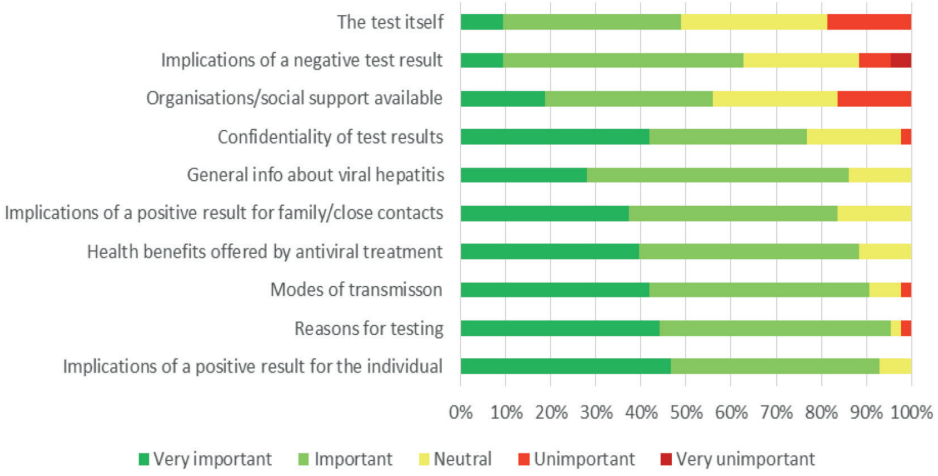

Figure 2. Importance of each topic in securing informed choice

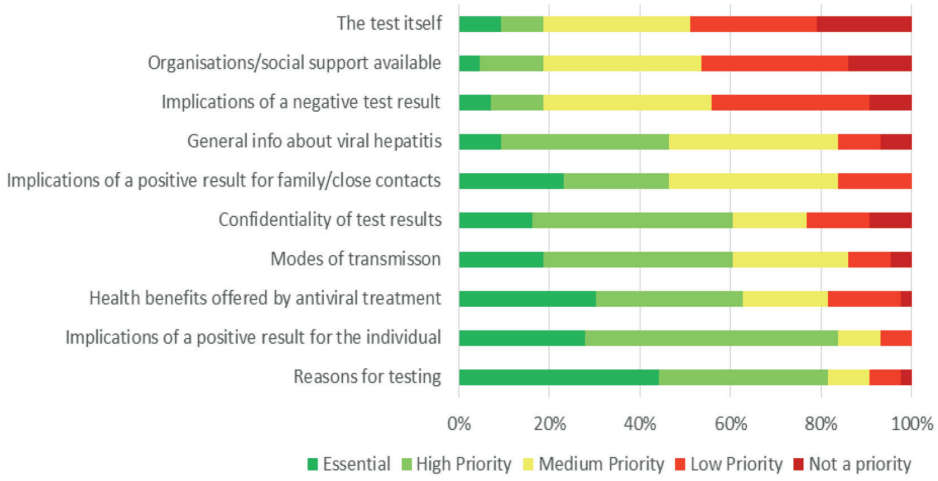

Figure 3. Priority of each topic in limited time

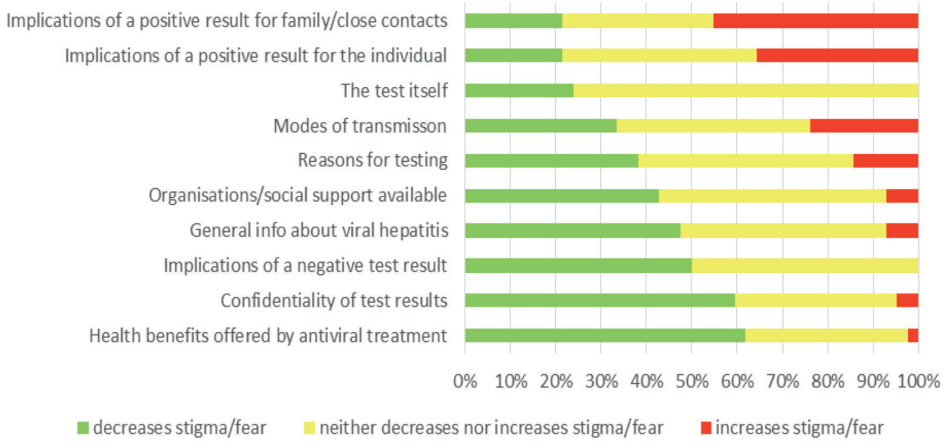

Figure 4. Effect of discussing each topic on stigma/fear.

Survey: Topics important in reducing stigma and fear

Participants were asked their opinion about the effect discussing each topic would have on feelings of stigma and fear when offering HBV/HCV screening to migrants. Forty-two respondents completed this question. 'Confidentiality of test results' and 'health benefits offered by treatment' had a median score of 3 (decreases stigma/fear) and the remaining topics had a median score of 2 (neither increases nor decreases stigma/fear). The modes for

the other topics were comparable with the median scores, except for 'general information about viral hepatitis' which had a mode of 3 (decreases stigma/fear) and 'implications of a positive test result for family/close contacts' which had a mode of 1 (increases stigma/fear). Half of the respondents indicated that 'implications of a negative test result' decreases stigma/fear and the other half indicated that it neither increases nor decreases stigma/fear. Each topic was ranked (Table 1) based on the proportion of respondents indicating that the topic decreases stigma/fear (Figure 4).

Defining the content of 'desirable' and 'feasible' pre-test information

Table 1 summarises the ranking of all ten topics (based on proportion of respondents) of the importance of topics overall and across the three domains. The list of topics is in descending order of importance according to the overall rank across the three domains.

Table 1. Ranking importance topics in securing informed choice, priority in limited time and in decreasing effect on stigma and fear based on proportion of respondents

	Informed choice (IC)	Limited time (LT)	Reducing stigma and fear (SF)	Overall rank (IC + LT + SF)/3
Reasons for testing	1	1	6	**2.67 (=1)**
Health benefits offered by treatment	4	3	1	**2.67 (=1)**
Implications of a positive test result for the individual	2	2	9	**4.33 (2)**
Modes of transmission	3	4	7	**4.67 (=3)**
Confidentiality of test results	7	5	2	**4.67 (=3)**
General information about viral hepatitis	5	7	4	**5.33 (4)**
Implications of a negative test result	8	8	3	**6.33 (5)**
Implications of a positive test result for his/her family/ close contacts	6	6	10	**7.33 (6)**
Organisations and social support available to patient	9	9	5	**7.67 (7)**
The test itself	10	10	8	**9.33 (8)**

DISCUSSION

Agreement about the desired content of pre-test information can only be achieved once the purpose of this information is clear.(46) This is the first study to explore and understand the objectives and components of pre-test information before offering screening for HBV/HCV among migrant populations. Our survey findings show a strong consensus that

'securing informed choice', 'improving acceptance', 'raising knowledge and awareness' and 'preparing for a positive result' are the most important objectives of pre-test information. Literature also suggests that facilitating informed choice and promoting screening uptake (improving acceptance) are the main purposes of information about screening.(47-51)

Interestingly 'improving acceptance (uptake) of screening' and 'raising knowledge and awareness' were rated as more important than 'securing informed choice.' This finding suggests that HCPs believe that the benefits of undergoing screening outweigh the harms, at an individual level, and that it is their role to encourage people (at risk of being infected) to undergo screening. Uptake of screening is also a key parameter in cost-effectiveness studies.(52) The notion that pre-test information is a means to improve knowledge, understanding, attitude and motivation and therefore uptake of screening among at-risk patients draws on behavioural change/health promotion theory.(39) This notion of pre-test information being a means to raise awareness to improve uptake is also seen in the few examples in literature of awareness campaigns and other interventions to promote testing among at-risk migrant groups.(28, 29, 31-35, 53-55) These good practice studies report that low levels of awareness about ill-health, viral hepatitis and risk factors, and a lack of uptake of health care in general, place at-risk migrants at higher risk of HBV/HCV-related morbidity and mortality. Low uptake and limited screening/treatment among migrants underscores the importance of expanding access to screening and linkage to care for at-risk migrant populations, and of using pre-test information/discussion opportunities to raise awareness and improve knowledge.(56)

The survey and the resulting checklist were specifically focused on migrants to Europe from endemic countries because these populations are disproportionately affected by chronic viral hepatitis. Furthermore, migrants are the key risk population for CHB and are estimated to account for almost all CHB infections in most of the low prevalence, high income northern and western EU/EEA Member States.(14) Migrants from high prevalence countries are at-risk of being chronically infected with HBV or HCV due to generalised transmission risk factors (mainly antenatal for HBV and iatrogenic for HCV) in the general population in their country of birth.(16) In contrast, most incident (acute) cases in low prevalence EU/EEA countries are reported among behavioural risk groups such as PWID, MSM and sex workers.(19, 20, 57) Associating the offer of HBV/HCV screening with risky sexual behavioural or drug use is suspected to increase stigma, fear and shame among migrants likely to have been exposed through generalised risk factors.(58) It was perhaps not surprising that there was consensus that the topic 'modes of transmission' was the third most stigmatising topic after implications for the individual and for family/close contacts. There was also consensus that discussing confidentiality of test results, health benefits offered by treatment and implications of a negative test result before an offer of screening are important topics in

reducing stigma and fear. It was more surprising that there was not a strong consensus (almost 30% were neutral) that reducing stigma and fear was an important objective of pre-test information. There is however considerable implicit overlap between objectives: improved acceptance of screening may also be due to not feeling stigma and fear towards HBV/HCV screening.(59)

The central focus of screening is on early identification of chronic cases specifically to ensure that these patients receive the right information and appropriate treatment to prevent disease progression and avoidable mortality. It is therefore unsurprising that the availability and benefits offered by treatment was ranked as the priority topic overall across the three domains of informed choice, stigma and fear, and limited time. The ranking of the topics in this study can, to a limited extent, be compared with a 2005 study by Gilbert et al who reported findings among experts in viral hepatitis. Their expert participants rated sequelae, primary prevention and transmission routes to be the most important topics in pre-test information and reported a mismatch between the pre-test topic priorities of experts and the general public.(39) Research into the information needs from the perspective of at-risk or diagnosed migrants is needed.

Conclusions

We aimed to use the findings to gather consensus on the desirable and feasible aspects of pre-test information from HCPs perspective. The findings were then used to develop a short two page 'pre-test information (discussion) checklist' as part of the HEPscreen Toolkit to provide HCPs with a brief overview of evidence on the concept of pre-test information and enable HCPs to provide a minimum standard of pre-test information that can secure informed choice, reduce stigma and fear, and be delivered if/when time for a discussion is limited. This checklist is available in the supplementary annex to this paper. Effective active case finding (screening) among at-risk migrant communities will require both a well-designed and planned awareness campaign alongside knowledgeable HCPs able to discuss the relevant issues with people who take up the offer of testing.

Practice Implications

The study significantly expands the conceptual and practical understanding of the objectives and content of, as well as some tensions associated with providing, pre-test information before HBV/HCV screening. The findings reported in this study, alongside the subsequently developed practical pre-test information checklist, can be used to design, implement and evaluate screening interventions among at-risk migrant populations.

Screening for hepatitis B and C in Europe:

The pre-test discussion

Recommendations for primary health care professionals offering screening

HEPscreen
SCREENING FOR HEPATITIS B AND C AMONG MIGRANTS IN THE EUROPEAN UNION

Introduction

Chronic infection with hepatitis B or C (HBV/HCV) causes slowly progressive liver damage that, without treatment, may lead to cirrhosis and/or liver cancer after many years. Antiviral treatment is available, dramatically increasing scope for the prevention of related liver disease. Clinical guidelines recommend screening for and raising awareness of chronic viral hepatitis among higher risk groups. An important but often neglected risk group in Europe are people who migrated from HBV/HCV endemic areas, i.e. Africa, Asia, Central/Eastern Europe and other countries of the former USSR.

Offering testing

GPs, community nurses and staff in public/sexual health services are well-placed and well-trusted to offer testing for hepatitis B/C to migrants. Opportunities include the GP registration process for new patients, routine or lifestyle checks and antenatal visits. When offering screening, health professionals should conduct a 'pre-test discussion'. This is an important ethical issue in screening and helps to:

- Secure informed choice
- Improve acceptance of screening
- Raise awareness and improve knowledge

Information given in pre-test discussion helps to:

- Prepare people for a positive test result
- Reduce feelings of stigma, shame and fear

The discussion process

- The discussion is a two-way exchange where information is provided and questions are answered.
- The discussion need not follow a specific format or strict rules; every professional has their own communication style.
- Not all points are equally relevant to all individuals, but making assumptions about knowledge of the person offered screening should be avoided.
- However, there are some key issues that should be covered (see pre-test discussion checklist overleaf).
- If needed, information should be adapted to gender, age, literacy level and culture of the person offered screening.
- For example, adjusting terminology to make it more understandable or being aware of religious or cultural taboos.
- If needed, use professional interpreters to overcome linguistic barriers and communication breakdown. Informal interpreters (e.g. family or friends) should be avoided for reasons of confidentiality.
- People from endemic areas are more likely to acquire HBV perinatally or as children.
- In HCV endemic areas, transmission risks include unsterile medical/dental procedures (such as vaccination or blood transfusions), unsterile shaving equipment and other puncture procedures (such as tattooing).
- Infection with such viruses is, in many cultures, stigmatising. Therefore linking these with injecting drug use or unsafe sex can increase stigma and fear.

The consent process

All testing must be done with informed consent. Local practice and professional guidance will determine whether this needs to be in writing. Usually, a clear note in the medical record that informed consent has been sought and obtained is sufficient.

Pre-test discussion topics

The box opposite contains key pre-test discussion points. Coverage of these issues can help to secure informed choice and improve acceptance of screening. It is important to recognise and reduce feelings of stigma, shame or fear about these viruses. Focus on topics that reassure or dispel myths. Avoid emphasis on topics that may give rise to feelings of stigma or fear

Other recommendations

- Providing written/printed information about hepatitis B and C in the individual's native language during the pre-test discussion may help overcome time constraints, language barriers and stigma.
- Finish off with agreements on when and how the results will be provided.

Access to treatment

In some European countries, immigration or insurance status has an impact on whether treatment is available for people. There may be some populations in your country for whom access to antiviral treatment is significantly or completely restricted. If treatment entitlement is uncertain or restricted, it is still sensible to offer screening. There are benefits of knowing one's diagnosis, including prevention of transmission to or from others, including future offspring.

Checklist pre-test discussion topics

- Reasons for testing (i.e. birth in an endemic country or clinical presentation).
- Health benefits offered by treatment, including treatment options*
- Confidentiality of test results*
- Implications of a negative test result (including HBV vaccination if indicated)*
- Implications of a positive test result for the individual (i.e. referral for further tests)
- General information about viral hepatitis
- Modes of transmission. Remember - unprotected sexual activities or illicit drug taking may not be as important transmission routes for people from endemic countries and discussion of these in some cultures can increase feelings of shame, stigma and fear. Consider this on a case-by-case basis
- Implications of a positive test result for the family or close contacts (i.e. contact tracing). Although brief mention of this topic is helpful to ensure informed choice, it can also increase stigma and fear. Be sensitive. Re-emphasise confidentiality.
- Further topics for discussion, if time permits: Information on the test itself (i.e. blood test, when and how results are to be provided, possibility of indeterminate result, etc.)
- Organisations and social support available to patient (support groups, etc.), if not mentioned in leaflets*

* These topics can provide reassurance and reduce feelings of stigma, shame and fear.

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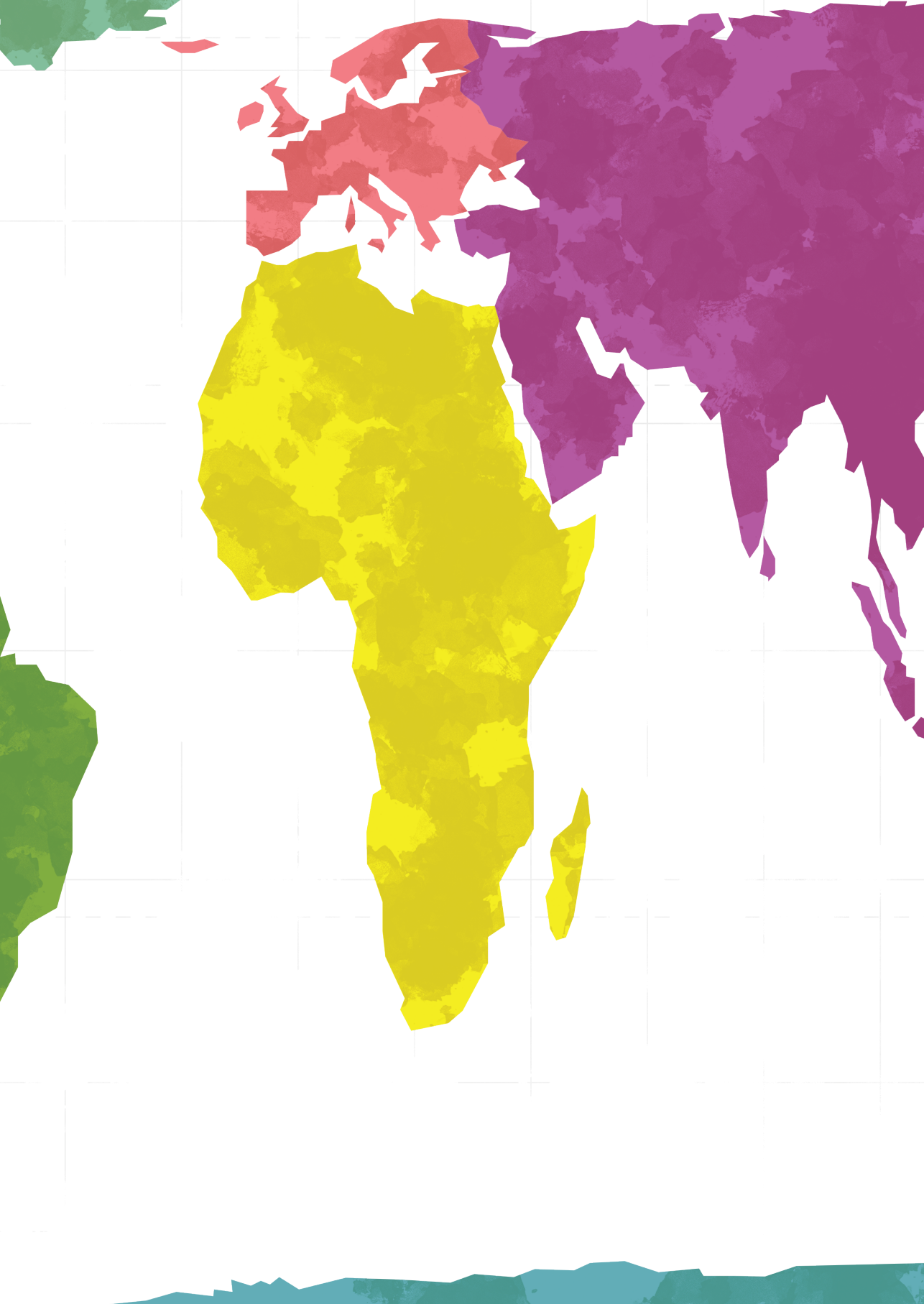

CHAPTER 10

Referral of newly diagnosed chronic hepatitis B and C patients in six EU countries: results of the HEPscreen Project

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ABSTRACT

Background: Effective linkage to specialist care following screening is crucial for secondary prevention of chronic viral hepatitis-related consequences.

Methods: To explore the frequency of referral of patients to secondary care from the health services involved in screening and to gather information on the services responsible for the provision of post-test counselling and contact tracing, four online surveys were conducted among general practitioners (GP), and experts working in sexual health services (SHS), antenatal care (ANC) and specialist secondary care in Germany, Hungary, Italy, The Netherlands, Spain and the UK.

Results: Overall, 60% of GPs report referring all patients to specialist care. Although 67% of specialists commonly receive patients referred by GPs, specialists in Germany rarely or never receive patients from ANC or from centres testing injecting drug users; and specialists in the Netherlands, Hungary and Germany rarely receive patients from SHS. Gastroenterologists/hepatologists are the professionals mainly responsible for the provision of counselling following a positive diagnosis of viral hepatitis according to two-thirds of specialists, 14% of SHS providers and 11% of ANC providers. Almost half of ANC providers (45%) stated that gynaecologists are the professionals responsible for the provision of counselling to positive pregnant women; among SHS providers, only 14% identified SHS as the services responsible.

Conclusion: Our findings suggest the existence of complex/ineffective referral practices or that opportunities to screen risk groups are missed. Recommendations clarifying the services responsible at each step of the referral pathway are needed in order to increase the success of screening programmes.

INTRODUCTION

Chronic viral hepatitis is among the top 10 fatal infectious diseases (ID) and the leading cause of liver cancer and cirrhosis. In the European Union (EU), the prevalence in the general population varies from 0.1% in the Netherlands to 5.6% in Romania for HBsAg and from 0.4% in Germany to 5.2% in Italy for anti HCV.(1) However the largely asymptomatic nature of these infections until the late stages of the disease, results in large proportions of infected individuals being undiagnosed.(2-4) In order to reduce the hepatitis-related burden of disease it is important to improve case detection by screening risk groups. In addition, counselling and treating (eligible) positive patients is important for limiting onward transmission and preventing the development of liver cirrhosis, liver failure and hepatocellular carcinoma. Early detection is in fact associated with improved treatment outcome.(5) Nonetheless, effective linkage to specialist care is crucial to maximise the health impact of screening. Ideally, all newly diagnosed patients should be referred for appropriate evaluation and management.(6, 7) However, surveys show that over half of the patients do not reach specialist care,(7) only up to 74% receive appropriate disease-related counselling(8) and up to 87% do not initiate treatment.(9,10) The aim of this study, part of the EU Health Programme-funded HEPscreen project (www.hepscreen.eu), was to provide insight into the current referral mechanisms between primary and specialist care for newly diagnosed patients in Germany, Hungary, Italy, the Netherlands, Spain and the UK, and to gather information on the services responsible for the provision of disease-related post-test counselling, contact tracing and vaccination of hepatitis B negative contacts of hepatitis B positive patients.

METHODS

Four online surveys were developed, aimed at professionals working in four healthcare services: general practice (GP), sexual health services (SHS) and/or genitourinary medicine (SHS), antenatal care (ANC) and specialist (SP) secondary care, i.e. gastroenterology/ hepatology and ID. The survey was semi-quantitative in design, allowing professionals to choose either from a number of given answer options or to indicate along a given scale their opinion or practice, in addition to provision of text boxes for further elaboration.

Survey structure and content

Common to all questionnaires was a respondent profile where data on the type of organisation, job title and medical specialism were collected. The survey was extensive and focused on screening and testing practice, pre- and post-test counselling, referral to secondary care, contact tracing, vaccination of individuals found negative, treatment and

clinical management. This study analysed the questions concerning referral of patients, disease-related post-test counselling and contact tracing: there were a total of 11 questions, although some were conditional.

Selection process of the participants

Purposive sampling was adopted to recruit professionals most able to reflect on these practices: experts were identified via professional networks and board membership of clinical associations. The aim in each professional group was to reach 5–10 experts, deemed able to reflect on the practices within their specialism.

Pre-testing and translation

Each survey was pilot tested, translated into the national language of the respective study country and uploaded into the open source online software LimeSurvey©. Experts were contacted via e-mail in July 2012 and further reminded twice during data collection. The survey closed in September 2012. The option of "unsure" was available in all questions. Descriptive analyses were performed with SPSS Statistics 21.

Referral

To explore the role of clinical indicators in the referral of patients identified by GPs, ANCs and SHSs, a two-point scale was used in these three surveys (to the question: 'Which patients are referred?', the possible options included (i) All patients; (ii) A selection based on the clinical indicators). If clinical indicators was selected, respondents were asked to further specify: 'viral load', 'HBe antigen status', 'ALT', or 'other'. To explore the stages in referral from diagnosing services into secondary care, ANC and SHS professionals were asked whether referral is directly to secondary care, or via GP or other services. To understand where specialists received referrals from, a three-point ordinal scale ('very common', 'variable or not routinely' and 'rarely or never') was used to measure how frequently patients are received from services most likely to screen for viral hepatitis: GPs, centres testing injecting drug users (IDUs), ANC, SHS and public health services (PHS) operating at the community level.

Disease-related post-test counselling

Four questions explored the roles and responsibilities of services in the provision of counselling: a four-point ordinal scale was used in the GP survey and a dichotomous scale was used in the ANC and the SHS surveys to assess whether patients are provided disease-related counselling; a three-point scale was used to assess whether patients are referred from GPs and ANC to other services for disease-related counselling. If yes, we asked to

which health service(s) (since more than one option could be selected, the total within a country could sum up to>100%). Finally, we asked in the ANC, SHS and SP surveys, which service has the main responsibility for counselling.

Contact tracing

All surveys included a question, using a three-point scale, about the offer of screening to household and/or sexual contacts of hepatitis B/C patients. If yes, we asked which services are responsible. Experts who had stated, in a previous section of the questionnaire, that HBV vaccination is offered to negative contacts of hepatitis B patients, were asked to indicate the services responsible for immunization.

RESULTS

Respondents

We received 220 responses from 930 recipients (response rate 24%), achieving the respondent target of 5–10 experts in all countries but Hungary and, except for antenatal care providers, Spain. In Germany, the respondent target was achieved for all professional groups, except for GPs (n=4). Most respondents were from clinical or professional associations (34%), national/regional government (22%) or universities (18%) (results by country are shown in Supplementary Table S1, online). Around half of GP, antenatal care provider and SHS survey respondents see few (1–10) chronic hepatitis patients per year, whereas 95% of specialists see chronic viral hepatitis patients on a weekly basis.

Referral from primary to specialist care for treatment: The views of the diagnosing services

Referral from GPs

All patients are referred for treatment and clinical management by the majority of GPs in Italy (71%), the UK (60%) and by the one respondent in Hungary (Table 1). Responses in the other three countries were almost evenly divided between those indicating that all patients (response given by 56% of GPs in the Netherlands and by 50% in Germany and Spain) and those reporting that a selection based on clinical indicators are referred (according to 50% in Germany and Spain and 44% in the Netherlands). The clinical indicators possibly used to select patients for referral are described in Supplementary Table S2, online.

Table 1. Referral of newly diagnosed hepatitis B or C patients to specialist care from the diagnosing services. The views of the diagnosing services and of specialists

Views of the diagnosing services						
Referral of hepatitis B/C + patients by GPs	**UK (n = 10)**	**DE (n = 4)**	**NL (n = 9)**	**HU (n = 1)**	**IT (n = 14)**	**ES (n = 2)**
All patients	60%	50%	44%	100%	71%	50%
A selection based on clinical indicators	20%	50%	56%	0%	29%	50%
Unsure	20%	0%	0%	0%	0%	0%
Referral of hepatitis B+ women from Antenatal Care Providers	**UK (n = 8)**	**DE (n = 36)**	**NL (n = 6)**	**HU (n = 4)**	**IT (n = 25)**	**ES (n = 8)**
All women	88%	53%	17%	100%	48%	63%
A selection based on clinical indicators	0%	22%	33%	0%	36%	13%
None	0%	0%	17%	0%	0%	0%
Unsure	13%	25%	33%	0%	16%	25%
Referral of hepatitis B/C + patients by Sexual Health Services	**UK (n = 10)**	**DE (n = 5)**	**NL (n = 8)**	**HU (n = 3)**	**IT (n = 1)**	**ES (n = 2)**
All patients	60%	40%	50%	100%	100%	50%
A selection based on clinical indicators	0%	0%	13%	0%	0%	50%
Referral via another service	10%	0%	25%	0%	0%	0%
Unsure	30%	60%	13%	0%	0%	0%
Referral from Antenatal Care Providers	**UK (n = 8)**	**DE (n = 36)**	**NL (n = 6)**	**HU (n = 4)**	**IT (n = 25)**	**ES (n = 8)**
Directly to gynaecologists	75%	22%	50%	0%	36%	25%
Directly to specialist secondary care	88%	56%	33%	100%	28%	38%
Referral to specialist secondary care via GP	13%	22%	33%	25%	36%	25%
Referral to specialist secondary care via another service	0%	0%	0%	0%	4%	13%
Unsure	0%	17%	17%	0%	4%	0%
Referral from Sexual Health Services	**UK (n = 10)**	**DE (n = 5)**	**NL (n = 8)**	**HU (n = 3)**	**IT (n = 1)**	**ES (n = 2)**
Directly to specialist secondary care	60%	60%	13%	67%	100%	50%
Referral to specialist secondary care via GP	20%	20%	63%	33%	0%	50%
Referral to specialist secondary care via another service	0%	0%	13%	0%	0%	0%
Unsure	20%	20%	13%	0%	0%	0%

Table 1. (continued)

Views of secondary care specialists	UK (n = 10)	DE (n = 9)	NL (n = 22)	HU (n = 10)	IT (n = 9)	ES (n = 4)
Frequency of receiving patients from GPs						
Very common	90%	78%	68%	60%	44%	50%
Variable or not routinely	0%	11%	32%	40%	56%	50%
Rarely or never	0%	11%	0%	0%	0%	0%
Unsure	10%	0%	0%	0%	0%	0%
Frequency of receiving patients from injecting drug user (IDU) Clinics						
Very common	60%	33%	32%	0%	33%	75%
Variable or not routinely	30%	11%	41%	60%	33%	25%
Rarely or never	0%	56%	27%	20%	33%	0%
Unsure	10%	0%	0%	20%	0%	0%
Frequency of receiving patients from Antenatal Care						
Very common	70%	0%	23%	10%	22%	50%
Variable or not routinely	20%	44%	59%	30%	33%	0%
Rarely or never	0%	56%	14%	50%	44%	50%
Unsure	10%	0%	5%	10%	0%	0%
Frequency of receiving patients from Sexual Health Services/genito-urinary medicine						
Very common	60%	11%	9%	0%	22%	25%
Variable or not routinely	30%	33%	14%	20%	33%	50%
Rarely or never	0%	56%	73%	60%	44%	25%
Unsure	10%	0%	5%	20%	0%	0%
Frequency of receiving patients from Public Health Services						
Very common	10%	33%	32%	0%	0%	0%
Variable or not routinely	30%	44%	45%	30%	33%	50%
Rarely or never	50%	22%	23%	60%	67%	25%
Unsure	10%	0%	0%	10%	0%	25%

Referral from antenatal care providers

All antenatal care experts in Hungary, nearly all in the UK (88%), two-thirds in Spain (63%) and nearly half in Germany (53%) and Italy (48%), indicated that HBV+ women are referred to specialist care for chronic viral hepatitis (Table 1). One-third in Italy (36%) and in the Netherlands (33%), along with a fifth in Germany (22%) stated that a subgroup of HBV+ women are referred. Referral is directly to specialists according to all in Hungary, and to the majority in the UK (88%), where; however, three quarters also reported referral to

gynaecologists, and Germany (56%). No majority opinion emerged about the services patients are mostly referred to in Italy and Spain. In the Netherlands, referral is directly to gynaecologists for half of the respondents, although the remaining answers (excluding the one unsure), were evenly distributed between 'via GP' and 'directly to specialist secondary care'.

Referral from Sexual Health Services

All respondents in Hungary and Italy, 60% in the UK and 50% in the Netherlands reported that all patients are referred by SHS to specialists (Table 1). In Spain, one of the two respondents stated that all patients are referred, the other reported that referral is based on viral load. The majority in the UK (60%), Germany (60%), Hungary (67%) and Italy (although n =1) indicated that SHS directly refer all patients. However, one-third in Hungary and one-fifth in the UK and Germany indicated that referral is via GPs. Referral via the GP is fairly common in the Netherlands (reported by 63%).

Referrals to secondary care by screening services

Receiving patients from GPs was very common for a large majority of specialists in the UK (90%), Germany (78%) and the Netherlands (68%), and for 60% in Hungary, 50% in Spain and 44% in Italy (Table 1). From one-third to nearly half in Italy, Spain, Hungary and the Netherlands, indicated that it was variable. Referral from antenatal care and IDU clinics was most common in the UK and Spain, but not routine in the other countries. Referral from SHS was reportedly very common in the UK (60%) but rare in the Netherlands (73%), Hungary (60%) and Germany (56%). No majority opinion emerged in Italy. In Germany, 56% indicated rarely/never receiving patients from IDU clinics, SHS and antenatal care.

The provision of post-test disease-related counselling GPs

All GPs in Germany and Spain and almost all (93%) in Italy and in the Netherlands, always or often provide disease-related counselling (Table 2). The respondent in Hungary indicated GPs often provide counselling. In the UK, half indicated that GPs always or often provide counselling, although almost one-third reported that post-test counselling is provided by GPs only occasionally. The majority in all countries but the Netherlands also refer patients to other services for counselling. Occasional referral to other services for counselling occurs according to most in the Netherlands (56%), and one-fifth in the UK and Italy. In Spain, the UK and Germany referral for counselling by GPs is mainly to gastroenterologists/hepatologists. In Italy infectious disease specialists (79%), and gastroenterologists/hepatologists (71%) were more frequently mentioned. In the Netherlands, GPs refer patients to a range of services, including infectious disease specialists (67%), Public Health Services (56%) and gastroenterologists/hepatologists (44%). In Hungary results suggest that patients are referred for counselling to Public Health Services (Table 2).

Table 2. Frequency of counselling provision following a positive test result for hepatitis B/C

Provision of post-test counselling by GPs	**UK (n = 10)**	**DE (n = 4)**	**NL (n = 9)**	**HU (n = 1)**	**IT (n = 14)**	**ES (n = 2)**
Always	40%	50%	56%	0%	21%	100%
Often	10%	50%	33%	100%	71%	0%
Sometimes	30%	0%	11%	0%	7%	0%
Rarely or never	0%	0%	0%	0%	0%	0%
Unsure	20%	0%	0%	0%	0%	0%
Referral to other services for counselling?						
Yes	60%	100%	44%	100%	79%	100%
Sometimes	20%	0%	56%	0%	21%	0%
Rarely or never	0%	0%	0%	0%	0%	0%
Unsure	20%	0%	0%	0%	0%	0%
Services/professionals to which patients are referred by their GPs	**UK (n = 8)**	**DE (n = 4)**	**NL (n = 9)**	**HU (n = 1)**	**IT (n = 14)**	**ES (n = 2)**
Gastroenterologists/hepatologists	88%	75%	44%	0%	71%	100%
Infectious disease specialists	38%	25%	67%	0%	79%	0%
Public Health Services	10%	0%	56%	100%	14%	0%
Provision of post-test-counselling by ANC providers	**UK (n = 8)**	**DE (n = 35)**	**NL (n = 6)**	**HU (n = 4)**	**IT (n = 24)**	**ES (n = 8)**
Yes	63%	57%	50%	50%	83%	100%
No	25%	6%	50%	50%	8%	0%
Unsure	13%	37%	0%	0%	8%	0%
Referral from ANC to other health services for counselling	**UK (n = 8)**	**DE (n = 36)**	**NL (n = 6)**	**HU (n = 4)**	**IT (n = 25)**	**ES (n = 8)**
Yes—mostly pre-birth	87%	50%	67%	75%	92%	63%
Yes—mostly post-birth	0%	19%	33%	25%	0%	38%
No	13%	0%	0%	0%	25%	0%
Unsure	0%	31%	0%	0%	4%	0%
Services patients are referred to by ANC providers	**UK (n = 7)**	**DE (n = 25)**	**NL (n = 6)**	**HU (n = 4)**	**IT (n = 23)**	**ES (n = 8)**
Gastroenterologists/hepatologists	86%	48%	17%	100%	44%	25%
Infectious disease specialists	57%	44%	17%	25%	52%	0%
Public Health Services	14%	4%	83%	0%	30%	13%
GPs	0%	16%	67%	0%	4%	50%
Gynaecologists	57%	12%	33%	0%	9%	38%
Others	0%	0%	0%	0%	4%	13%

Table 2. (continued)

Services responsible for providing post-test counselling according to ANC providers	**UK (n = 8)**	**DE (n = 36)**	**NL (n = 6)**	**HU (n = 4)**	**IT (n = 25)**	**ES (n = 8)**
GPs	0%	0%	0%	0%	4%	25%
Public Health Services	0%	6%	33%	25%	12%	0%
Infectious disease specialists	25%	8%	17%	0%	20%	0%
Gastroenterologists/hepatologists	25%	14%	17%	50%	12%	0%
Midwives/maternity units	13%	0%	17%	0%	4%	25%
Obstetricians/gynaecologists	13%	67%	0%	25%	36%	50%
Others	25%	3%	17%	0%	4%	0%
Unsure	0%	3%	0%	0%	8%	0%
Provision of post-test-counselling by SHS	**UK (n = 10)**	**DE (n = 5)**	**NL (n = 8)**	**HU (n = 3)**	**IT (n = 1)**	**ES (n = 2)**
Yes	80%	20%	50%	33%	100%	50%
No	20%	0%	50%	67%	0%	50%
Unsure	0%	80%	0%	0%	0%	0%
Services responsible for providing post-test counselling according to SHS providers	**UK (n = 10)**	**DE (n = 5)**	**NL (n = 8)**	**HU (n = 3)**	**IT (n = 1)**	**ES (n = 2)**
GPs	10%	0%	0%	0%	0%	0%
PHS	0%	0%	75%	0%	0%	0%
Infectious disease specialists	20%	20%	0%	67%	0%	50%
Gastroenterologists/hepatologists	20%	0%	0%	33%	100%	0%
SHS	30%	0%	0%	0%	0%	50%
Other	0%	40%	0%	0%	0%	0%
Unsure	0%	20%	0%	0%	0%	0%
The professional requesting the test/all of the above	20%	20%	25%	0%	0%	0%
Services responsible for providing post-test counselling according to secondary care specialists	**UK (n = 9)**	**DE (n = 10)**	**NL (n = 22)**	**HU (n = 10)**	**IT (n = 9)**	**ES (n = 4)**
GPs	0%	11%	9%	0%	22%	50%
PHS	0%	0%	27%	0%	0%	0%
Infectious disease specialists	0%	11%	5%	10%	22%	0%
Gastroenterologists/hepatologists	90%	67%	50%	90%	56%	50%
Other	10%	0%	5%	0%	0%	0%
Unsure	0%	11%	5%	0%	0%	0%

Note: Responses given by GPs, ANC providers and SHS/ GUM specialists. Services identified as mainly responsible for providing counselling to hepatitis B/C positive patients according to ANC providers, professionals working in SHS/GUM clinics and secondary care specialists

Antenatal Care Providers

The view in Spain and Italy was that antenatal care providers are involved in counselling HBV+ pregnant women; this was also the majority opinion in the UK and Germany. In the Netherlands and Hungary, the opinion was evenly divided between 'yes' and 'no'. In all countries pre-birth referral for counselling was common practice, except in the Netherlands, where around two-thirds indicated mostly pre-birth, one-third indicated mostly post-birth referral and Public Health Services tend to be responsible (were indicated by 83%), although GPs were indicated by two-thirds and specialists by one third. In the UK responsibility for counselling is shared by infectious disease specialists, gastroenterologists/hepatologists and antenatal care providers, but not GPs or Public Health Services. In Germany, HBV+ pregnant women are referred for counselling either to gastroenterologists/hepatologists (48%) or infectious disease specialists (44%); however, the main responsibility for providing counselling lies with antenatal care providers themselves, according to two thirds of respondents. Half in Hungary indicated gastroenterologists/hepatologists were responsible for counselling. In Spain antenatal care providers seem to be responsible for post-test counselling; however, women are also referred to GPs, gastroenterologists/hepatologists or Public Health Services for counselling. In Italy the responsibility is shared between antenatal care providers and specialists, with little involvement of GPs or Public Health Services. Women are referred from antenatal care providers mostly to infectious disease specialists (52%) or gastroenterologists/hepatologists (44%).

Sexual Health Services

SHS are generally involved in counselling following a positive test result in the UK (80%), although a range of services were identified as having the main responsibility for counselling. In contrast, SHS are not generally involved in providing counselling in Germany: here, the service requesting the test, infectious disease specialists and dermatology/venereology, were identified as responsible. Three quarters in the Netherlands identified Public Health Services as responsible for providing post-test counselling, but responses were more unclear about the involvement of SHS. In Hungary, specialists are responsible for counselling, whereas SHS appear to be less involved. SHS in Italy refer patients for post-test counselling to gastroenterologists/hepatologists. In Spain, while some SHS provide counselling, others refer patients to infectious disease specialists.

Secondary care specialists

Most specialists in all countries indicated that the main responsibility for disease-related counselling lies with gastroenterologists/hepatologists. However, a significant proportion in the Netherlands, Italy and Spain also identified other services as responsible: Public Health Services in the Netherlands (27%), infectious disease specialists in Italy (22%), and GPs in Italy (22%) and Spain (50%).

Contact tracing

In the UK, screening contacts of HBV+ patients is very frequently practiced in SHS (100% of SHS specialists reported that all contacts are screened for HBV infections) and commonly practiced in specialist care (among gastroenterologists, hepatologists and infectious disease specialists, 70% reported that all contacts are screened, and 20% reported that screening is for a selection of contacts), whereas it seems that it is not common among GPs (Tables 3). Varied response were obtained from specialists and SHS providers on screening of contacts of HCV+ patients, while GPs were mostly unsure (60%). In Germany screening contacts of hepatitis B/C patients appears to be frequent practice among GPs and specialists. Among antenatal care providers, 42% were unsure; 39% reported that antenatal care providers are involved in screening contacts of HBV+ women. In the Netherlands, screening contacts of HBV patients seems to be common practice among GPs, antenatal care providers and specialists, as over two-thirds of respondents in all surveys except the SHS survey (13%) reported that all contacts are offered hepatitis B screening. This seems not to be the case for contacts of HCV+ patients, for whom only 56% of the GPs and 41% of the specialists, but none of the SHS survey respondents, stated that it is standard practice to offer testing. Screening contacts of chronic hepatitis B/C patients is common practice according to the majority of respondents in Hungary and Italy. In Spain, screening contacts of HBV+ patients is recommended to all contacts according to most specialists (75%), half of the SHS and GP surveys' respondents, but only to 38% of antenatal care providers. Responses on contact tracing for hepatitis C are divergent among professional groups (Tables 3 and 4).

The responsibility for vaccinating negative contacts of HBV+ patients lies with the Public Health Services in the Netherlands and in Italy, with the GPs in the UK and Spain, and is shared between Public Health Services and GPs in Germany and Hungary (Table 4). In Supplementary Figures S1–S6 online, the post-test patient's pathway in each country is synthesized in a flowchart.

Table 3. Screening practices in household or sexual contacts of HBV or HCV positive patients

Hepatitis B screening practices contacts of HBV + patients						
GP	**UK (n = 10)**	**DE (n = 4)**	**NL (n = 9)**	**HU (n = 1)**	**IT(n = 14)**	**ES (n = 2)**
Yes—all contacts	40%	100%	89%	100%	93%	50%
Yes—a selection of contacts	10%	0%	11%	0%	0%	0%
No	0%	0%	0%	0%	7%	50%
Unsure	50%	0%	0%	0%	0%	0%
Antenatal care	**UK (n = 8)**	**DE (n = 36)**	**NL (n = 6)**	**HU (n = 4)**	**IT (n = 25)**	**ES (n = 8)**
Yes—all contacts	25%	39%	66%	75%	60%	37.5%
Yes—a selection of contacts	12.5%	5%	0%	0%	8%	0%
No	12.5%	14%	17%	25%	16%	12.5%
Unsure	50%	42%	17%	0%	16%	50%
Sexual Health Services	**UK (n = 10)**	**DE (n = 5)**	**NL (n = 8)**	**HU (n = 3)**	**IT (n = 1)**	**ES (n = 2)**
Yes—all contacts	100%	40%	12.5%	67%	100%	50%
Yes—a selection of contacts	0%	20%	50%	0%	0%	0%
No	0%	0%	12.5%	0%	0%	50%
Unsure	0%	40%	25%	33%	0%	0%
Specialists	**UK (n = 10)**	**DE (n = 9)**	**NL (n = 22)**	**HU (n = 10)**	**IT (n = 9)**	**ES (n = 4)**
Yes—all contacts	70%	89%	82%	70%	89%	75%
Yes—a selection of contacts	20%	0%	18%	0%	11%	25%
No	0%	0%	0%	0%	0%	0%
Unsure	10%	11%	0%	30%	0%	0%
Hepatitis C screening practices in contacts of HCV + patients						
GP	**UK (n = 10)**	**DE (n = 4)**	**NL (n = 9)**	**HU (n = 1)**	**IT (n = 14)**	**ES (n = 2)**
Yes—all contacts	20%	100%	56%	100%	72%	50%
Yes—a selection of contacts	10%	0%	11%	0%	7%	0%
No	20%	0%	11%	0%	7%	50%
Unsure	60%	0%	22%	0%	14%	0%

Table 3. (continued)

Sexual Health Services	**UK (n = 10)**	**DE (n = 5)**	**NL (n = 8)**	**HU (n = 3)**	**IT (n = 1)**	**ES (n = 2)**
Yes—all contacts	30%	40%	0%	67%	100%	50%
Yes—a selection of contacts	40%	0%	50%	0%	0%	0%
No	0%	20%	12.5%	0%	0%	50%
Unsure	30%	40%	37.5%	33%	0%	0%
Specialists	**UK (n = 10)**	**DE (n = 9)**	**NL (n = 22)**	**HU (n = 10)**	**IT (n = 9)**	**ES (n = 4)**
Yes—all contacts	10%	78%	41%	70%	78%	75%
Yes—a selection of contacts	50%	11%	27%	0%	22%	25%
No	30%	0%	23%	10%	0%	0%
Unsure	10%	11%	9%	20%	0%	0%

Table 4. Health services responsible for screening contacts of HBV+/HCV+ patients and services identified as responsible for the vaccination of contacts of HBV+ patients

	Services identified	**UK (n = 3)**	**DE (n = 16)**	**NL (n = 4)**	**HU (n = 3)**	**IT (n = 17)**	**ES (n = 3)**
Survey: Antenatal Care	GPs	0%	25%	0%	33%	47%	67%
	Antenatal Care	67%	31%	75%	67%	29%	0%
	ID specialists	0%	12.5%	0%	0%	0%	33%
	Gastroenterologists/hepatologists	33%	0%	0%	0%	6%	0%
	Obstetricians/ gynaecologists	0%	19%	0%	0%	6%	0%
	Other	0%	0%	25%	0%	0%	0%
	Unsure	0%	12.5%	0%	0%	12%	0%
	Services identified	**UK (n = 5)**	**DE (n = 4)**	**NL (n = 8)**	**HU (n = 1)**	**IT (n = 13)**	**ES (n = 1)**
Survey: GP	GPs	40%	50%	25%	100%	69%	100%
	PHS	20%	50%	62.5%	0%	31%	0%
	SHS	20%	0%	0%	0%	0%	0%
	Hospitals/clinics	0%	0%	0%	0%	0%	0%
	Other	20%	0%	12.5%	0%	0%	0%
	Unsure	0%	0%	0%	0%	0%	0%

Table 4. (continued)

	Services identified	UK (n = 10)	DE (n = 3)	NL (n = 6)	HU (n = 2)	IT (n = 1)	ES (n = 1)
Survey: Sexual Health Services	GPs	10%	0%	33%	0%	0%	0%
	PHS	10%	67%	33%	50%	100%	0%
	ID specialists	0%	0%	0%	50%	0%	0%
	Gastroenterologists/hepatologists	0%	0%	0%	0%	0%	0%
	SHS	20%	0%	17%	0%	0%	100%
	Hospitals/clinics	0%	0%	0%	0%	0%	0%
	Other	30%	0%	0%	0%	0%	0%
	Unsure	30%	33%	17%	0%	0%	0%
	Services identified	**UK (n = 10)**	**DE (n = 8)**	**NL (n = 22)**	**HU (n = 8)**	**IT (n = 9)**	**ES (n = 4)**
Survey: Specialists	GPs	60%	62.5%	23%	0%	33%	75%
	PHS	20%	0%	50%	17%	0%	0%
	SHS	0%	0%	0%	0%	0%	0%
	Hospitals/clinics	0%	12.5%	0%	83%	56%	0%
	Other	20%	0%	18%	0%	11%	25%
	Unsure	0%	25%	9%	0%	0%	0%
Vaccination of contacts of hepatitis B positive patients							
	Services identified as responsible:	**UK (n = 2)**	**DE (n = 10)**	**NL (n = 4)**	**HU (n = 2)**	**IT (n = 10)**	**ES (n = 3)**
Survey: Antenatal Care	GPs	0%	40%	0%	0%	10%	33%
	PHS	50%	20%	100%	100%	90%	33%
	ID specialists	0%	30%	0%	0%	0%	0%
	Gastroenterologists/ hepatologists	50%	0%	0%	0%	0%	0%

DISCUSSION

With this study, we aimed to explore the post-test pathways for chronic viral hepatitis currently in place in six EU countries via an online survey of experts and representative healthcare professionals. Other than from GPs, referral of chronic hepatitis B and C patients was very varied and heterogeneity of responses within countries even within the same professional group were observed. Only in the Netherlands and Germany did clinical indicators like viral load or ALT guide patient referral.

Clear referral pathways should be central in the design of screening interventions. In the guidelines on the management of hepatitis C produced by the World Health Organization,(11) ensuring that newly diagnosed patients are referred for appropriate care has been recognized as an important challenge. The concept of 'under-treatment' was introduced to refer to the disparity between the number of chronically infected individuals and the number of patients receiving treatment.(10) The most important limiting step to treatment appears to be the proper identification of chronically infected individuals. In two recent surveys conducted by the European Liver Patients Association among its members, only 21.5% of patients knew of their status at the time of their diagnosis and only 27% knew they were at risk.(12) However, appropriate referral to specialist care is another important step in the treatment cascade: probably fewer than half of chronically infected patients with HBV are referred for appropriate care.(10)

Not receiving disease-related counselling can have serious implications in terms of poor patient's awareness and knowledge of the disease, diagnostic testing, adherence to treatment regimens, liver disease monitoring and onward transmission.

The recent approval of new, direct-acting antivirals, means that more effective and safer treatments are now available for chronic hepatitis C. As for hepatitis B, the existing drugs significantly decrease the risk of liver damage and many promising new drugs are being developed.(13,14) Nevertheless, without adequate screening programmes and linkage to care, mortality from chronic viral hepatitis is projected to rise and peak around 2020–30. (15,16)

The implementation of a care pathway has been shown to reduce the variability in clinical practice, improve clinical outcomes and reduce health-care costs.(17,18) To our knowledge, the scientific literature regarding referral practices of patients in the six countries is scarce and studies allude to complex and non-standardized practices, often conducted as part of time-limited, small-scale screening programmes.(7, 19–30) This finding from the literature was reflected in the responses to our survey.

A limitation of the study is the sometimes small sample size, especially for Hungary and Spain, which greatly limits the generalizability of our findings. However, our aim was to reach up to 10 key experts for each professional group in each country. Given the careful selection of survey participants based on their affiliation to specific professional boards or clinical associations, and considering that professionals were specifically requested to participate as representatives of their respective fields in their country, it is justified to assume that the responses gathered convey a fair depiction of the actual referral practices in the six EU countries.

Despite some clear common practices, mainly regarding GP, heterogeneity of responses on how frequently patients are referred from the other well-used, well-trusted services were observed: specialists in Germany reported rarely or never receiving patients from ANC and IDU clinics and in the Netherlands, Hungary and Germany it was rare for gastroenterologists or ID specialists to receive patients from SHS. Furthermore, diagnosing services expressed a variety of opinions about the services mainly responsible for the provision of post-test counselling. These findings suggest either the existence of complex or ineffective referral practices, that not all patients reach secondary care or that services most able to offer screening miss opportunities to screen high-risk groups.

In the UK and in the Netherlands screening contacts of HBV+ patients seems to be common practice, whereas this is not the case for contacts of HCV+ patients. In Italy especially GPs and secondary care specialists deemed common practices screening contacts of HBV+ patients, while responses regarding HCV revealed diversity in practices. In Germany and Hungary, contact tracing seems to be frequent practice.

Discordant opinions could be partially explained by healthcare system context i.e. regional/local referral mechanisms or differences in the role of the diagnosing services (SHS or IDU clinics), as opposed to quality of care or provision. In Italy, e.g. a clear denomination for SHS is often lacking and care for sexually transmitted diseases is provided by different professional groups. However, the lack of unison within countries even among experts belonging to the same professional group suggests a lack of clarity about responsibilities of the different services.

The increased scope for secondary prevention of chronic viral hepatitis can only be achieved with effective screening programmes that successfully detect risk groups and link all newly diagnosed patients to specialist care. Our findings can serve as an impetus to formulate guidelines targeted at specific professional groups, explicitly specifying which services are to be deemed responsible at each step of the referral pathway, so as to increase the success of screening programmes and stop the growth of this silent epidemic.

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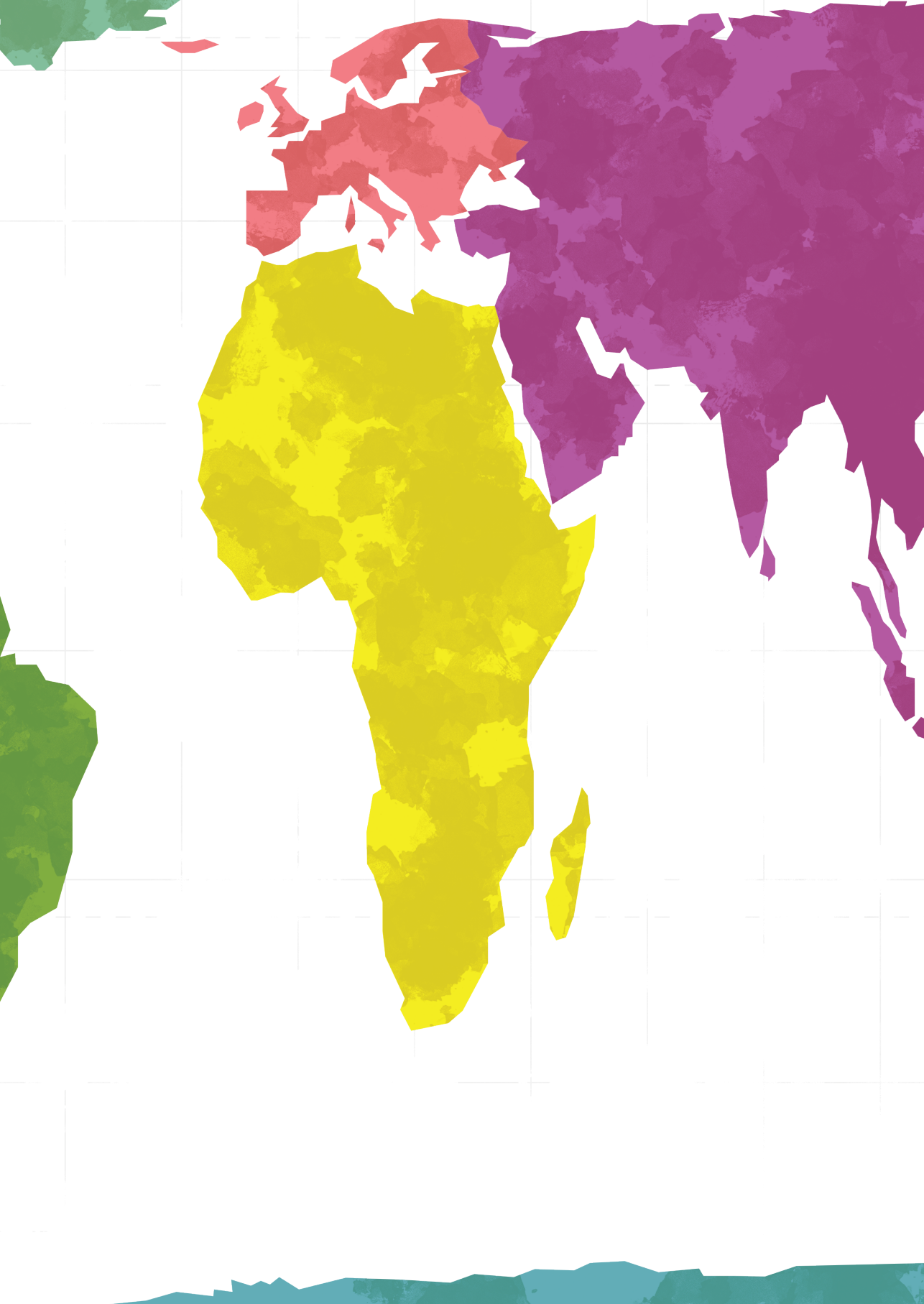

CHAPTER 11

The role of the general practitioner in the screening and clinical management of chronic viral hepatitis in six EU countries

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ABSTRACT

Introduction. Chronic viral hepatitis is still a major public health concern in the EU. In order to halt the progression of the disease and to prevent onward transmission, timely recognition and accurate clinical management are crucial. The aim of the present study was to investigate the role of the general practitioner (GP) in the screening of persons at risk and in the clinical management of chronic viral hepatitis patients in six EU countries.

Methods. An online survey among GPs and secondary-care specialists was conducted in the UK, Germany, the Netherlands, Hungary, Italy and Spain. In the GP survey, we used a four-point Likert scale to find out how commonly risk groups are screened. In both surveys, we measured GPs involvement in monitoring clinical indicators in patients undergoing antiviral treatment, and explored whether patients in four clinical scenarios are referred back to primary care.

Results. Between five and 10 experts per professional group were surveyed, except for Spain (GPs: n = 2; Specialists: n = 4) and, in the case of the GP survey, Hungary (GPs: n = 1) and Germany (GPs: n = 4). Migrants are variably or not routinely screened for hepatitis B/C in the majority of cases. The majority of GPs reported that hepatitis B/C screening was routinely offered to people who inject drugs. In Hungary, Italy and in the Netherlands, screening sex workers is not a regular practice. As to whether GPs offer screening to men who have sex with men, responses varied; in Germany, the Netherlands and Italy, screening was "variably" or "commonly" implemented, while in Hungary the practice seems to be sporadic. In the UK, screening for hepatitis B seems to be common practice among GPs, while hepatitis C testing is only occasionally offered to this risk group. Most GPs (>44%) in all countries except Hungary reported that hepatitis B/C screening was very commonly offered to HIV patients. The role of GPs in monitoring hepatitis cases and the referral of cases back to GPs by specialists varied both within and between countries. GPs are unlikely to monitor clinical outcomes other than side effects in patients undergoing treatment. Patients who have had a sustained virological response are usually referred back to GPs, whereas patients undergoing antiviral treatment and those who do not respond to treatment are rarely referred back.

Conclusions. The GP's decision to offer screening to risk groups often seems to be an individual choice of the healthcare professional. Raising GPs' awareness of the disease, for example through the adoption of effective strategies for the dissemination and implementation of the existing guidelines for general practice, is strongly needed. The role of GPs and specialists involved in the management of chronically infected patients should also be clarified, as opinions sometimes differ markedly even within each professional group.

INTRODUCTION

Viral hepatitis B and C are of major public health concern in the European Union, although there are distinct geographical variations in the prevalence and incidence of viral hepatitis across countries. In the EU, the burden of disease is generally low in the north-western countries and higher in the south-eastern region: the prevalence in the general population varies from 0.4% to 5.2% for anti-HCV and from 0.1% to 5.6% for HBsAg (1, 2). However, as there is a lack of representative data in higher-risk populations, such as migrants from countries where hepatitis is endemic (3), the true prevalence is probably higher.

In order to halt the progression of the disease to advanced hepatic fibrosis, cirrhosis, and/or hepatocellular carcinoma, and to prevent onward transmission, timely recognition and accurate clinical management of the disease are of extreme importance. Both the general practitioner (GP) and the secondary-care specialist are involved in the diagnosis of chronic viral hepatitis and in the clinical management of infected patients. Several studies have explored the primary-care physician's role and experiences in treatment and shared- care with specialists in North America (4-6), in Australia (7-9) and in some parts of Asia (10, 11). To the best of our knowledge, however, the remit of the GP in the clinical management of the disease in the EU member states has not been extensively evaluated.

The aim of the present study, which is part of the EU funded Project "HEPscreen: Screening for hepatitis B and C among migrants in the European Union", was to investigate, by means of a semi-quantitative online survey, the role of the GP in the screening of persons at risk and in the clinical management of chronic viral hepatitis patients in six EU countries: Germany, Hungary, Italy, the Netherlands, Spain and the United Kingdom.

METHODS

Two semi-quantitative online surveys were developed and administered, respectively, to general practitioners (GPs) and to secondary-care specialists (SPs), i.e. gastroenterologists, hepatologists and infectious disease specialists, working in the six EU countries. Both surveys were pilot tested, translated into the national languages of the study countries, uploaded into the open-source online software package LimeSurvey©, and sent by email to health care professionals, who were board members of clinical associations and professional networks. Rather than reaching a large representative sample of practising clinicians, the aim was to involve 5-10 experts deemed able to reflect on practices within

their specialty in both professional groups. Respondents were contacted via email in July 2012 and further reminded twice during data collection, which closed in September 2012. Data were exported from LimeSurvey to SPSS 19.2 (Inc. Chicago, IL) for descriptive analysis.

In the GP survey, we aimed to find out how commonly population groups at higher risk, namely migrants from endemic countries, people who inject drugs (PWID), sex workers, men who have sex with men (MSM), HIV positive patients and patients with abnormal liver function test (LFT) results, are screened for hepatitis B/C by GPs in the six countries. To this end, we used a four-point Likert scale ("very common"; "variable or not routinely"; "rarely or never"; "unsure"). In both the GP and specialist survey, the same scale was used to determine whether GPs were involved in the clinical management of patients: specifically, whether they were involved in monitoring alanine aminotransferase (ALT), viral load and side effects in patients undergoing antiviral treatment. We also explored whether patients were referred back to primary care in four clinical/patient scenarios, i.e. i) patients not qualifying for treatment after the initial evaluation; ii) those undergoing antiviral treatment; iii) those who have a sustained virological response (SVR) due to treatment; and iv) those who are non-responders to treatment. The replies given by the two professional groups were compared.

RESULTS

Respondent profile (Table 1)

The respondent target of between five and 10 experts per professional group was achieved, except in the cases of Spain (GPs: n = 2; Specialists: n = 4), Hungary (GPs: n = 1) and Germany (GPs: n = 4) (Table 1). The majority of specialists (77%) were gastroenterologists/ hepatologists; 21% were infectious disease specialists and a small proportion were community/practice nurses. Overall, around half of the participating GPs see a few (1-10) chronic hepatitis patients per year, whereas more than 90% of the secondary-care specialists see chronic hepatitis patients on a weekly basis.

Table 1. Survey respondents by professional group and by country

	UK n (%)	DE n (%)	NL n (%)	HU n (%)	IT n (%)	ES n (%)	Total n (%)
GPs	10 (25)	4 (10)	9 (22.5)	1 (2.5)	14 (35)	2 (5)	40 (100)
Specialists	10 (15.6)	9 (14.1)	22 (34.4)	10 (15.6)	9 (14.1)	4 (6.3)	64 (100)
Total n (%)	20 (19.2)	13 (12.5)	31 (29.8)	11 (10.6)	23 (22.1)	6 (5.8)	104 (100)

n: number of health professionals who participated in the survey.%: proportion of those invited who responded.

Screening by GPs for groups at higher risk (Table 2)

Migrants from endemic countries

Results from the GP survey showed that 75% of respondents in Germany, 56% in the Netherlands, the one in Hungary and one of the two in Spain stated that it was very common to offer hepatitis B testing to migrants from endemic regions. On the other hand, approximately half of the respondents in the UK (60%) and Italy (50%) and the other respondent in Spain answered that this was not routine. Except for Hungary, where the one respondent was unsure, most GPs in the study countries stated that they either routinely or variably offered screening for hepatitis C to migrants from endemic regions.

People who inject drugs (PWID)

The majority of GPs from the UK, Germany and Italy, along with the one in Hungary and the two in Spain, reported that they routinely offered hepatitis B/C screening to PWID. In the Netherlands, although screening for hepatitis C appears to be commonly practised by GPs for PWID, screening for hepatitis B varied between very commonly (44%) or variably (44%) offering the test.

Sex workers

In Germany and the UK most GPs (75% and 70%, respectively) answered that it was very common to offer a hepatitis B test to sex workers, and the two respondents in Spain were also of this opinion. The single Hungarian GP stated that it was a variable practice. In the Netherlands, respondents were split between judgements of "very common" and "variable". In Italy, no apparent trend could be discerned. The majority of GPs in the UK, Germany and the Netherlands, and both respondents in Spain, stated that it was very common to recommend hepatitis C testing to sex workers. In Italy, most replies were split between "very common" and "variable". The respondent in Hungary reported that it was not routinely practised.

Men who have sex with men (MSM)

As to whether GPs offer screening to MSM, replies indicated that it was "variably" and "commonly" practised in Germany, the Netherlands and Italy, while in Hungary it seems to be a sporadic practice. In the UK, while screening for hepatitis B seems to be common practice among GPs, the majority view is that hepatitis C testing is offered only occasionally to MSM.

Table 2. Frequency of screening for hepatitis B or C for population groups at higher risk by primary-care physicians in the six countries

Migrants						
HBV	**UK (n = 10)**	**DE (n = 4)**	**NL (n = 9)**	**HU (n = 1)**	**IT (n = 14)**	**ES (n = 2)**
Very common	20%	75%	56%	100%	14%	50%
Variable or not routinely	60%	25%	22%	0%	50%	50%
Rarely or never	10%	0%	22%	0%	29%	0%
Unsure	10%	0%	0%	0%	7%	0%
HCV	**UK (n = 10)**	**DE (n = 4)**	**NL (n = 9)**	**HU (n = 1)**	**IT (n = 14)**	**ES (n = 2)**
Very common	40%	75%	67%	0%	29%	50%
Variable or not routinely	30%	25%	11%	0%	57%	50%
Rarely or never	10%	0%	22%	0%	14%	0%
Unsure	20%	0%	0%	100%	0%	0%
People who inject drugs (PWID)						
HBV	**UK (n = 10)**	**DE (n = 4)**	**NL (n = 9)**	**HU (n = 1)**	**IT (n = 14)**	**ES (n = 2)**
Very common	90%	75%	44%	100%	64%	100%
Variable or not routinely	0%	25%	44%	0%	14%	0%
Rarely or never	0%	0%	0%	0%	14%	0%
Unsure	10%	0%	12%	0%	8%	0%
HCV	**UK (n = 10)**	**DE (n = 4)**	**NL (n = 9)**	**HU (n = 1)**	**IT (n = 14)**	**ES (n = 2)**
Very common	50%	75%	67%	100%	72%	100%
Variable or not routinely	30%	25%	22%	0%	14%	0%
Rarely or never	0%	0%	11%	0%	14%	0%
Unsure	20%	0%	0%	0%	0%	0%
Sex workers						
HBV	**UK (n = 10)**	**DE (n = 4)**	**NL (n = 9)**	**HU (n = 1)**	**IT (n = 14)**	**ES (n = 2)**
Very common	70%	75%	44%	0%	36%	100%
Variable or not routinely	0%	25%	45%	100%	29%	0%
Rarely or never	0%	0%	11%	0%	14%	0%
Unsure	30%	0%	0%	0%	21%	0%

Table 2. (continued)

HCV	UK (n = 10)	DE (n = 4)	NL (n = 9)	HU (n = 1)	IT (n = 14)	ES (n = 2)
Very common	60%	75%	56%	0%	36%	100%
Variable or not routinely	20%	25%	33%	100%	43%	0%
Rarely or never	0%	0%	11%	0%	14%	0%
Unsure	20%	0%	0%	0%	7%	0%
Men who have sex with men (MSM)						
HBV	**UK (n = 10)**	**DE (n = 4)**	**NL (n = 9)**	**HU (n = 1)**	**IT (n = 14)**	**ES (n = 2)**
Very common	60%	50%	44%	0%	36%	0%
Variable or not routinely	20%	50%	56%	100%	36%	50%
Rarely or never	0%	0%	0%	0%	21%	0%
Unsure	20%	0%	0%	0%	7%	50%
HCV	**UK (n = 10)**	**DE (n = 4)**	**NL (n = 9)**	**HU (n = 1)**	**IT (n = 14)**	**ES (n = 2)**
Very common	20%	50%	44%	0%	36%	50%
Variable or not routinely	50%	50%	45%	100%	43%	50%
Rarely or never	0%	0%	11%	0%	21%	0%
Unsure	30%	0%	0%	0%	0%	0%
1st Abnormal Liver Function Test Results						
HBV	**UK (n = 10)**	**DE (n = 4)**	**NL (n = 9)**	**HU (n = 1)**	**IT (n = 14)**	**ES (n = 2)**
Very common	40%	50%	44%	100%	64%	50%
Variable or not routinely	50%	50%	45%	0%	22%	0%
Rarely or never	0%	0%	11%	0%	14%	50%
Unsure	10%	0%	0%	0%	0%	0%
2nd Abnormal Liver Function Test Results						
HBV	**UK (n = 10)**	**DE (n = 4)**	**NL (n = 9)**	**HU (n = 1)**	**IT (n = 14)**	**ES (n = 2)**
Very common	60%	100%	89%	100%	64%	50%
Variable or not routinely	30%	0%	11%	0%	36%	0%
Rarely or never	0%	0%	0%	0%	0%	50%
Unsure	10%	0%	0%	0%	0%	0%

Table 2. (continued)

1st Abnormal Liver Function Test Results						
HCV	**UK (n = 10)**	**DE (n = 4)**	**NL (n = 9)**	**HU (n = 1)**	**IT (n = 14)**	**ES (n = 2)**
Very common	40%	50%	33%	100%	64%	50%
Variable or not routinely	40%	50%	34%	0%	29%	50%
Rarely or never	0%	0%	33%	0%	7%	0%
Unsure	20%	0%	0%	0%	0%	0%
2nd Abnormal Liver Function Test Results						
HCV	**UK (n = 10)**	**DE (n = 4)**	**NL (n = 9)**	**HU (n = 1)**	**IT (n = 14)**	**ES (n = 2)**
Very common	60%	100%	56%	100%	79%	50%
Variable or not routinely	20%	0%	33%	0%	22%	50%
Rarely or never	0%	0%	11%	0%	0%	0%
Unsure	20%	0%	0%	0%	0%	0%
Patients with HIV						
HBV	**UK (n = 10)**	**DE (n = 4)**	**NL (n = 9)**	**HU (n = 1)**	**IT (n = 14)**	**ES (n = 2)**
Very common	80%	75%	67%	0%	79%	50%
Variable or not routinely	0%	25%	22%	100%	0%	50%
Rarely or never	0%	0%	0%	0%	7%	0%
Unsure	20%	0%	11%	0%	14%	0%
HCV	**UK (n = 10)**	**DE (n = 4)**	**NL (n = 9)**	**HU (n = 1)**	**IT (n = 14)**	**ES (n = 2)**
Very common	50%	75%	44%	0%	71%	100%
Variable or not routinely	30%	25%	22%	100%	14%	0%
Rarely or never	0%	0%	11%	0%	7%	0%
Unsure	20%	0%	23%	0%	8%	0%

Patients with HIV

Most GPs (>44%) in all countries reported that it was very common practice to offer hepatitis B/C screening to HIV patients, except in Hungary, where the respondent stated that screening was not routinely offered.

Patients with abnormal liver function test results

A first abnormal LFT result would very commonly prompt approximately half of the GP respondents in each country and the one in Hungary to screen a patient for hepatitis B, while the others stated that this would not routinely be the case. On the other hand, a second abnormal LFT result would alert most GPs to recommend a hepatitis B test to their patients. While a first abnormal LFT result would only lead half of the GPs to request a hepatitis C test, apart from Italy and Hungary, where most would ask for a hepatitis C test, a second or repeat abnormal LFT would prompt the majority of GPs in all countries to screen for hepatitis C.

The involvement of GPs in the clinical management of the disease (Table 3)

ALT

In Germany, the majority of respondents indicated that it was very common for GPs to monitor ALT in patients undergoing antiviral treatment. A similar, but less marked, trend could be seen in Italy, where over half the GPs selected "very common". GPs in Spain appeared to be involved in monitoring ALT variably according to the vast majority of respondents. The trends in these three countries contrast with that observed in the Netherlands, where nearly three quarters (71%) indicated that GPs were rarely or never involved in monitoring ALT. In the UK and in Hungary, over half (55%) indicated that GPs were rarely or never involved, the remaining replies being distributed across the other answer options.

Viral load

The results from both the GPs' and specialists' surveys show that, in the UK, the Netherlands, Hungary and Spain, most GPs are rarely or never involved in monitoring viral load among patients undergoing antiviral treatment. Also in Italy, despite the diverse spread of opinion, the largest proportion (39%) indicated that GPs were rarely or never involved. In Germany, a slight trend towards "very common" was observed.

Side effects

A diversity of opinion emerged from both surveys in most countries. The clearest picture emerged from Germany, where the majority view (62%) was that GPs were very commonly involved in monitoring side effects. The dominant view in Italy was more towards very common (35%) or variable (52%) monitoring of side effects by GPs, whereas the majority view inclined more towards variable to rarely or never in the UK, the Netherlands and Hungary. In Spain no majority opinion emerged.

Table 3. GPs' involvement in monitoring clinical indicators and side effects of antiviral treatment

GPs involvement in monitoring ALT						
ACCORDING TO GPs	**UK (n = 10)**	**DE (n = 4)**	**NL (n = 9)**	**HU (n = 1)**	**IT (n = 14)**	**ES (n = 2)**
Very common	20%	75%	0%	100%	64%	50%
Variable or not routinely	40%	0%	22%	0%	21%	50%
Rarely or never	20%	0%	56%	0%	14%	0%
Unsure	20%	25%	22%	0%	0%	0%
ACCORDING TO SPECIALISTS	**UK (n = 10)**	**DE (n = 9)**	**NL (n = 22)**	**HU (n = 10)**	**IT (n = 9)**	**ES (n = 4)**
Very common	0%	56%	0%	10%	33%	0%
Variable or not routinely	10%	11%	23%	10%	67%	100%
Rarely or never	90%	11%	77%	60%	0%	0%
Unsure	0%	22%	0%	20%	0%	0%
COMBINED RESULTS	**UK (n = 20)**	**DE (n = 13)**	**NL (n = 31)**	**HU (n = 11)**	**IT (n = 23)**	**ES (n = 6)**
Very common	10%	62%	0%	18%	52%	17%
Variable or not routinely	25%	8%	23%	9%	39%	83%
Rarely or never	55%	8%	71%	55%	9%	0%
Unsure	10%	23%	6%	18%	0%	0%
GPs involvement in monitoring viral load						
ACCORDING TO GPs	**UK (n = 10)**	**DE (n = 4)**	**NL (n = 9)**	**HU (n = 1)**	**IT (n = 14)**	**ES (n = 2)**
Very common	0%	50%	0%	0%	36%	0%
Variable or not routinely	30%	25%	11%	0%	43%	50%
Rarely or never	50%	25%	67%	100%	21%	50%
Unsure	20%	0%	22%	0%	0%	0%
ACCORDING TO SPECIALISTS	**UK (n = 10)**	**DE (n = 9)**	**NL (n = 22)**	**HU (n = 10)**	**IT (n = 9)**	**ES (n = 4)**
Very common	0%	33%	0%	0%	22%	0%
Variable or not routinely	0%	22%	0%	10%	11%	25%
Rarely or never	100%	22%	100%	70%	67%	75%
Unsure	0%	22%	0%	20%	0%	0%
COMBINED RESULTS	**UK (n = 20)**	**DE (n = 13)**	**NL (n = 31)**	**HU (n = 11)**	**IT (n = 23)**	**ES (n = 6)**
Very common	0%	38%	0%	0%	30%	0%
Variable or not routinely	15%	23%	3%	9%	30%	33%
Rarely or never	75%	23%	90%	73%	39%	67%
Unsure	10%	15%	6%	18%	0%	0%

Table 3. (continued)

GPs involvement in monitoring side effects						
ACCORDING TO GPs	**UK (n = 10)**	**DE (n = 4)**	**NL (n = 9)**	**HU (n = 1)**	**IT (n = 14)**	**ES (n = 2)**
Very common	10%	75%	0%	0%	50%	100%
Variable or not routinely	50%	0%	22%	100%	36%	0%
Rarely or never	20%	25%	56%	0%	14%	0%
Unsure	20%	0%	22%	0%	0%	0%
ACCORDING TO SPECIALISTS	**UK (n = 10)**	**DE (n = 9)**	**NL (n = 22)**	**HU (n = 10)**	**IT (n = 9)**	**ES (n = 4)**
Very common	10%	56%	0%	10%	11%	0%
Variable or not routinely	40%	11%	46%	20%	78%	50%
Rarely or never	50%	11%	55%	40%	11%	50%
Unsure	0%	22%	0%	30%	0%	0%
COMBINED RESPONSES	**UK (n = 20)**	**DE (n = 13)**	**NL (n = 31)**	**HU (n = 11)**	**IT (n = 23)**	**ES (n = 6)**
Very common	10%	62%	0%	9%	35%	33%
Variable or not routinely	45%	8%	39%	27%	52%	33%
Rarely or never	35%	15%	55%	36%	13%	33%
Unsure	10%	15%	7%	27%	0%	0%

Referral back to GPs/primary care from specialist secondary care (Table 4)

Patients who do not qualify for treatment after an initial evaluation

In the Netherlands and in Spain, the majority of respondents in both surveys agreed that patients who do not qualify for treatment after an initial evaluation are only variably or not routinely referred back to primary-care practitioners. Specialists' opinion was in contrast with that of GPs in the UK, where 90% of specialists (vs 10% of GPs) indicated that these patients were rarely or never referred back to GPs. In Italy, although the majority of specialists (56%) selected "variable", around one third indicated "rarely or never", while 57% of GPs selected "very common". In Germany, the majority opinion was divided between patients being very commonly (54%) and variably (39%) referred back to GPs. In Hungary, no dominant opinion could be observed.

Table 4. Frequency of referral back to GPs for: i) patients who do not qualify for treatment after the initial evaluation; ii) patients undergoing antiviral treatment; iii) patients with sustained virological response due to treatment; and iv) patients who are non-responders to treatment

i) Patients who do not qualify for treatment after initial evaluation

ACCORDING TO GPs	**UK (n = 10)**	**DE (n = 4)**	**NL (n = 9)**	**HU (n = 1)**	**IT (n = 14)**	**ES (n = 2)**
Very common	50%	50%	33%	100%	57%	50%
Variable or not routinely	10%	50%	56%	0%	21%	0%
Rarely or never	10%	0%	11%	0%	21%	50%
Unsure	30%	0%	0%	0%	0%	0%
ACCORDING TO SPECIALISTS	**UK (n = 10)**	**DE (n = 9)**	**NL (n = 22)**	**HU (n = 10)**	**IT (n = 9)**	**ES (n = 4)**
Very common	10%	56%	14%	20%	11%	0%
Variable or not routinely	0%	33%	59%	30%	56%	100%
Rarely or never	90%	0%	27%	30%	33%	0%
Unsure	0%	11%	0%	20%	0%	0%
COMBINED RESULTS	**UK (n = 20)**	**DE (n = 13)**	**NL (n = 31)**	**HU (n = 11)**	**IT (n = 23)**	**ES (n = 6)**
Very common	30%	54%	19%	27%	39%	17%
Variable or not routinely	5%	39%	58%	27%	35%	67%
Rarely or never	50%	0%	23%	27%	26%	17%
Unsure	15%	8%	0%	18%	0%	0%

ii) Patients undergoing antiviral treatment

ACCORDING TO GPs	**UK (n = 10)**	**DE (n = 4)**	**NL (n = 9)**	**HU (n = 1)**	**IT (n = 14)**	**ES (n = 2)**
Very common	0%	75%	11%	0%	57%	0%
Variable or not routinely	40%	0%	22%	0%	14%	0%
Rarely or never	40%	25%	56%	100%	29%	100%
Unsure	20%	0%	11%	0%	0%	0%
ACCORDING TO SPECIALISTS	**UK (n = 10)**	**DE (n = 9)**	**NL (n = 22)**	**HU (n = 10)**	**IT (n = 9)**	**ES (n = 4)**
Very common	10%	0%	0%	10%	22%	25%
Variable or not routinely	0%	44%	5%	0%	0%	0%
Rarely or never	90%	44%	95%	60%	78%	75%
Unsure	0%	11%	0%	30%	0%	0%

Table 4. (continued)

COMBINED RESULTS	UK (n = 20)	DE (n = 13)	NL (n = 31)	HU (n = 11)	IT (n = 23)	ES (n = 6)
Very common	5%	23%	3%	9%	43%	17%
Variable or not routinely	20%	31%	10%	0%	9%	0%
Rarely or never	65%	38%	84%	64%	48%	83%
Unsure	10%	8%	3%	27%	0%	0%
iii) Patients with sustained virological response due to treatment						
ACCORDING TO GPs	**UK (n = 10)**	**DE (n = 4)**	**NL (n = 9)**	**HU (n = 1)**	**IT (n = 14)**	**ES (n = 2)**
Very common	10%	50%	22%	0%	57%	0%
Variable or not routinely	30%	25%	56%	0%	14%	0%
Rarely or never	20%	25%	11%	100%	29%	100%
Unsure	40%	0%	11%	0%	0%	0%
ACCORDING TO SPECIALISTS	**UK (n = 10)**	**DE (n = 9)**	**NL (n = 22)**	**HU (n = 10)**	**IT (n = 9)**	**ES (n = 4)**
Very common	70%	67%	59%	40%	22%	50%
Variable or not routinely	10%	22%	36%	0%	44%	25%
Rarely or never	10%	0%	5%	30%	33%	25%
Unsure	10%	11%	0%	30%	0%	0%
COMBINED RESULTS	**UK (n = 20)**	**DE (n = 13)**	**NL (n = 31)**	**HU (n = 11)**	**IT (n = 23)**	**ES (n = 6)**
Very common	40%	61%	49%	36%	44%	33%
Variable or not routinely	20%	23%	42%	0%	26%	17%
Rarely or never	15%	8%	6%	36%	30%	50%
Unsure	25%	8%	3%	27%	0%	0%
iv) Patients non-responders to treatment						
ACCORDING TO GPs	**UK (n = 10)**	**DE (n = 4)**	**NL (n = 9)**	**HU (n = 1)**	**IT (n = 14)**	**ES (n = 2)**
Very common	20%	50%	11%	0%	64%	0%
Variable or not routinely	20%	25%	44%	100%	21%	0%
Rarely or never	20%	25%	22%	0%	14%	100%
Unsure	40%	0%	22%	0%	0%	0%

Table 4. (continued)

ACCORDING TO SPECIALISTS	UK (n = 10)	DE (n = 9)	NL (n = 22)	HU (n = 10)	IT (n = 9)	ES (n = 4)
Very common	10%	11%	0%	0%	11%	25%
Variable or not routinely	0%	44%	0%	10%	33%	0%
Rarely or never	90%	33%	100%	50%	55%	75%
Unsure	0%	11%	0%	40%	0%	0%
COMBINED RESULTS	**UK (n = 20)**	**DE (n = 13)**	**NL (n = 31)**	**HU (n = 11)**	**IT (n = 23)**	**ES (n = 6)**
Very common	15%	23%	3%	0%	44%	17%
Variable or not routinely	10%	38%	13%	18%	26%	0%
Rarely or never	55%	31%	77%	46%	30%	83%
Unsure	20%	8%	7%	36%	0%	0%

Patients undergoing antiviral treatment

Overall, the majority of respondents in all countries (84% in the Netherlands, 83% in Spain, 65% in the UK, 64% in Hungary, 48% in Italy and 38% in Germany) stated that patients undergoing antiviral treatment were rarely or never referred back to GPs. Only in Germany and Italy did the majority of GPs (75% and 57%, respectively) indicate that these patients were very commonly referred back to GPs, although around one quarter selected "rarely or never". In Germany, although 44% of specialists reported "rarely or never" referring back patients undergoing antiviral treatment, the same percentage indicated that referral was variable. In Italy, 78% of secondary-care specialists indicated that these patients were rarely or never referred back to GPs (while 57% of GPs stated that it was very common).

Patients with a sustained virological response due to treatment

In the UK, despite divergent opinions from GPs, most GP and specialist respondents reported that referral back to GPs was very common for patients who have SVR on account of treatment. This was also the dominant opinion in Germany (61%) and in the Netherlands (49%), where, however, 42% stated that patients with these characteristics were variably or not routinely referred back to GPs. In Hungary, opinion was divided between "very commonly" and "rarely or never". In Italy, although the majority judged referral to be very common, one third selected "rarely or never" and one quarter "variably or not routinely". Opinion was also divided in Spain, where half of the respondents selected "rarely or never", one third "very common", and 17% "variably or not routinely".

Non-responders to treatment

Non-responders to treat-ment are rarely or never referred back to GPs, according to the majority of respondents in all countries except Italy, where 44% stated that referral back to GPs was very common for these patients (the percentage was higher among GPs: 64%). In Germany, most reported that referral back to the GP occurred variably or not routinely.

DISCUSSION

In patients with chronic viral hepatitis, shared management based on close collaboration between the GP and the specialist physician, through the identification of their respective tasks, is necessary for the appropriate diagnostic and therapeutic management of the patient along the care pathway. Since most people with chronic hepatitis are asymptomatic until cirrhosis or hepatocellular carcinoma are established, the initial diagnosis and management of chronic hepatitis relies on primary-care physicians to identify and screen high-risk individuals (12). The GP can contribute significantly by promptly identifying and screening of those at risk, by providing counselling and information, by referring the patient to the specialist for disease staging and also by liaising/cooperating with the hospital services involved in the specialist management of patients.

Non-uniform practices are likely to create or exacerbate health inequalities, and might be an important cause of the "under-treatment" phenomenon, i.e. the disparity between the number of chronic hepatitis patients and the number of patients actually receiving treatment (13). To our knowledge, this is the first study conducted contemporarily in six EU countries with the aim of investigating the role of the GP in the screening practices for risk groups and in the clinical management of chronic viral hepatitis patients. Given the careful selection of the survey participants and national representatives of the experts in their respective fields, it may justifiably be assumed that the replies gathered provide a fair picture of the GP's remit in the countries considered. However, caution is needed in interpreting the results where the respondent target of five to ten experts could not be reached (in Spain and Hungary). According to our results, the GP's role and referral back to GPs vary within and between countries. What seems certain is that GPs are unlikely to monitor any clinical outcomes (such as viral load) other than some side effects in patients undergoing treatment, indicating that this is considered the remit of specialists in secondary care.

Results from a Turkish study showed that GPs were not able to follow up chronic viral hepatitis B and C patients because of their limited awareness of diagnostic facilities and treatment options (14). Indeed, while the majority of GPs had adequate knowledge of HBV and HCV transmission and of risk factors, a low percentage was well informed about the

treatment of chronic patients with elevated ALT. In particular, the Turkish study identified gaps in GPs knowledge of the appropriate use of diagnostic tests and interventions to identify and manage patients with chronic viral hepatitis. The authors concluded that further coordination with secondary-care specialists was warranted in order to ensure that patients were followed up in the primary-care setting (14).

Strategic programmes of health education and awareness-raising, for both professionals and risk groups, should be established. In the EU, two different strategies are used to identify persons with HBV or HCV infection: population screening and health care provider-initiated testing (based on identified risk-factors). Population screening is not cost-effective, owing to the low prevalence of HBV and HCV infections in the general EU population, while the health care provider-initiated identification of HBV or HCV infection among defined risk groups is a valuable instrument in secondary prevention. Making GPs aware of risk factors, such as demographic, behavioural, occupational and medical risk factors, and clinical signs or symptoms of hepatitis, may efficiently improve case identification. Patients with chronic HBV or HCV infection should be referred for medical care and case-management, and those testing negative but with risk factors for acquiring HBV or HCV infection should receive counselling on prevention (those at risk of HBV infection should also be offered vaccination) (15).

In the USA, approaches to the screening, diagnosis and management of viral hepatitis patients vary considerably among primary-care physicians. Indeed, studies in the USA have shown deficiencies in the way some primary-care providers diagnose, treat or refer patients with HCV (16-23). One such study investigated the association between the characteristics of the physician or practice and screening and treatment for HCV infection: more experienced physicians (longer in practice) and those based in affluent, suburban settings were more likely to order ALT tests (16). In another study, a cross-sectional mail survey of 217 family physicians revealed insufficient levels of knowledge about screening and counselling for chronic hepatitis and hepatocellular carcinoma; in addition, around half of the physicians referred patients with chronic HBV or HCV to the specialist for further management (12). Our results show that patients who have had a sustained virological response are generally referred back to the GP, while patients undergoing antiviral treatment and those who do not respond to treatment are rarely referred back to primary care.

As new treatment options, especially for hepatitis C, have become available in recent years, access and adherence to treatment are important determinants of the success of screening programmes (2).

Since 2012, population-based anti-HCV screening of all adults born between 1945 and 1965 has been recommended in the USA, where the prevalence of anti-HCV is highest in black non-Hispanics (6.42%) and in Mexican Americans (3.26%) (24). In the EU, particular attention should be paid to providing screening and treatment for hepatitis B and C for migrant groups at high risk of chronic infection. The adoption of a targeted screening and treatment programme in primary care could be an effective strategy. Results from our study in the UK, suggest that standard screening prac- tices are lacking, and allude to a shared role for GPs in the clinical monitoring of ALT, viral load and side effects. Referral back to the GP of patients undergoing antiviral treatment is not common, although GPs and specialists differed markedly in their estimates of the frequency of referral back to GPs of patients who do not qualify for treatment. In a recent UK study, GPs expressed concerns about screening and treating patients in primary care, considering their workload and also the sustainability of such a strategy (25). Immigrants mentioned practical barriers, such as language and communication difficulties, limited time on account of long working hours, and, in some cases, limited trust and confidence in general practice-based care (25).

Indeed, chronic hepatitis B and C infections are often undiagnosed in primary care. According to the 'Hepatitis B and C surveillance in Europe – 2012' report, in the minority of cases in which information on the testing facility was available, 27% of hepatitis B and 21% of hepatitis C cases were diagnosed in general practice (26). One German study, involving 21,008 subjects, reported that the prevalence of HBsAg, anti-HCV and HCV-RNA was 0.52%, 0.95%, and 0.43%, respectively. Infections were previously unknown in 85% and 65% of HbsAg and anti-HCV positive individuals, respectively (27). German hepatitis B and C treatment guidelines recommend HBsAg and anti-HCV screening in several pre-defined risk groups. According to the participants in our survey, most GPs in Germany report commonly screening population groups at higher risk. The management of patients un- dergoing treatment seems to be shared between GPs and specialists. Easy to apply guidelines with defined risk scenarios may help to diagnose previously unknown infections (27). Previous results from the HEPscreen Project showed that the availability of training programmes to improve skills and knowledge of viral hepatitis differed across the six EU countries. Among the experts interviewed (268 health professionals), 80% and 73% were aware of hepatitis B and hepatitis C guidelines, respectively, in their country (28). The findings of the present study could provide impetus to the formulation of precise and clear guidelines targeting primary-care physicians and secondary-care specialists. These should explicitly specify, in a shared-care model, the different responsibilities in the management of chronic hepatitis patients, so as to deliver more effective healthcare.

CONCLUSIONS

Although the GP's role in the screening and clinical management of chronic viral hepatitis is crucial to timely diagnosis and linkage to specialist care, the diversity of responses often observed suggests inadequate awareness of explicit recommendations, which results in a lack of uniform practices among experts. The GP's decision to offer screening to risk groups often seems to be an individually motivated choice of the health care professional. The inconsistencies observed in screening practices may mean that many chronic infections remain undetected. This underscores the need to raise GPs' awareness of this silent epidemic, for example through the adoption of effective strategies for the dissemination and implementation of the existing guidelines for general practice. The role of GPs and specialists involved in the management of chronically infected patients should also be clarified, as opinions sometimes differed markedly even within each professional group.

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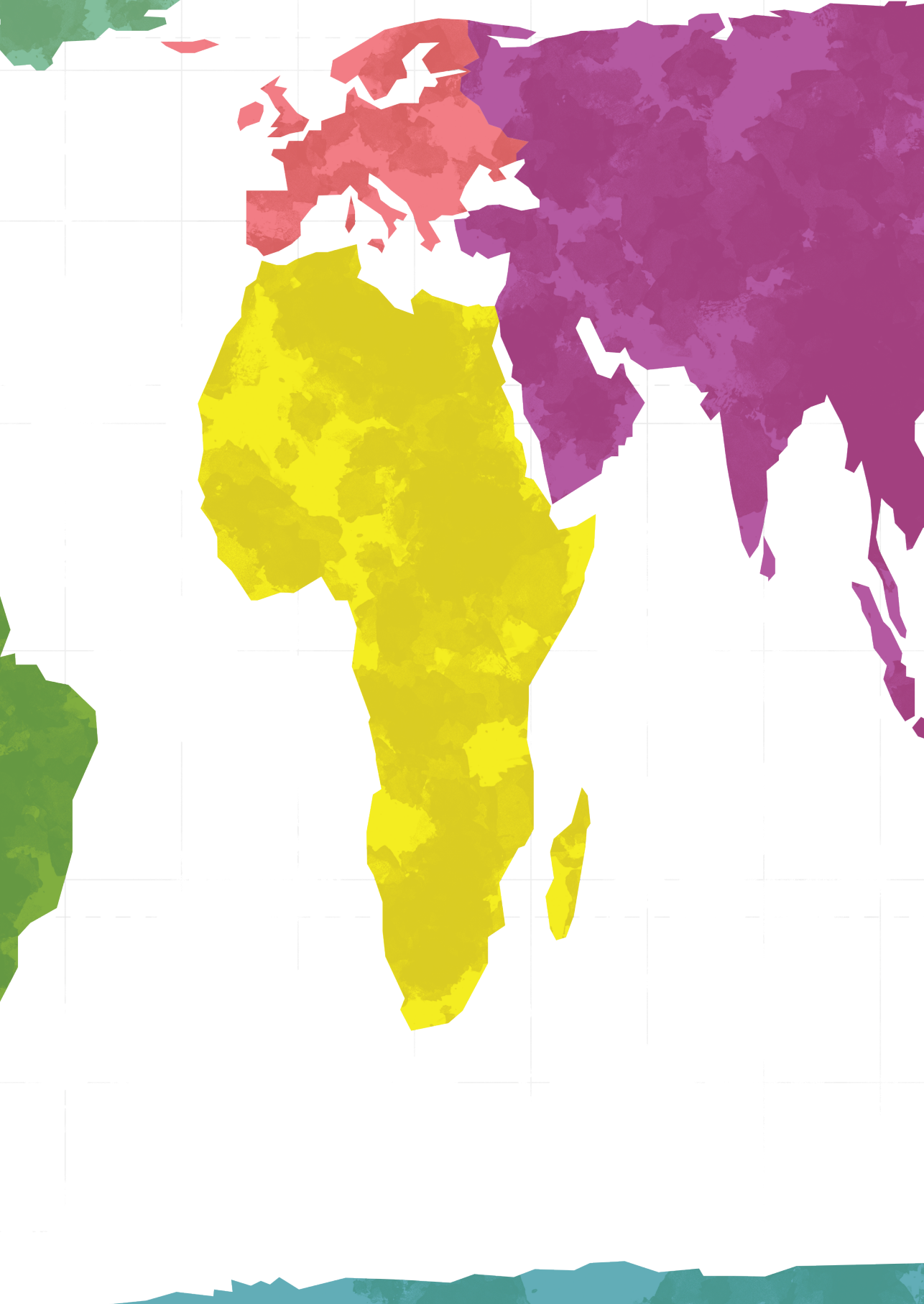

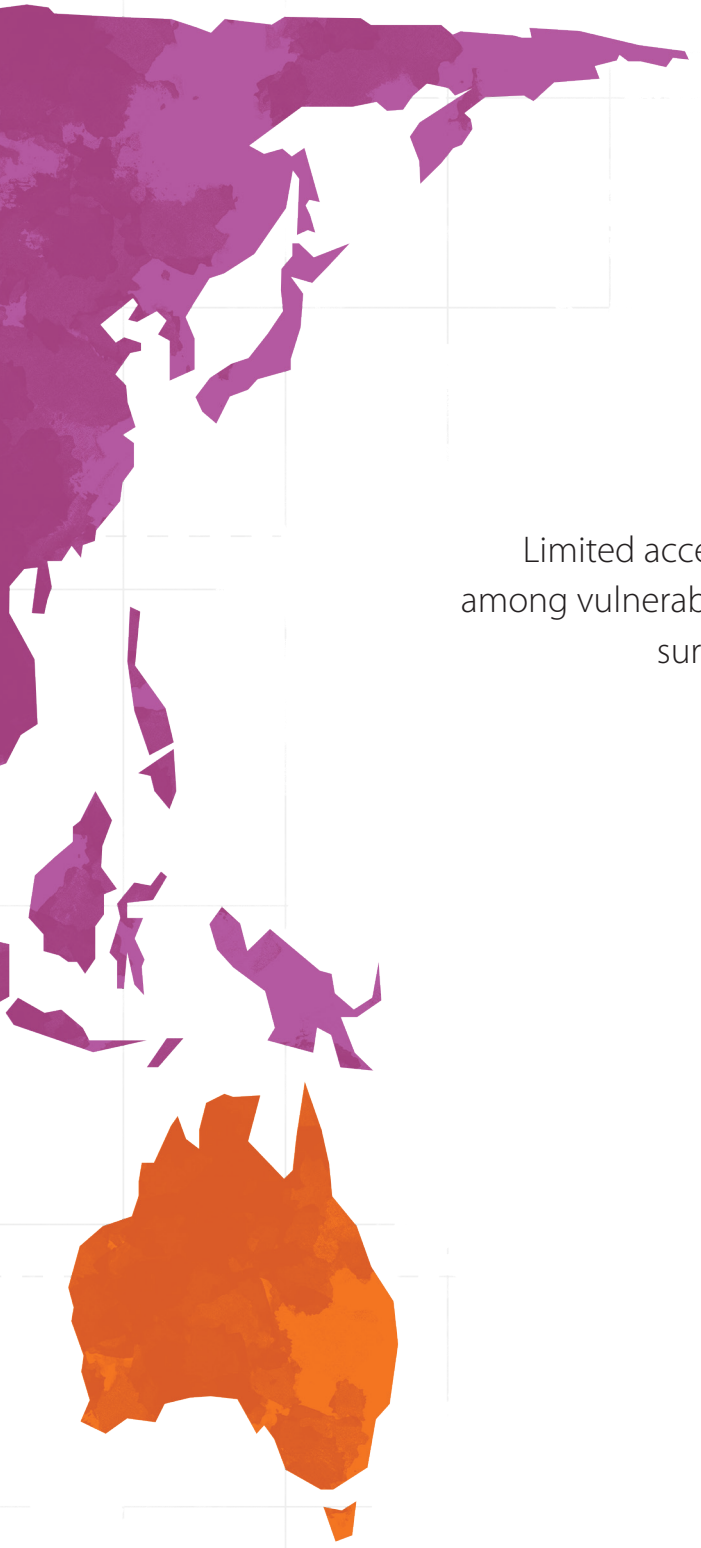

CHAPTER 12

Limited access to hepatitis B/C treatment among vulnerable risk populations: an expert survey in six European countries

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ABSTRACT

Background: To investigate access to treatment for chronic hepatitis B/C among six vulnerable patient/population groups at-risk of infection: undocumented migrants, asylum seekers, people without health insurance, people with state insurance, people who inject drugs (PWID) and people abusing alcohol.

Methods: An online survey among experts in gastroenterology, hepatology and infectious diseases in 2012 in six EU countries: Germany, Hungary, Italy, the Netherlands, Spain and the UK. A four-point ordinal scale measured access to treatment (no, some, significant or complete restriction).

Results: From 235 recipients, 64 responses were received (27%). Differences in access between and within countries were reported for all groups except people with state insurance. Most professionals, other than in Spain and Hungary, reported no or few restrictions for PWID. Significant/complete treatment restriction was reported for all groups by the majority in Hungary and Spain, while Italian respondents reported no/few restrictions. Significant/complete restriction was reported for undocumented migrants and people without health insurance in the UK and Spain. Opinion about undocumented migrants in Germany and the Netherlands was divergent.

Conclusions: Although effective chronic hepatitis B/C treatment exists, limited access among vulnerable patient populations was seen in all study countries. Discordance of opinion about restrictions within countries is seen, especially for groups for whom the health care system determines treatment access, such as undocumented migrants, asylum seekers and people without health insurance. This suggests low awareness, or lack, of entitlement guidance among clinicians. Expanding treatment access among risk groups will contribute to reducing chronic viral hepatitis-associated avoidable morbidity and mortality.

INTRODUCTION

Infection with hepatitis B (HBV) virus and C virus (HCV) affects the liver and can result in a broad spectrum of disease outcomes. People with chronic hepatitis B (CHB) and/or C virus infection remain infectious and are at risk of serious liver disease such as cirrhosis or hepatocellular cancer (HCC). Worldwide, chronic viral hepatitis infection is responsible for over 70% of deaths due to HCC and nearly 60% of deaths due to cirrhosis.[1,2] Around 480–520 million people are estimated to be chronically infected with HBV/ HCV, although there are strong regional differences in burden of disease. The largest burden of HCV is found in Central/Eastern Asia and the Middle East whereas HBV prevalence is highest in SubSaharan Africa and Asia.[3] There is also some geographical variation in HBV and HCV prevalence in Europe.[4] Most CHB infections in Europe are detected among migrants from HBVendemic areas. Chronic hepatitis C is also more common among migrants (due to non-sterile health care, dental and shaving practices and equipment in low-and middle-income countries of origin), although a large proportion is found among current/past injecting drug users.[5] Differences in the proportion of chronic hepatitis C cases detected among migrants compared with people who inject drugs (PWID) are reported in Europe; in the United Kingdom (UK), e.g. PWID account for over 90% of cases,[6] whereas migrants from endemic areas account for most infections in the Netherlands, Germany, Italy and Spain.[7,8]

Chronic infections are mostly asymptomatic and progress over a period of 20–30 years towards cirrhosis and HCC. Effective treatment exists for both chronic hepatitis B and C and, from 2014, highly effective direct-acting antivirals that can cure chronic hepatitis C are available.[9,10] Early identification, before decompensation and/or development of HCC, is strongly associated with improved treatment outcome.[11] Therefore, screening for chronic infection among a range of risk groups, but particularly among people born in hepatitis B/C endemic areas and PWID, is recommend as a form of secondary prevention.[6,12] Screening among migrants from areas with >2% viral hepatitis prevalence has also been shown to be cost-effective.[13] Although incident cases are decreasing, models predict that the peak mortality for HCVrelated causes is ahead of us and a large undiagnosed burden of disease exists; that the proportion of people infected that are unaware, undiagnosed and not in treatment is considerably larger than the proportion diagnosed and in treatment.[8] For example, a large screening study in primary care in Germany found that 85% of HBsAg and 65% of anti-HCV positive individuals were unaware of their infection.[14] However, there are few published studies of migrant-specific viral hepatitis screening programmes in Europe.[15–18] PWID-specific studies are more common although screening among this high-risk group is not systematic in any European country, due to both health system and patient-group characteristics, including criminalisation.[19] The literature also suggests that

migrant populations experience difficulties in accessing health care and experience worse health outcomes as a result.[20–22] Little is known about access to treatment across Europe among marginalised groups at risk of hepatitis B/C infection.

We aimed to investigate access to treatment for chronic hepatitis B/C in six EU countries (Germany, Hungary, Italy, the Netherlands, Spain and the United Kingdom (UK)) among six patient/population groups. These included undocumented migrants, asylum seekers, people without health insurance, people with state insurance, PWID and people who abuse alcohol. This study is part of HEPscreen,[23] an EU Health Programme-funded project focused on screening for chronic viral hepatitis among migrants in Europe.

METHODS

A semi-quantitative online survey was developed, pilot tested and translated into the national languages of the study countries and uploaded into Lime Survey™ open source online survey software. The aim of the survey was to understand care pathways in clinical services for patients diagnosed with chronic viral hepatitis in the six study countries using nominal, ordinal and qualitative questions. We report here the results focused on access to treatment among specific patient/population groups; the more clinically focused questions about the use of diagnostics, referral and the role of different clinical specialists are to be reported elsewhere. The survey was sent to experts in hepatology, gastroenterology and infectious diseases based in six EU countries: Germany, Hungary, Italy, the Netherlands, Spain and the UK. We identified experts via board membership of clinical and professional associations, leadership of hepatology treatment and research centres, and authors of relevant scientific articles. Our objective was to reach a sample of 5–10 knowledgeable experts from each country rather than develop a representative sampling frame. In recognition of the low response rate to surveys among practising clinicians, we identified a large sample of 243 recipients.

We asked whether treatment for chronic hepatitis was restricted for each of the six patient/population groups and developed a fourpoint ordinal scale to measure this: 'no restrictions', 'some restrictions', 'significant restrictions' and 'completely restricted'. An 'unsure' option was also available. We collected respondent data by asking for organisation type and whether they were involved in the care of patients/had a clinical role. Among those with a clinical role, we asked for their medical specialism and used a three-point ordinal scale to gather data on frequency of seeing chronic hepatitis B/C patients (weekly, monthly and annually).

Recipients were contacted via e-mail in July 2012 and further reminded twice during data collection. The survey closed in September 2012. Data was exported from Lime Survey to SPSS 19.0.2 for descriptive analysis of frequencies and proportions.

RESULTS

Respondents

Eight of 243 recipients actively opted out after receiving the invitation. From the remaining 235 recipients, a total of 64 responses were received (27%). The response rate differed across the six study countries: 11% in Germany, 24% in the UK, 25% in Spain, 27% in Hungary, 48% in the Netherlands and 60% in Italy. In five of the six countries, Spain being the exception, we achieved the target of between 5 and 10 experts. Three of these 64 respondents had not completed the whole survey and were excluded. All but three of the 61 are currently involved in the care of patients and 95% of these see chronic hepatitis patients on a weekly basis. Due to the clinical nature of the topics, analysis was restricted to only data supplied by those with a clinical role (n=58). Of these, the majority (77%) are specialists in gastroenterology or hepatology, a fifth are specialists in infectious disease, and a small number (n=3) are community/practice nurses. The respondent profile pattern in all countries was similar to this overall pattern except in Italy and the Netherlands; in Italy, nearly half (44%) are specialists in infectious disease and in the Netherlands, a larger proportion (81%) are gastroenterologists/hepatologists. Most are based in academic (61%) or general hospitals (28%).

Access to treatment for undocumented migrants

Most respondents in all countries but Italy reported that antiviral treatment for chronic viral hepatitis is completely or significantly restricted for undocumented migrants. This is especially so in Hungary where three quarters reported treatment to be completely restricted, in the UK where two thirds indicated significant or complete restriction, and in Spain where three quarters selected significant or complete restriction. Over three quarters in Italy reported that there are no or some restrictions in place. Opinion was divided in the Netherlands and Germany (Table 1).

Access to treatment for asylum seekers

Two-thirds of those in Hungary and half in Spain reported significant or complete restrictions in treatment for chronic hepatitis patients with asylum seeker status. In contrast, all but one respondent in Germany, over half in the UK, and three quarters of those in the Netherlands

and Italy reported no or few restrictions for asylum seekers. However, there are some in the UK, Germany and the Netherlands who indicated that significant restrictions are in place (Table 2).

Access to treatment for people without health insurance and people with only state insurance

Over 75% in Italy reported no or few restrictions for those without health insurance whereas significant or complete restrictions were reported by the majority of respondents in Hungary (75%), Spain (75%), the UK (56%) and the Netherlands (46%). Opinion was divided in Germany (Table 3). We included the group 'state insurance only' to further explore the influence of (private) health insurance on access to treatment and found that the vast majority of respondents indicated that there are no restrictions (Table 3). In the UK, Germany, the Netherlands and Italy, nearly all respondents selected no restrictions. Although 50% in Hungary indicated that no restrictions exist for this group, one quarter selected significant restrictions.

Access to treatment for PWID and patients who abuse alcohol

The majority of respondents in the UK, Germany, the Netherlands and Italy indicated no or few restrictions in antiviral treatment for PWID infected with chronic hepatitis (table 4). In contrast, three quarters of professionals in Hungary reported significant or complete restrictions, with half reporting complete restrictions. Half in Spain reported there to be significant restrictions in place, although others indicated no or some restrictions. As with PWID, the majority of respondents in the UK, Germany, the Netherlands and Italy reported no or few restrictions in treatment to be in place for chronically infected patients who abuse alcohol. It was the opposite in Hungary, as over 75% reported complete or significant restrictions. Opinion was divided in Spain but suggests the existence of restrictions in access to treatment for patients who abuse alcohol.

Table 1. Reported treatment restrictions among undocumented migrants

	UK (n=9)	DE (n=6)	NL (n=22)	HU (n=8)	IT (n=9)	ES (n=4)
No restrictions	11%	17%	14%	0%	33%	25%
Some restrictions	0%	17%	27%	13%	44%	0%
Significant restrictions	44%	17%	27%	0%	0%	25%
Complete restrictions	22%	33%	23%	75%	11%	50%
Unsure	22%	17%	9%	13%	11%	0%

Table 2. Reported treatment restrictions among asylum seekers

	UK (n=9)	DE (n=6)	NL (n=22)	HU (n=8)	IT (n=9)	ES (n=4)
No restrictions	56%	33%	50%	0%	56%	25%
Some restrictions	0%	50%	23%	0%	22%	0%
Significant restriction	22%	17%	18%	38%	0%	0%
Complete restriction	0%	0%	0%	25%	11%	50%
Unsure	22%	0%	9%	38%	11%	25%

Table 3. Reported treatment restrictions among people with no/state insurance

	UK (n=9)		DE (n=6)		NL (n=22)		HU (n=8)		IT (n=9)		ES (n=4)	
	No	State	No	State	No	State	No	State	No	State	No	State
No restrictions	11%	78%	0%	100%	18%	82%	0%	50%	44%	89%	25%	50%
Some restrictions	11%	0%	50%	0%	18%	9%	16%	25%	33%	11%	0%	50%
Significant restriction	56%	0%	33%	0%	32%	0%	0%	25%	11%	0%	25%	0%
Complete restriction	0%	0%	0%	0%	14%	0%	75%	0%	11%	0%	50%	0%
Unsure	22%	22%	17%	0%	18%	9%	13%	0%	0%	0%	0%	0%

Table 4. Reported treatment restrictions among PWID and people who :abuse alcohol (Alc.)

	UK (n=9)		DE (n=6)		NL (n=22)		HU (n=8)		IT (n=9)		ES (n=4)	
	PWID	Alc.	PWID	Alc.	PWID	Alc.	PWID	Alc.	PWID	Alc.	PWID	Alc.
No restrictions	22%	22%	33%	17%	55%	36%	0%	13%	44%	33%	25%	0%
Some restrictions	56%	56%	50%	67%	36%	59%	25%	13%	33%	44%	25%	50%
Significant restriction	11%	11%	17%	17%	5%	5%	25%	38%	11%	0%	50%	25%
Complete restriction	0%	0%	0%	0%	5%	0%	50%	38%	11%	22%	0%	25%
Unsure	11%	11%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

DISCUSSION

Although effective treatment for chronic hepatitis B/C exists and even cure for chronic hepatitis C, results from this study show that access to treatment is limited for a number of vulnerable populations at risk of chronic infection in most countries we studied. Restrictions were most often reported by experts in Hungary and Spain, while as a group, undocumented migrants have the most limited access to treatment. We also found discordance of opinion about restrictions within countries, especially for groups for whom the health care system defines access to treatment, such as undocumented migrants, asylum seekers and people without health insurance.

For screening to be considered ethical and appropriate and to result in health gain, there should be treatment available for diagnosed patients.[24] The Wilson and Jungner criteria list availability of effective treatment and an agreed policy on who to treat as two of 10 principles that should be met to conduct screening. Treatment availability and eligibility are often seen from a biomedical perspective, in terms of clinical or prognostic factors only. As the six study countries organise their health care differently, eligibility and availability can also be understood from a health system perspective. We were interested to find out whether there are population-group specific restrictions in place as understood by clinicians most involved in providing it. The profile of our respondents indicates that this aim was fulfilled; nearly all respondents are clinical specialists in gastroenterology, hepatology or infectious diseases and see infected patients on a weekly basis.

As in many parts of the world, there are differences in health system organisation between EU countries that make it an interesting environment in which to conduct health systems and health services research; in our EU-funded project, we adopted a European perspective and sought to compare six Member States. In Bismarckian-based welfare states, like the Netherlands and Germany, citizens must 'buy' health insurance provision from insurance companies who cannot discriminate on the basis of individual health conditions or risk factors and contributions depend on an individual's financial resources.[25,26] It is, therefore, not surprising that we do observe some or significant restrictions in access to treatment among people without health insurance here (table 3). In Beveridge-style welfare states, like Italy, Spain and the UK, the notion of national insurance as collective contributions towards social and health service provision is familiar and a national health service with associated universal free access is in place.[27] Other than a small minority who purchase private health insurance coverage, the concept of 'buying' health insurance as a means to entitlement in these universal health systems is undesirable and alien to most. This universalism is mirrored in responses from Italy where no or only some restrictions exist for all six patient/population groups. It is, however, somewhat surprising that restriction to treatment among

those without insurance is reported in Spain and the UK, countries with health systems where insurance is not expected to play a role. However, both systems rely on some form of registration to receive social support, such as a National Insurance/NHS number in the UK or a residence permit in Spain. Access to health care would be limited without this registration, not because patients do not have health insurance coverage but because those without state insurance cover are effectively considered undocumented migrants or persons for whom health care entitlement is uncertain.[28] As a result of the financial crisis affecting Spain from 2008, various austerity and cost-containment measures were introduced into the health and social welfare system. One change, introduced after our survey was conducted, was the restriction of access to health care among undocumented migrants (and others considered to be uninsured under the universal, residence permitbased system) to emergency and ante- and post-natal care only.[29] The implication is likely to be more severe restrictions than the already significant restrictions we observe in our results. In Hungary, the health care system is a hybrid of a Semashko-style Soviet system and a Bismarckian-influenced model where (social) health insurance coverage is key to access but the legacy of out-ofpocket payments remains.[30] In fact, respondents from Hungary reported the most restrictions among population groups, especially among undocumented migrants, asylum seekers and people without insurance.

Another surprising finding was the discordance about restrictions within each country, especially for population groups for whom the health care system or policy context defines access to treatment, such as undocumented migrants, asylum seekers and people without health insurance. We suggest that this lack of consensus about restrictions in access to treatment may either be an important explanation of, or in fact caused by, the limited existence of screening programmes that target these higher risk populations. Undocumented migrants and asylum seekers are rarely screened for viral hepatitis and, if found chronically infected, do not actually reach secondary care.[31] Previous studies also found lower preventative health care usage and poorer health outcomes from viral hepatitis among migrant groups.[32,33]

This lack of consensus also suggests that specific guidance about health care entitlement is either not available, unclear or not known to medical professionals most involved in treating viral hepatitis. In the absence of clear guidance about access to specific services/ provision in the health care system, professional discretion when treating patients is likely to be applied.[34] To deal with ambiguous health care entitlement criteria, two professional coping strategies have been suggested: 'functional ignorance' where the legal status of somebody who needs health care is neither asked for nor monitored; and 'partial acceptance', where, e.g. specific sub-groups of migrants without permission to stay may have the right to certain limited hospital and outpatient treatment in the case of sickness or accidents, as

well as to preventive care.[35] The extent to which the adoption of either strategy influences health outcomes, in terms of screening and referral to specialist care for treatment, warrants further investigation.

Discordance of opinion could be explained by other health system factors. For example, within the Dutch health care system, there are only a selected number of hospitals that are able to provide antiviral treatment to patients without health insurance.[36] The regional organisation of municipal and other public services in Germany (Länder) and Spain (Comunidad Autónoma) may also be reflected in differing arrangements of health care including entitlement, especially for marginalised groups like undocumented migrants. In the case of Spain, regional authorities define the benefits package for the local population according to local preferences and needs and are responsible for public health service planning.[37]

For PWID patients and patients who abuse alcohol, restricted treatment is less likely to be explained by the health system or policy context and more likely due to associated clinical implications.[9,10] Most professionals in most study countries, other than in Spain and Hungary, reported no or few restrictions for PWID. Case detection, treatment and clinical management of PWID is an important public health issue given the high risk of HCV transmission associated with injecting drug use as well as the large proportion of current/past injecting drug users among the burden of chronic hepatitis C cases in the European population.[4,7] However, previous studies suggest that many PWID remain undetected and if screened, do not reach specialist secondary care.[19,32,38] Over half in all study countries (table 4) reported the existence of some restrictions for patients who abuse alcohol. Alcohol use among people infected with chronic viral hepatitis affects disease progression and increases the risk of cirrhosis and HCC. Alcohol intake is, therefore, undoubtedly a key treatment consideration among chronic viral hepatitis patients and although it is not an explicit contraindication for treatment,[9] alcohol and drug use are identified as the reason for ineligibility of treatment by 83% of treating clinicians in the UK.[39]

The current climate of economic austerity has led to restrictions access to both health and social welfare provision among vulnerable populations and to the effective new treatments that can potentially cure chronic hepatitis C infection.[40] It is, therefore, possible that access to treatment among the populations investigated here has become more restricted since the time of this study. The significant health gains possible through our expanded understanding of viral hepatitis and the scope for secondary prevention can only be realised through expanded access to screening and antiviral treatment to urgently find those most affected.[8]

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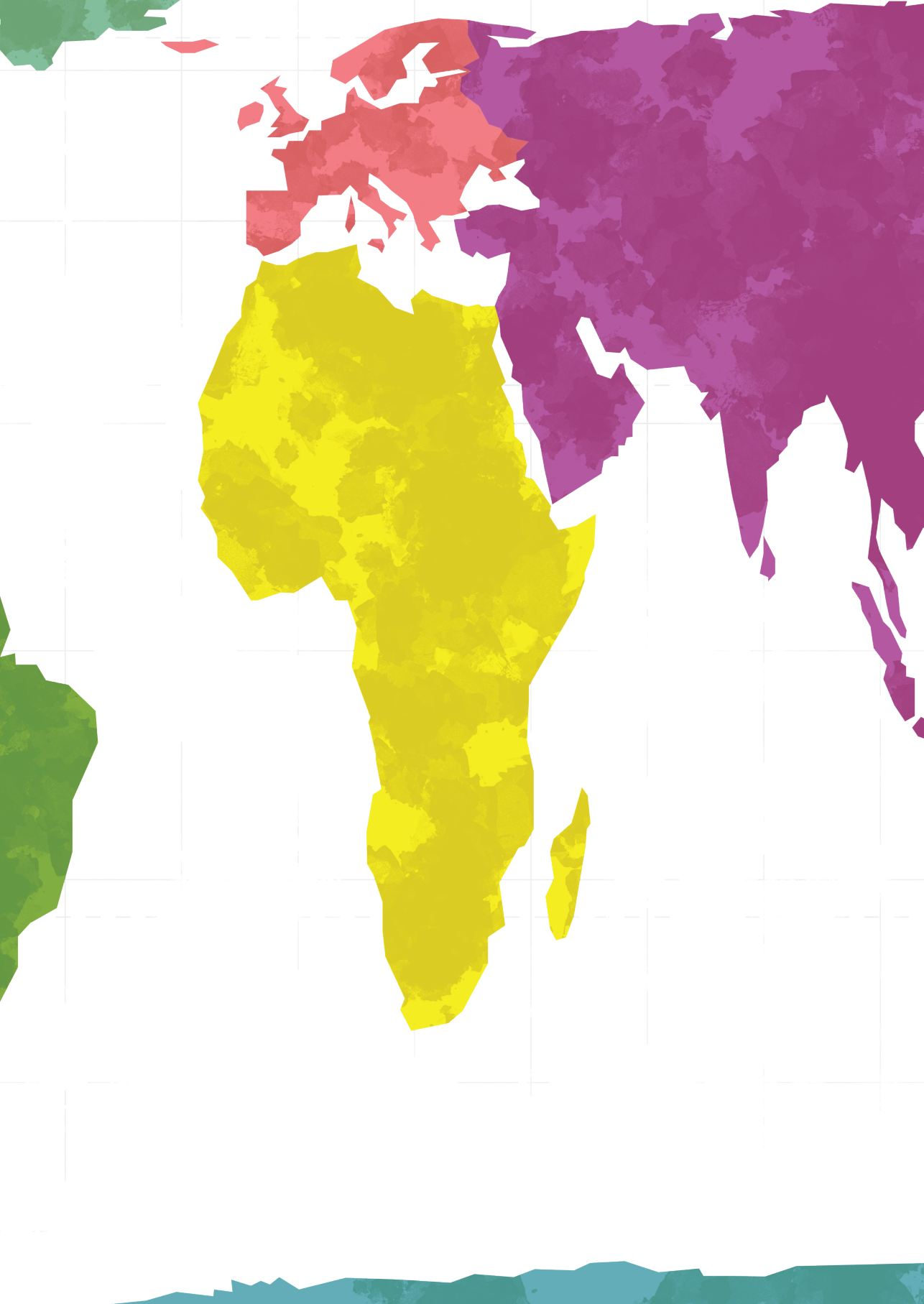

CHAPTER 13

Hepatitis B/C diagnostics and treatment restrictions in Germany, Hungary, Italy, the Netherlands, Spain and the United Kingdom

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ABSTRACT

Background/Aims: Advances in viral hepatitis treatment have increased the scope for secondary prevention although differential availability of antivirals across Europe is suggested. We investigated restrictions in treatment and use of diagnostics in six European countries: Germany, Hungary, Italy, the Netherlands, Spain and the United Kingdom.

Methods: An online survey among experts in gastroenterology, hepatology and infectious diseases in 2012 investigated diagnostics and antivirals approved up to 2012. An updated survey sent to the same sample investigated 2014-approved hepatitis C drugs. Frequency of diagnostic test usage and scale of antiviral restrictions were both measured using three-point ordinal scales.

Results: Of 243 recipients, 61 responses to the 2012 survey and 29 responses to the 2015 survey were received. Few differences across countries were found in diagnostics used in initial patient assessments; blood markers and non-invasive tests are more common than invasive and expensive diagnostics (e.g. biopsy and genotyping). Differences between countries were observed in the use of first- and second-generation protease inhibitors for chronic hepatitis C treatment. Complete restriction of first-generation drugs were reported in Hungary, Italy and Spain. Sofosbuvir, simeprevir, daclatasivr and simeprevir/ledipasvir were restricted to severely fibrotic/cirrhotic (F3/F4) patients in the United Kingdom, the Netherlands and Italy.

Conclusions: This study among practising clinicians directly involved in treating patients provides insight into actual clinical management of chronic viral hepatitis, specifically antiviral treatment availability and diagnostic testing, in six European countries. Widespread availability of antivirals for chronic hepatitis B further strengthens the rationale to expand access to screening. However, despite European approval and guidelines, differential availability of chronic hepatitis C treatment regimens exists across Europe, suggesting that national health care system resourcing, alongside clinical effectiveness, influence treatment availability. Realising the possible health gains from treatment will require expansion both in geographic availability and in the patients considered eligible for treatment.

INTRODUCTION

Chronic hepatitis B and C virus infections are mostly asymptomatic and, if untreated, can progress over 20-30 years towards cirrhosis and hepatocellular carcinoma (HCC) (1). Between 480 and 520 million people, mostly in Asia and Africa, are estimated to be chronically infected, although there are regional differences in burden of disease (2, 3). Antiviral treatment for hepatitis B/C has the potential to prevent associated morbidity and mortality (4, 5). As early identification, before progression to liver decompensation and/or development of HCC, is associated with improved treatment outcome, screening for chronic infection is recommended among risk groups as a cost-effective form of secondary prevention (6-9). Yet, most chronic infections are undiagnosed (10), many patients do not reach secondary care (11, 12) and only a minority of chronically infected individuals are on treatment (13, 14).

The centralised approval system for pharmaceutical innovations for viral diseases in Europe, the European Medicines Agency (EMA), appraises applications for marketing authorisation in all EU countries. Decisions on pricing and reimbursement are generally made at the national level however, and differences between Member States in availability of new medication, especially for chronic hepatitis C, have been suggested (15). Epidemiological, health system, clinical and economic factors offer some explanation of this variation, although limited data hamper a systematic understanding (16, 17).

Highly sensitive and specific diagnostics, for blood markers and the severity of liver disease, are recommended in referral and clinical management (4, 5, 18, 19). Despite the European-like nature of these recommendations, studies into current referral pathway mechanisms across Europe are scarce. Recent international and national strategies highlight the importance of strengthening health systems to respond to the public health challenge of chronic viral hepatitis in an era when eradication is a possibility. The proceedings from the first World Hepatitis Summit, convened in response World Health Assembly resolution 67.6 on viral hepatitis, highlight that many nations have been slow to make new treatments available at the clinical level and that pricing affects expanded access to affected populations

The Summit also sought to strengthen global and national responses to the public health challenge for viral hepatitis, a key component of which is expanded access to diagnostics and antiviral treatment (20). To support knowledge-driven eradication efforts and as of part of the 2011-2014 EU Health Programme-funded HEPscreen project (21), we investigated current practices in chronic viral hepatitis treatment in Germany, Hungary, Italy, the Netherlands, Spain and the United Kingdom (UK). We posed two specific research questions:

how common are eight diagnostic tools used in the initial assessment of patients; are there restrictions in the use of antiviral treatment options for chronic hepatitis B/C approved in Europe and, if so, what are these restrictions.

METHODS

The field of chronic hepatitis C treatment rapidly evolved during our study period (2012-2015), and in response we developed two semi-quantitative online surveys. The first (in 2012) was based on the EASL HBV (4) and HCV (22) guidelines; the second (2015) was based on the 2014 EASL HCV guideline (5). Both surveys were sent to experts in viral hepatitis treatment identified via boards of clinical/professional associations, leadership of hepatology treatment/research centres and scientific literature. Our objective was to reach 5-10 experts in each study country deemed able to report on practices in their country, among their peers, rather than just at their individual practice level. In recognition of the historically low response to surveys among practising clinicians, we identified a large sample of 243. The same sample was then used for the second survey about 2014-approved antivirals. Both surveys collected other data including organisation type and whether respondents are involved in the care of patients/have a clinical role. Among those with a clinical role, we collected data on their medical specialism and how often they see hepatitis B/C patients (weekly, monthly, annually). According to the CCMO (the Central Committee on Research Involving Human Subjects) guidelines to which the coordinating institute adheres, research which requires filling in a questionnaire just once generally does not fall under the scope of the Medical Research Involving Human Subjects Act (WMO)(23) and specific ethical approval from a medical ethical committee was therefore not required.

Diagnostics

For the first survey, a list was prepared of all diagnostics recommended in the EASL guidelines to confirm chronic infection and assess liver disease severity, including: HBeAg, ALT, other biochemical markers (such as AST, GGT, serum albumin etc), viral load, genotype, ultrasound, liver biopsy, and elastography. Respondents were asked to indicate how commonly each diagnostic was used in the initial evaluation of patients using a three-point ordinal scale: 'very common', 'variable/not routinely', and 'rarely/never' ('unsure' was also available).

Treatment options

For the first survey, we included conventional or pegylated interferon α and five nucleoside/nucleotide analogues (NAs) (entecavir, tenofovir, lamivudine, telbivudine and adefovir), as treatment options for chronic hepatitis B (4). The 2011 HCV guideline recommends the use of pegylated interferon α with oral ribavirin as first-line treatment for chronic hepatitis C.

Other treatment options at this time point were limited to telaprevir and boceprevir, in combination with pegylated interferon α and ribavirin. EMA approval was granted relatively recently (boceprevir in August 2011; telaprevir in October 2011). The second survey included the four 2014-approved options (sofosbuvir, simeprevir, daclatasivr and a combination drug simeprevir/ledipasvir) (5).

Treatment restrictions

Respondents were asked to indicate if each treatment option was restricted using a three-point ordinal scale: 'no limitations', 'some limitations' and 'complete limitation/cannot be prescribed' ('unsure' was also available). If 'some limitations' was selected, five specific restrictions were then available to select all those that apply, 'can only be prescribed…': 'if resistance to another drug has developed'; 'for a limited duration'; 'by selected hospitals (e.g. tertiary centres)'; and 'in selected geographic areas'. The fifth was 'other restrictions', with a request to give details in a text field.

Data collection

The first survey was pilot tested, revised, translated into the national languages of the study countries and uploaded into the online survey software Lime Survey™. Recipients were contacted via email in July 2012 and further reminded twice during data collection. The survey closed in September 2012. The second survey was also translated into the national languages and uploaded into Lime Survey™. Recipients were contacted via email in March 2015 and further reminded twice during data collection. The survey closed in May 2015. Data from both surveys were exported from Lime Survey to SPSS 19.0.2 for analysis.

RESULTS

Respondents

We received 64 responses to the first survey, achieving the respondent target of between 5-10 experts in all countries but Spain. Although five respondents did not complete the questions related to restrictions in antiviral therapy, there was information about diagnostic markers. All but three of 64 are currently involved in the care of patients and 95% of these see chronic hepatitis patients on a weekly basis. Due to the clinical nature of the topics, analysis was restricted to those with a clinical role (n=61). The majority of clinicians (77%) are specialists in gastroenterology/hepatology, a fifth are infectious disease specialists and three are community/practice nurses. Mostly the pattern in countries was similar to this except in Italy and the Netherlands; in Italy, nearly half (44%) are infectious disease specialists whereas in the Netherlands, 81% are gastroenterology/hepatology specialists. Most are

based in academic teaching hospitals (61%) or general hospitals (28%). A similar profile was seen among the 30 respondents (overall response rate of 13%) to the 2015 survey, although only in Hungary and the Netherlands was the target of 5-10 respondents achieved. All 30 have a clinical role, 90% are gastroenterologists/hepatologists, 93% see chronic hepatitis B/C patients on a weekly basis, and most are based in academic (63%) or general hospitals (27%). Interestingly, the one respondent from Spain is a prison health specialist.

Diagnostic testing in initial patient evaluations (Table 1)

HBeAg, ALT, viral load and other diagnostic markers (such as AST, GGT or serum albumin) are generally very commonly measured in initial patient evaluations in all countries; most, if not all, respondents selected 'very common' for each diagnostic and no-one indicated 'rarely/never'. Opinion about genotyping is divided in all countries, except Spain and Germany where it is very commonly tested. Although three quarters in the UK and around two thirds in the Netherlands and Italy also indicated genotype testing was 'very common', some indicated 'variable' (22% in the UK and Italy, 14% in the Netherlands) or that it is 'rarely/never' tested (18% in the Netherlands, 11% in Italy). There was no clear majority about genotyping in Hungary. Of the three recommended diagnostics for cirrhosis, ultrasound is most common and liver biopsy is least common in initial patient evaluations. For ultrasound, most in all countries indicated 'very common' and no-one selected 'rarely/never'. Opinion within countries, especially Germany and Hungary, varied about liver biopsy. Most indicated it is not routinely used and a notable proportion in the Netherlands (23%), along with two in Hungary and one in Germany indicated liver biopsy was 'rarely/never' used in initial patient evaluations. For elastography, opinion is divided between very common and variable except in the Netherlands, where a third indicated elastography was 'rarely/never' used. Comparable results emerge from Germany and Hungary; around half indicated 'variable' use of elastography but around a third selected 'very common'.

Hepatitis B treatment

The results for entecavir and tenofovir are presented together as both are potent HBV inhibitors with a high barrier to resistance and recommended as first line mono-therapies. Lamivudine, telbivudine and adefovir are recommended where more potent drugs with a higher barrier to resistance are unavailable or inappropriate. Three of the 61 respondents that did not answer these questions were excluded (thus, n=58).

Table 1. Reported use of diagnostics in initial patient evaluations

HBeAg	**UK (n=9)**	**DE (n=7)**	**NL (n=22)**	**HU (n=10)**	**IT (n=9)**	**ES (n=4)**
Very common	100%	57%	95%	80%	89%	100%
Variable/not routinely	0%	29%	5%	0%	11%	0%
Rarely/never	0%	0%	0%	0%	0%	0%
Unsure	0%	14%	0%	20%	0%	0%
ALT	**UK (n=9)**	**DE (n=7)**	**NL (n=22)**	**HU (n=10)**	**IT (n=9)**	**ES (n=4)**
Very common	100%	86%	95%	70%	100%	100%
Variable/not routinely	0%	0%	0%	0%	0%	0%
Rarely/never	0%	0%	0%	0%	0%	0%
Unsure	0%	14%	5%	30%	0%	0%
Other biochemical markers	**UK (n=9)**	**DE (n=7)**	**NL (n=22)**	**HU (n=10)**	**IT (n=9)**	**ES (n=4)**
Very common	100%	86%	95%	80%	78%	100%
Variable/not routinely	0%	0%	0%	0%	22%	0%
Rarely/never	0%	0%	0%	0%	0%	0%
Unsure	0%	14%	5%	20%	0%	0%
Viral load	**UK (n=9)**	**DE (n=7)**	**NL (n=22)**	**HU (n=10)**	**IT (n=9)**	**ES (n=4)**
Very common	100%	86%	91%	70%	100%	75%
Variable/not routinely	0%	0%	9%	10%	0%	25%
Rarely/never	0%	0%	0%	0%	0%	0%
Unsure	0%	14%	0%	20%	0%	0%
Genotype	**UK (n=9)**	**DE (n=7)**	**NL (n=22)**	**HU (n=10)**	**IT (n=9)**	**ES (n=4)**
Very common	78%	86%	68%	20%	67%	100%
Variable/not routinely	22%	0%	14%	30%	22%	0%
Rarely/never	0%	0%	18%	30%	11%	0%
Unsure	0%	14%	0%	20%	0%	0%
Ultrasound	**UK (n=9)**	**DE (n=7)**	**NL (n=22)**	**HU (n=10)**	**IT (n=9)**	**ES (n=4)**
Very common	78%	71%	95%	80%	100%	75%
Variable/not routinely	22%	14%	5%	0%	0%	0%
Rarely/never	0%	0%	0%	0%	0%	0%
Unsure	0%	14%	0%	20%	0%	25%
Liver biopsy	**UK (n=9)**	**DE (n=7)**	**NL (n=22)**	**HU (n=10)**	**IT (n=9)**	**ES (n=4)**
Very common	33%	14%	5%	20%	22%	0%
Variable/not routinely	67%	43%	73%	40%	78%	100%
Rarely/never	0%	14%	23%	20%	0%	0%
Unsure	0%	29%	0%	20%	0%	0%
Elastography	**UK (n=9)**	**DE (n=7)**	**NL (n=22)**	**HU (n=10)**	**IT (n=9)**	**ES (n=4)**
Very common	44%	29%	9%	30%	56%	50%
Variable/not routinely	44%	57%	59%	50%	44%	50%
Rarely/never	0%	0%	32%	0%	0%	0%
Unsure	11%	14%	0%	20%	0%	0%

Pegylated interferon α

The majority in all countries but Italy reported no limitations in the use of pegylated interferon α. Two thirds in Italy along with around a quarter in the Netherlands and Hungary, and one respondent in both Germany and the UK indicated 'some restrictions', specifically: 'for a limited duration' in all countries, and 'selected hospitals only' in, Hungary, Italy, the Netherlands and the UK . Other restrictions included clinical indications such as genotype, ALT and the non-suitability for patients with cirrhosis.

Entecavir and tenofovir

The results for entecavir and tenofovir are the same in Germany, Italy, the Netherlands and the UK: most indicated no restrictions and no-one indicated that either cannot be prescribed. In Hungary, whilst entecavir can generally be used without restriction, over a third indicated that tenofovir is completely restricted. In Spain, tenofovir is available without restriction. In Spain and Italy, 'resistance to other drugs' was a restriction for entecavir. One respondent in the Netherlands, two in Hungary and three in Italy reported 'some restrictions' for both options, specifically 'selected hospitals'. Restrictions for tenofovir included 'resistance to other drugs' (Hungary) and the contra-indications/side effects of kidney disease or renal failure (the Netherlands and Italy) (Table 2).

Table 2. Reported restrictions in the use of entecavir (E*) or tenofovir (T**)

Level of restriction	UK (n=9)		DE (n=6		NL (n=22)		HU (n=8)		IT (n=9)		ES (n=4)	
	E*	T**	E*	T**	E*	T**	E*	T**	E*	T**	E*	T**
None	89%	89%	83%	83%	96%	96%	75%	25%	67%	67%	75%	100%
Some	0%	0%	17%	17%	5%	5%	25%	25%	33%	33%	25%	0%
Complete	0%	0%	0%	0%	0%	0%	0%	38%	0%	0%	0%	0%
Unsure	11%	11%	0%	0%	0%	0%	0%	13%	0%	0%	0%	0%

Lamivudine

In Spain, all respondents indicated there are no restrictions in the use of lamivudine. Although most in the UK (50%), Germany (60%) and the Netherlands (82%) also reported no restrictions, a minority reported some or complete restriction. Results in Italy are divided between 'no' and 'some restrictions'. Among those selecting 'some restrictions', these include 'for a limited duration only' in Germany and Italy, and 'selected hospitals only' in Hungary, Italy and the Netherlands. Lamivudine was also described as rarely used (the UK), non-first

line drug choice (Hungary) associated with a high risk of resistance (the Netherlands) and use only as a pre-emptive prophylaxis in selected immuno-compromised patients (Italy) or for those with cirrhosis and a low viral load (UK).

Telbivudine

Of all the CHB antivirals, complete restriction was reported most often for telbivudine, except in Spain where all indicated no restrictions. Although the majority in Germany and the Netherlands selected no restrictions, a third in Germany and 14% in the Netherlands, along with half in Hungary and over a third in the UK, reported that telbivudine is completely restricted. Among those selecting 'some restrictions' (Italy, the Netherlands, Spain and the UK), these include: 'limited duration' (Italy); 'selected hospitals only' (the Netherlands and Italy); formulary/drug agency limitations (the UK); and use only in patients with a low viral load (Italy and the Netherlands).

Adefovir

Most respondents in all countries indicated there are no restrictions for adefovir. However, one respondent in the UK, Germany and Italy, and three in the Netherlands, indicated complete restriction. Among those that reported 'some restrictions' (Germany, Hungary, Italy and the Netherlands), 'selected hospitals only' was reported in all but Germany. Other restrictions included it not being a first line option (Germany and Hungary) and having limited efficacy compared to other antivirals (Italy and the Netherlands).

Hepatitis C treatment

As for CHB treatment, analysis of hepatitis C treatment options was restricted to those who have clinical responsibilities and completed the relevant section (n=58).

Pegylated interferon α

All respondents in Spain and the UK, and most in all but Italy reported no restrictions in the use of pegylated interferon α. Over half in Italy, around a quarter in the Netherlands, two respondents in Hungary and one in Germany indicated that 'some restrictions' exist including 'selected hospitals' (Germany, Hungary, Italy and the Netherlands) and 'for a limited duration' (all but Germany). In Italy and the Netherlands restrictions were reported for patients with co-morbidities, especially psychiatric disorders. No-one selected complete limitation or unsure.

Ribavirin

The same results as interferon α were observed for ribavirin in Germany, Hungary, Spain and the UK. Results are also comparable in Italy; although over half reported no restrictions, the remainder indicated 'some limitations', along with nearly a fifth in the Netherlands, two in Hungary and one in Germany. Specific restrictions included 'selected hospitals' (all four countries) and 'for a limited duration' (Hungary, Italy and the Netherlands). Cardiac disease, anaemia and renal impairment were mentioned indications for stoppage in Italy and the Netherlands.

Boceprevir and telaprevir

Results are the same for both options in Hungary, Italy, Spain and the Netherlands whereas results in Germany and the UK suggest that telaprevir is less restricted (Table 3). All but one respondent in Hungary indicated that both cannot be prescribed at all. In the Netherlands, 73% reported no limitations and no-one indicated complete restriction. In Italy, although two thirds selected 'some restrictions', the remainder indicated telaprevir was completely restricted. Although half in the UK selected some restrictions, a third indicated no restrictions are in place for boceprevir; for telaprevir, more respondents (50%) indicated that there are no restrictions. Two thirds in Germany reported no restrictions in the use of boceprevir, rising to 83% for telaprevir; one respondent selected 'some restrictions' for both options. All in Spain selected 'some restrictions'. Specific restrictions are almost identical in all countries and are reported together below.

Table 3. Reported restrictions in the use of boceprevir (B*) and telaprevir (T**)

Level of restriction	UK (n=9)		DE (n=6		NL (n=22)		HU (n=8)		IT (n=9)		ES (n=4)	
	B*	T**	B*	T**	B*	T**	B*	T**	B*	T**	B*	T**
None	33%	44%	67%	83%	73%	73%	0%	0%	0%	0%	0%	0%
Some	56%	44%	17%	17%	27%	27%	0%	0%	67%	67%	100%	100%
Complete	0%	0%	0%	0%	0%	0%	88%	88%	33%	33%	0%	0%
Unsure	11%	11%	17%	0%	0%	0%	13%	13%	0%	0%	0%	0%

Specific restrictions for boceprevir and telaprevir

'Restriction to selected hospitals' was selected in all countries and 'for a limited duration' was reported in the Netherlands (though only for telaprevir), Italy and Spain. 'Resistance to other drugs' was selected in Spain. A diverse mix of other restrictions were also reported including variable approval rates (UK), clinical indications such as genotype (the Netherlands) and the

degree of liver disease/damage (Spain), side effects such as anaemia and allergic reactions (Italy and the Netherlands), drug interactions (the Netherlands), patient response to past treatment (Spain), the need for considerable professional knowledge (the Netherlands) and, interestingly, the prohibited use in prisoners (Spain). In the UK, one respondent described boceprevir as more expensive than telaprevir and that it should only be used if telaprevir is contra-indicated.

Sofosbuvir, simeprevir, daclatasvir and simeprevir/ledipasvir (Table 4)

In Spain, all four options are reported to be completely limited. All in Germany report that there are no restrictions in the use of sofosbuvir or simeprevir/ledipasvir. All in Italy and the UK and the majority in Hungary and the Netherlands report that there are some restrictions in sofosbuvir, notably restriction to certain hospitals (all four countries), limited duration (Italy and Hungary) and only if resistance to another drug has developed (Hungary). One in Hungary reported that sofosbuvir cannot be prescribed. There was at least one in each country who indicted simeprevir cannot be prescribed. There was diversity of opinion in all countries but Spain, with respondents in each response category in the Netherlands and the UK, a split between 'none' and 'complete' in Germany and a split between 'some' and 'complete' in Hungary and Italy. In Hungary, all four who indicated 'some' restrictions exist specified that simeprevir is restricted for use in certain hospitals. Restriction to patients infected with genotype 1 or 4 was reported in the Netherlands. All in the UK and most in Hungary, Italy and the Netherlands indicated that there are 'some' restrictions in the use of daclatasvir. These were diverse for Hungary and Italy, with drug resistance, time and only certain hospitals selected in both. Restriction to certain hospitals was also mentioned in the UK and Netherlands along with genotype (the Netherlands). All in Italy and most of those in the UK and Hungary indicated 'some' restrictions exist for simeprevir/ledipasvir; specifically, restriction to certain hospitals (Hungary, Italy and the UK), time (Hungary and Italy) and drug resistance (Hungary). In contrast, most of those in the Netherlands (53%) and one in Hungary and the UK indicated that simeprevir/ledipasvir cannot be prescribed. Further restrictions reported included: the need for national guidelines for simeprevir and daclatasvir in the UK; a no reimbursement for all four antivirals as part of national health insurance arrangements in the Netherlands; and most significantly, frequent mention of restriction of use only in patients with advanced disease, specifically F3/4 stage cirrhosis in Italy, the Netherlands and the UK.

DISCUSSION

The first aim of our study was to understand which diagnostics are used when patients reach specialist care and to see if there are differences between study countries. The second aim was to find out whether there are restrictions in the availability of antivirals approved for chronic hepatitis B/C treatment in six EU countries as understood by practising clinical specialists providing treatment. The profile of our respondents indicates this goal was met; nearly all respondents are gastroenterology, hepatology or infectious disease specialists who see chronic hepatitis B/C patients on a weekly basis. These clinicians are likely to know what antiviral options available, under what circumstances and for which patients.

We found there are remarkably few differences between countries in the use of diagnostic tests in initial patient evaluations; blood markers and non-invasive tests for liver disease (ultrasound) are used before more invasive and expensive (biopsy, elastography and genotype) diagnostics. The only discernible differences are in the use of genotyping, which is more common in Spain and Germany than in the other four countries, and in HBeAg testing, which is less common in Germany than in the other countries. Commonality in use of diagnostics suggests fairly consistent implementation of recommendations detailed in clinical guidelines and other studies of specific diagnostics (4, 5, 24). The phrase 'initial patient evaluation' is of course open to interpretation. A stepwise evaluation is the most likely scenario with an initial evaluation of HBeAg (for chronic hepatitis B patients), ALT and viral load, with ultrasound or biopsy done for a subset. Clinical markers including cirrhosis, genotype, contra-indications (mostly psychological and nephrological), co-morbidities and previous treatment response are used to assess eligibility for treatment.

We were also able to compare availability of antiviral drug options in the six countries. In general, CHB treatment is more widely available than treatment for chronic hepatitis C. With the exception of all the newer hepatitis C antivirals, most specialists in most countries can use all treatment options with few serious restrictions. Restriction to use in certain hospitals was commonly identified, especially in Hungary, Italy and the Netherlands which would perhaps explain why within-country differences are observed. However, there is remarkable homogeneity in responses within countries about each option. Homogeneity also suggests success in reaching expert clinicians able to reflect on the circumstances in their profession in their country.

Table 4. Reported restrictions in the use of sofosbuvir (Sof*), simeprevir (Sim*), Daclatasvir (Dec*) and simeprevir/ledipasvir (S/L*)

Level of restriction	UK (n=4)				DE (n=2)				NL (n=15)			
	Sof*	Sim*	Dec*	S/L*	Sof*	Sim*	Dec*	S/L*	Sof*	Sim*	Dec*	S/L*
None	0%	50%	0%	0%	100%	50%	50%	100%	13%	47%	40%	7%
Some	100%	25%	100%	75%	0%	0%	0%	0%	87%	47%	53%	33%
Complete	0%	25%	0%	25%	0%	50%	50%	0%	0%	7%	7%	53%
Unsure	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	7%
Level of restriction	**HU (n=5)**				**IT (n=3)**				**ES (n=1)**			
	Sof*	Sim*	Dec*	S/L*	Sof*	Sim*	Dec*	S/L*	Sof*	Sim*	Dec*	S/L*
None	0%	0%	0%	0%	0%	33%	0%	0%	0%	0%	0%	0%
Some	80%	80%	60%	80%	100%	33%	67%	100%	0%	0%	0%	0%
Complete	20%	20%	40%	20%	0%	33%	33%	0%	100%	100%	100%	100%
Unsure	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%

The differences between countries in the availability of both first-generation protease inhibitors boceprevir/telaprevir and 2014-approved innovations are especially interesting. This finding provides some insight into the differential speed at which pharmacological innovations approved in Europe cascade to the national level and become available to clinicians. In four of the six countries, the latest innovations appear to be limited to certain hospitals but, most significantly, to patients with advanced disease, specifically F3/4 cirrhosis. While these patients are most urgently in need of treatment, to maximise the health gains from secondary prevention, these highly effective options would need to become available for patients without cirrhosis.

Our research provides a snap shot of clinical perspectives at one specific point in time in six EU/EEA countries, and the results are not generalizable outside these six countries. Treatment availability can also be subject to change as new policy directives, funding or guidelines expand access to different patients. As our research was conducted soon after the European-level approval of most HCV medications, the severity of reported restrictions could have reduced over time. Further, the low response rate may undermine wider generalisability within the specific study country and introduce selection bias, specifically that the most motivated and interested clinicians respond. The aim was to reach expert clinicians involved in treating patients chronically infected with viral hepatitis and, whilst the response rate is indeed a weakness, the profile of the respondents indicates that our sample is representative of the clinicians we sought to reach.

There are few studies to compare these results with, especially for the newer therapies. News reports suggest that complete restriction of new hepatitis C antivirals have provoked protest in Spain (25). The innovative 2015-published 'Strategic Plan for Tackling Hepatitis C in the Spanish National Health System' supports the findings in this study that the priority for treatment with the newest DAAs are fibrotic patients, among other severely affected patients with multi-morbidity (Type-2 diabetes, lymphoma etc.), although there is a commitment to review the treatment indications at periodic intervals (26). Some studies suggest that most CHB patients who reach specialist care are treated with first line nucleotides (24, 27, 28). Studies also suggest restrictions related to patient characteristics, including compliance with the treatment regimen (8), age and gender (28), immigration status, and awareness of treatment options (29). Even before the possibility to undergo diagnostic evaluation and treatment, there is evidence that diagnosed patients are not reaching secondary care, not being clinically managed effectively or not on treatment (12, 13, 30, 31). The large burden of disease in populations that may have difficulty accessing health care, such as migrants or people who inject drugs, is also suggested to explain the lack of detection, referral and treatment initiation (32).

Most of the burden of viral hepatitis remains undiagnosed and Europe is still behind the peak in the related mortality curve (10, 14). There is an urgent need to identify people eligible for treatment through screening and referral to specialist care. However, maximising possible health gains from treatment, especially the potential cure of chronic hepatitis C, will require expansion in both geographic availability and the clinical characteristics of patients considered eligible for treatment. The rapid publication and adoption of global and national strategies during and after this study was conducted illustrate how far the field of viral hepatitis research and policy are evolving. Notable within this global governance context are the first World Health Organisation (WHO) strategy on Hepatitis C (33), the WHO Global Strategy on Viral Hepatitis (34), and the first World Hepatitis Summit (20). These set ambitious and far-reaching targets and goals for nations to work towards the eradication of hepatitis B and C, including those related to treatment initiation, access to diagnostic testing and strengthening health systems. Findings in this study can serve as useful baseline measures in these areas to the member states included and assist other member states to understand the clinical realities diagnosing and treating patients infected with chronic hepatitis B and C through similar research.

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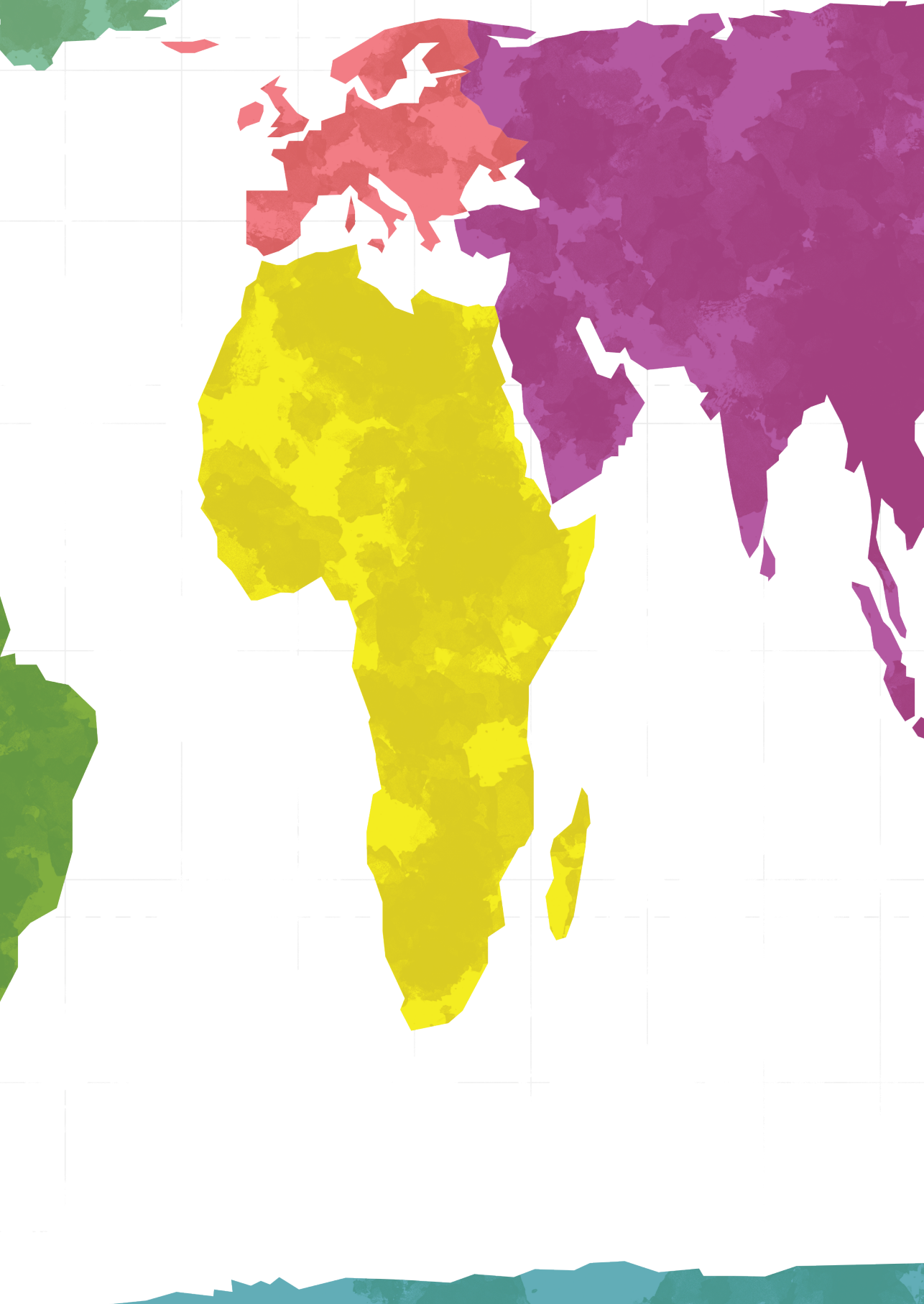

CHAPTER 14

General Discussion

The aims of this thesis were twofold: 1) to understand the epidemiology of CHB/CHC in the EU/EEA; and 2) to understand the conditions at the health system level and the characteristics of screening interventions that effectively diagnose and retain at-risk migrants in a cascade of care. The discussion adopts a public health perspective on the cascade of care to answer the following three research questions.

1) To what extent are migrants from endemic countries a risk group for chronic hepatitis B and C in Europe?
2) What can be learned from different migrant-focused models of HBV/HCV screening?
3) How can the impact of screening among migrants be maximised?

A schematic representation of a cascade of care for viral hepatitis produced by the World Health Organisation for the Global Health Sector Strategy for Viral Hepatitis 2016-2021 is shown in Figure 1.(1)

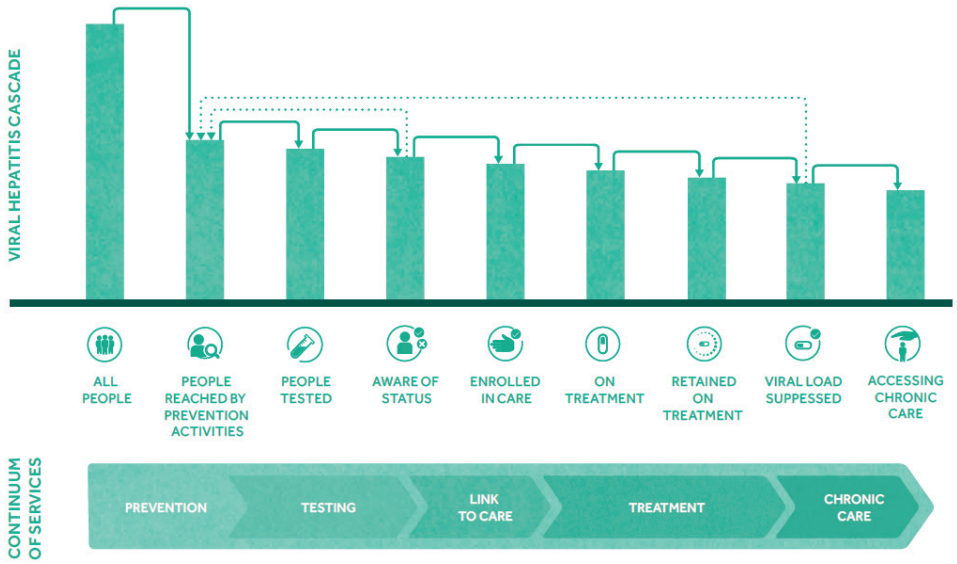

Figure 1. A cascade of care for viral hepatitis (1)

The cascade of care perspective provides a strategic organising framework to conceptualise three things: 1) the need for 'upstream' and 'downstream' interventions to achieve elimination; 2) the movement of people through the cascade; and 3) the more specific interventions

become moving downstream. A public health level cascade perspective also provides a framework for monitoring progress towards elimination.(1) The aim is to populate each stage of the cascade with estimated or modelled data to understand the overall burden of disease at the population level and what proportion of that total (estimated) caseload is diagnosed, in care, on treatment or cured/suppressed.(2)

Figure 2 builds on this strategic perspective and highlights specific interventions that maximise impact at each stage. This schematic representation can also be used by screening and treatment interventions at the planning stage to envisage linkage between different services and what a patient journey might look like. It can also be used to evaluate the efficacy and efficiency of screening and linkage to care programmes by reporting successful referral or attrition through the stages of care, as reported by the HEPscreen pilot studies in Chapter 6.

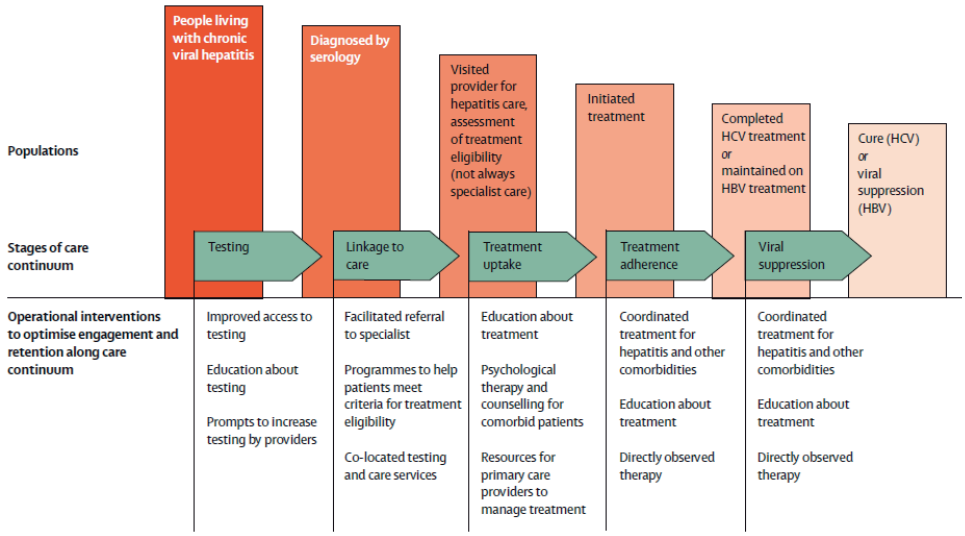

Figure 2. An intervention-based conceptualisation of a continuum of care (3)

RESEARCH QUESTION 1: TO WHAT EXTENT ARE MIGRANTS FROM ENDEMIC COUNTRIES A RISK GROUP FOR CHRONIC HEPATITIS B AND C IN EUROPE?

Migrants from endemic countries account for 10% of the EU/EEA population yet account for an estimated 25% of all CHB and 14% of all CHC infections in the EU/EEA. Thus, from both an epidemiological and public health equity perspective, migrants are a disproportionately affected risk group for chronic viral hepatitis infection.

To expand this discussion, we see three conceptualisations of the notion of 'extent'. Extent can be conceptualised as in the short answer above in terms of relative magnitude i.e. the relative contribution of migrants to the overall number of cases in each EU/EEA Member State and in the EU/EEA as whole. The second conceptualisation is related to this notion of relative magnitude but involves a comparison of migrants in relation to other risk groups for CHB/CHC – so, how does the expected prevalence among migrants compare to that in other key risk groups? We can also conceptualise extent based on how far migrants are the focus of existing secondary prevention interventions, encasing the notion of 'extent' in issues of distributive justice, fairness and equality.

Expanding the short answer of 'extent' in terms of relative contribution, we show in Chapters 4 and 5 that migrants comprise a minority of the population but contribute significantly to the estimated caseload of chronic viral hepatitis in most EU/EEA countries, although more so for CHB than for CHC. We also find there are clear differences in the relative contribution across the 31 EU/EEA Member States (Figure 3 in both Chapter 4 (for CHB) and Chapter 5 (CHC)). These differences at Member State-level depend on four key parameters: the prevalence in the host EU/EEA country; the size of the total population of the host country; the number of migrants from endemic countries; and the prevalence in countries of birth of migrants. In general, migrants from endemic countries account for more of the burden of CHB/CHC in the low prevalence countries in the Northern and Western EU/EEA Member States than in the higher prevalence Member States in Central, Eastern and Southern Europe.

The second conceptualisation of 'extent' – how does the expected prevalence among migrants compare to other risk groups – is addressed throughout Part I of this thesis. There are two components to this: how reliable is country of birth-derived prevalence as a proxy for the prevalence in migrants and secondly, what is the prevalence among other at-risk groups. In Chapters 4 and 5, we conclude via a systematic review and epidemiological analysis that the prevalence in country of birth is a reliable proxy for the prevalence among migrants for both CHB and CHC. However, we found there to be very few studies that report on the prevalence among migrants representative of the general population and even

fewer specifically designed as sero-prevalence studies. Prevalence can be understood as a measure of exposure risk – the higher the prevalence, the higher the exposure risk. Equally, the greater the risk of exposure in the general population, the higher the prevalence. The distribution and frequency of transmission risks in the general population in different countries differ for the two viruses. These differences influence the extent to which migrants are a risk group, as we now explain.

Perinatal and childhood exposure to HBV are the key drivers of transmission in hepatitis B endemic countries and these risk factors broadly affect the general population.(4-6) It is to be expected therefore that migrants born in HBV endemic countries are at higher risk of CHB infection due to the high(er) risk of perinatal HBV exposure.

It is less clear to what extent birth in a high HCV prevalence country is a risk factor for exposure given the drivers and dynamics of HCV over time. Specifically, there has been a significant decline in prevalence over time in most middle and high income countries that has led to a strong birth cohort effect worldwide with the baby boomer generation (born between 1945 - 1965) the most affected cohort in North America and Europe.(2, 7-9) Furthermore, HCV exposure risk factors differ from country to country, especially the contribution of health-care acquired HCV infection compared to behaviourally-acquired HCV, specifically unsafe/unsterile drug injecting practices. In higher prevalence low and middle income countries (LMIC), HCV is largely acquired via parenteral procedures in health-care services with inadequate infection control practices. This is described by the WHO as a generalised pattern of infection and the act of migrating to a low prevalence country largely removes the risk of health-care acquired (generalised) HCV infection.(10) The primary difference between a "birth cohort" pattern and a generalised pattern of infection is the duration of time that the generalised exposure has existed and whether it has been removed or mitigated. In (lower prevalence) middle and higher income countries, infection control practices introduced over the last ~20 years have largely controlled health-care acquired HCV infection (11) and injecting drugs using unsterile equipment is the key driver of HCV transmission. In most middle and high income countries therefore, the risk of exposure to HCV is low in the general population and mostly related to participation in high risk behavioural practices. Recent studies, especially from the US, highlight that people are still acquiring blood-borne viruses (BBVs) via unsafe drug injecting, and that the incidence of new HCV infections is increasing as a result especially in sub-populations of the general population such as rural women of reproductive age.(12) There is similar evidence from the EU/EEA that injecting drug use (IDU)-acquired HCV continues, that harm reduction services are sub-optimal and that limited data on people who inject drugs (PWID) across the cascade of care may hamper elimination efforts.(13, 14) Given the decades of knowledge and experience we have in public health about the harms associated with unsafe IDU practises

and how to prevent IDU-acquired BBVs, ongoing BBV transmission especially among young adults should be an urgent matter of concern and a call to action for countries to invest in effective harm reduction services.

We can compare country of birth-derived estimates (the proxy for the prevalence among migrants used in Chapter 4 and 5) to that derived from other risk groups described in Chapter 3. We would argue that from this perspective of 'extent' as a function of comparative prevalence across risk groups, PWID and people incarcerated in prison are the key risk population for CHC infection given the high prevalence, the dynamic interaction/overlap between the two populations (due to criminalisation of high transmission risk behaviours specifically IDU and sex work) and the efficacy of IDU in transmitting HCV.(15, 16) We conclude, based on the evidence in Chapters 3, 4 and 5, that migrants born in HBV endemic countries are the key population for CHB infection in most EU/EEA countries, but especially in the lower prevalence Northern and Western countries. We would also argue that the overrepresentation of migrants among the incarcerated population in some countries is a driver of the high prevalence of HBsAg in the prison population.(17, 18)

The final conceptualisation draws on theories of distributional justice, specifically equity and prioritisation (19), to discuss to what 'extent' migrants are a risk group. From this philosophical perspective, we can define a risk group based on how likely they are to experience final (poor) health outcomes as a consequence of CHB/CHC infection through being unable to access or being underserved by secondary prevention interventions to avoid these final consequences of morbidity and mortality. We argue that based on the findings in this thesis and in wider literature, migrants are currently underserved by existing screening and treatment programmes in the EU/EEA and as such, we argue for further investment in, and scaling up of, interventions that specifically reach, diagnose and retain migrants from endemic countries in a care pathway for chronic viral hepatitis. Evidence for this position comes firstly from the results from the systematic search for migrant-derived prevalence estimates in Chapters 4 and 5. Here, our findings suggest that screening among at risk migrant populations is limited in time, scope and geographical coverage. These findings chime with those found by another systematic review which found very few published screening studies among at-risk migrants in Europe.(20) Immigration status is also independently associated with not reaching specialist care and not receiving treatment for chronic viral hepatitis.(21) Previous studies also found lower usage of preventative health care services among migrants and poorer health outcomes in general for chronically infected migrants compared to non-migrants.(22, 23)

Turning back to the cascade of care perspective, the evidence highlighted in this thesis and in the discussion of this specific research question can help to define at a strategic level the population(s) for targeted action. More specifically, it can help to understand the extent to which migrants born in endemic countries should be a focus of prevention activities (steps one/two in the cascade) in a specific EU/EEA Member State. It can also help to understand (existing/potential) barriers affecting the smooth transition of chronic cases through the cascade. This latter point is now expanded on in research questions two and three.

RESEARCH QUESTION 2: WHAT CAN BE LEARNED FROM DIFFERENT MIGRANT-FOCUSED MODELS OF HBV/HCV SCREENING?

We identified five key learning points for effective HBV/HCV screening: 1) a simple care pathway; 2) the involvement/partnership with secondary care to facilitate referral; 3) offering on site screening together with awareness-raising/pre-test information; 4) the availability of interpreters/translated materials to reduce language barriers; and 5) the use at the planning stage of country of birth prevalence to define the migrant communities at highest risk of chronic viral hepatitis infection.

The first two learning points (a simple care pathway and a partnership between primary and secondary care services) are related to each other and aim specifically to minimise participant attrition across the cascade of care. Findings described in Chapter 6 show how more complex care pathways lead to higher participant drop out. We also found (in Chapter 10) via a survey among practising clinicians that standard referral practices in the six EU countries included in this study are complex involving multiple stages and multiple services. These characteristics are likely to exacerbate the findings in wider literature that many patients do not receive their diagnosis, do not reach secondary care and are not on treatment for their CHB/CHC infection.(23-27) We found in Chapter 6 and in other literature (28-30) that a partnership between primary care/public health services and secondary care can facilitate smooth referral and to ensure that diagnosed cases reach specialist care for further investigation and treatment. Further, a centralised coordinated referral system that can ensure individual patients are followed up seemed more conducive to successful retention in the cascade of care compared to larger, more dispersed referral mechanisms involving multiple hospitals and multiple referral pathways.

The third leaning point relates to screening uptake. Uptake is also sensitive to the number of steps an individual is required to take in order to actually take up the offer of HBV/HCV screening. It is clear from the experience in Chapter 6 that more complex pathways

involving a number of steps leading to screening is likely to increase the attrition of migrant participants who may also drop out due to language and other barriers (such as insecure employment and other socio-economic disadvantages). Uptake seems highest in individual-focused models offering screening in one-to-one confidential health care encounters.(31) This is partly because uptake is easier to measure in models offering one-on-one screening than in outreach models where, for instance, an entire workforce (as in the Grampian pilot described in Chapter 6), anyone attending a civic or social centre (in the Barcelona outreach pilot described in Chapter 6) or an entire local population (28, 30) could be considered to be part of the target population. Indeed, none of the studies of outreach screening among migrants we know of measure or report screening uptake (28, 30, 32-35) the manner in which we attempt to in Chapter 6.

With regard to learning point 4, we investigated the availability of language support services in six EU countries in Chapter 8. Findings from the pilot studies described in Chapter 6 also highlight the importance of providing translated materials/interpreters to overcome language barriers experienced by linguistically diverse migrants. Findings across these chapters and in wider literature suggest that language support services can improve the quality of clinical care provided to linguistically diverse migrants, improve retention in the cascade of care and reduce inequalities in health outcomes.(26, 36, 37)

The final learning point is related to the potential for the screening model to successfully detect cases of chronic HBV/HCV infection. Expected prevalence of the target population is an important characteristic in weighing the ethical considerations (harms vs. benefits at the population level) of offering screening.(38-40) Prevalence is also a key input in cost-effectiveness models.(41-45) We demonstrate via a systematic review in Chapters 4 and 5 in Part I that the prevalence of HBsAg and anti-HCV in a country of birth are both a reliable proxy for the prevalence of these virological markers in migrants born in these countries. We also see from experience in Chapter 6 that offering screening among migrants born in low prevalence countries (such as those in Latin America) does not successfully diagnose cases of chronic viral hepatitis. Therefore, we suggest the greatest utility is to offer screening to migrants born in high(er) prevalence countries; and to use demographic and epidemiological information at the national/local (most appropriate) level to determine which communities these are at the planning stage. Furthermore, defining the migrant communities of interest can then allow for further specific tailoring of screening interventions according to the linguistic and other socio-cultural characteristics of the target population(s).

Our experience gained throughout the HEPscreen project highlights the fragmented nature of knowledge about offering HBV/HCV screening among migrants born in endemic countries. The models described in Chapter 6 and in other studies (28, 32, 34, 35, 46-57) can

be broadly grouped into four types: 1) *outreach-based* offering awareness-raising and/or screening in community, social or civic locations or in workplaces (such as the innovative pilot in Grampian, Scotland described in Chapter 6); 2) *invitation-based* using municipal or patient registry data to select and invite at-risk migrants for HBV/HCV screening in health care services; 3) *opportunistically* offering screening to at-risk migrants attending health care services for other issues; and 4) *extending an existing migrant-focused screening programme* to include viral hepatitis. Our experience underlines the need for more implementation studies of screening among migrants, especially studies that compare different models of screening, report results across the cascade of care and report costs across the cascade of care (such as cost per person screened, diagnosed and started on treatment). It is to these key measures of impact that this discussion now turns.

RESEARCH QUESTION 3: HOW CAN THE IMPACT OF SCREENING AMONG MIGRANTS BE MAXIMISED?

There are two key conditions needed to maximise the impact of screening among migrants: 1) good data across the cascade of care; and 2) scaling up key interventions and good practices as part of a strategic approach. Good data across the cascade of care is necessary to understand (national) progress towards elimination. Scaling up good practices in designing and delivering screening to at-risk migrants as part of a strategic plan improves population health and makes effective use of scarce health care resources.

Data at the first stage of the cascade of care, specifically good epidemiological data about the distribution and scale of CHB/CHC across the population, is necessary to determine in the first instance to what extent migrants from endemic countries are a key risk group for chronic viral hepatitis in a specific country (or area). National/local (public) health planners can draw on demographic and epidemiological data (country of birth prevalence and population size) to identify which migrant communities are most at risk of being chronically infected with HBV/HCV, and to target interventions for these communities. We show in Chapters 4 and 5 that the contribution of migrants to the overall burden of chronic viral hepatitis differs greatly across EU/EEA Member States. The data from these chapters can assist public health decision makers to prioritise health conditions, populations and interventions given that (public) health care resources are finite. In most Northern and Western EU/EEA Member States, migrants from endemic countries account for at least a quarter of CHC infections and are the priority population for CHB infection. However, in countries where migrants account for a minimal number of infections and the prevalence of HBV/HCV in the general population is intermediate or high (≥2%), there may be more utility in prioritising national birth cohort screening (especially for HCV) or offering screening to

behavioural high (transmission) risk groups such as PWID. Results from such programmes, especially results related to prevalence, can then be used to further update and refine our epidemiological understanding of chronic viral hepatitis.

Other key data for elimination planning include the number (and proportion) diagnosed, the number (and proportion) of people on treatment and the number (and proportion) of people reporting viral suppression/SVR/cure. To support collection of data across the cascade of care, the WHO have defined 10 key indicators in the Monitoring and Evaluation Framework for Viral Hepatitis B and C (shown in Figure 3 below).(58) Along with monitoring progress towards elimination, reliable estimates for each of these indicators can also be politically motivating and should be used to inform (public) health care planning and investment. A national viral hepatitis registry is suggested in the World Health Organisation Global Elimination Strategy as the most effective method in which to capture this data. (1) Some European countries are making progress towards establishing a national registry, most notably in literature is Denmark.(53) This data can also be used to further calibrate and refine elimination forecast modelling.(2) Data can also allude to breaks in the cascade of care to stimulate investment and improvement in reducing barriers to referral and retention in treatment.

Secondly, good practice screening and treatment interventions must be scaled up to have a significant impact public health.(59) Scaling up screening and treatment is also highly time sensitive and urgent due to the global concentration of chronic viral hepatitis infection in working age adult populations born (1945-1965) prior to the introduction of key primary prevention interventions.(2, 60) Models predict that the crucial time period for action to prevent mortality due to CHB/CHC-related causes is between now and 2030.(59) There is much to be done in this 15 year window.(14)

Scaling up requires a strategic approach. Establishing a national/local viral hepatitis strategy, investment plan and partnership that brings together key stakeholders can help to ensure that resources are effectively distributed and that interventions are coherently scaled up, accurately targeted, based on good practices and properly evaluated.(14) A strategic partnership can be an effective mechanism to plan and monitor action, to identify gaps in provision, aggregate and analyse data and to evaluate progress towards elimination.

National/local strategies and partnerships should also set out specific strategic actions focused on migrants from endemic countries. These strategic actions should follow the cascade of care approach to determine how and where people (migrants) born in endemic countries can access/be reached by screening interventions, how a diagnosis will be communicated, and, crucially, what efforts will be made to ensure people with evidence of

CHB/CHC infection reach specialist care for clinical monitoring, treatment (if indicated) and contact tracing. To maximise the proportion diagnosed, it is important to provide numerous conduits into the cascade of care by offering screening via a combination of the four models (set out in research question 2) in a range of health services. A suite of interventions can provide comprehensive and diverse screening coverage to reach heterogeneous groups of migrants in community locations, primary health care services and workplaces, and via existing screening programmes.

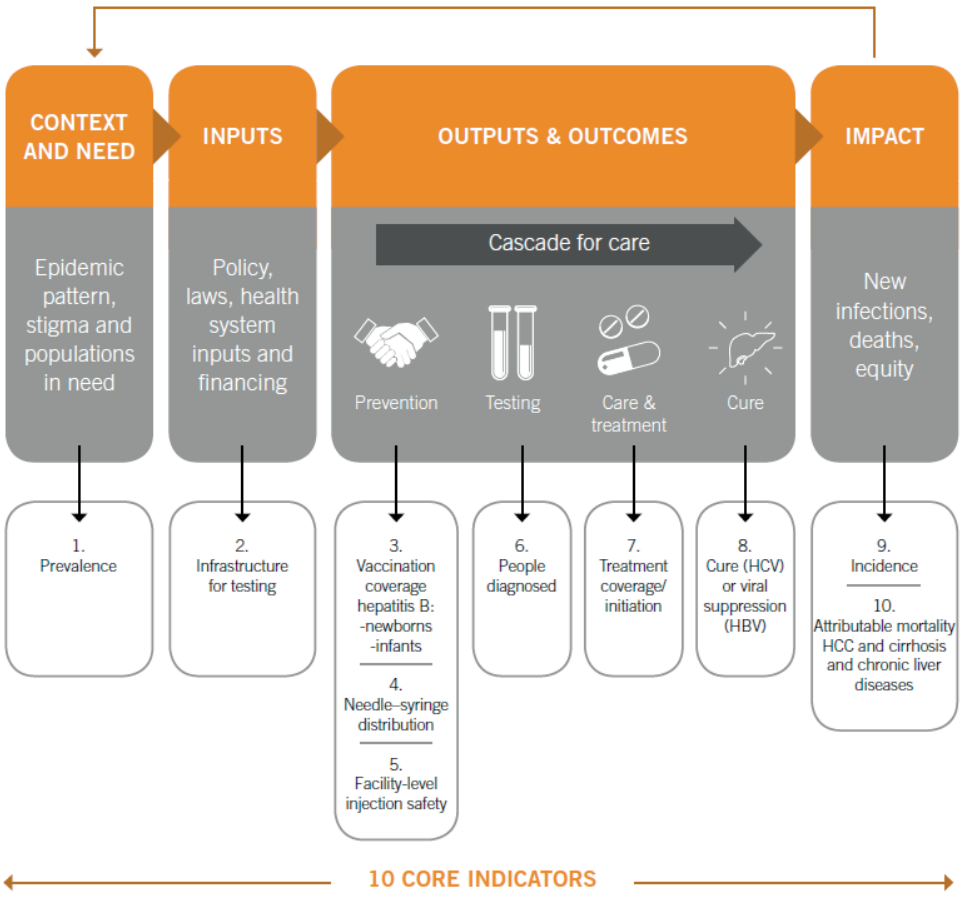

Figure 3. The ten key indicators across the cascade of care: the World Health Organisation's monitoring and evaluation framework for hepatitis B and hepatitis C virus elimination 2016–2021

Specific screening interventions should also draw on the good practice resources in pre- and post-test counselling, in contact tracing and vaccination, and referral and retention alluded to throughout this thesis, contained within the HEPscreen Toolkit (61) and reported as part of the HEPscreen scientific output, (37, 62-64) or elsewhere.(3)

Alongside these two key conditions, the impact of screening on resources both from the health system perspective and the individual/patient level should be considered. Health planners need evidence on how the cost-effectiveness of HBV/HCV screening among migrants can be maximised and on how to offer screening if human and financial health care resources are limited. To maximise the cost-effectiveness of screening, interventions should seek to:

a. Maximise the case yield (number of chronic cases) by focusing on intermediate/high prevalence migrant communities, especially for HBV screening (42);
b. Minimise the resources required to deliver a good practice intervention through prudent (financial) planning, strong project management and a partnership approach drawing on existing resources (related to infrastructure and human capital).

Interventions should therefore consider two key questions in advance. First, what is the expected case yield in the target population using country of birth prevalence as a proxy (Chapters 4 and 5), or how likely is it that chronic HBV/HCV infections will be detected by screening in this specific migrant community? And secondly, where are and what are the opportunities for attrition in the cascade of care, and how can these be avoided or minimised? Whilst cost-effectiveness analyses (CEAs) of screening are heterogeneous in design (41, 42), and an all parameter sensitivity analysis is not always conducted, prevalence and attrition across the cascade of care (including referral and treatment adherence) are key parameters in (modelled) cost-effectiveness studies.(42, 45)

A more challenging policy question, one that is not easily answered in research, is what would elimination actually cost for countries? Screening and treatment interventions among specific/generalised cohorts and groups may be cost-effective in terms of acceptable costs per QALY gained, but what would be the net budgetary impact of planning, implementing, coordinating and evaluating all required for elimination? This is largely unknown, although a recent modelling study in France showed that treating all CHC-infected people with new DAAs regardless of fibrosis stage is cost-effective but would add €3.5–7.2 billion, depending on the specific DAA combination, to the health care budget.(65) This cost does not include efforts required to identify these infections through screening, nor does it include CHB.

Consideration of the financial impact on health systems of HBV/HCV screening among migrants is especially relevant in the global economic and political climate from which this thesis emerged. A policy of austerity in public finances has been adopted by many industrialised high income countries in the decade since the financial crash of 2007/8.(66) Specifically, the reduction of funding for prevention activities (such as harm reduction services (67)) and in health care entitlement for migrants (68-71) will impact public health decision-makers abilities to design and implement HBV/HCV screening for migrants. We demonstrate as part of the HEPscreen Toolkit produced alongside this thesis how HBV/HCV screening among migrants can be delivered when human and financial resources are limited. All of the various models of screening described (in the Toolkit, in Chapter 6 and in the discussion of research question two) can be adapted according to resource limitations in the health care system.

Screening interventions should also consider how to minimise the time/resource impact of attending screening on the target population, for instance the costs incurred for appointments (such as travel costs, work-related absence and short-notice adjustment of family/carer responsibilities) especially for migrants reached via outreach screening rather than in health care settings. We demonstrate via the Grampian pilot that workplace-based outreach screening is a feasible means to offer screening to migrants during working hours. The success this pilot study had in detecting chronic viral hepatitis, in reaching a large number of migrants and in engaging employers (who were willing to provide time, logistics and space to support screening) presents a good practice example that others can replicate in future. We describe in Chapter 6 that socio-economic vulnerability is a barrier to attending follow up appointments for viral hepatitis-related care. Offering screening in outreach settings can reach people without access to the health care system (a lack of insurance, undocumented status), as described in Chapter 6 and in wider literature.(46, 47, 72, 73) Arranging health care entitlement as part of the planning for outreach screening is thus both ethically prudent and crucial to maximise impact.

Research and practice implications

Throughout this discussion, we allude to the key findings and learning points from the work conducted in the thesis. In the following section, we make explicit mention of how future research and public health practice can make use of, build on and take further the work conducted as part of HEPscreen and as part of this thesis. The recommendations are split into four themes: A) screening; B) cost-effectiveness; C) epidemiology; and D) national policy. Most of these recommendations come directly from our experience in this thesis; some come from limitations and future priority issues arising from key literature informing and shaping the work contained in this thesis.

Recommendations for future research and practice

A) Screening

1. There is clear and urgent need for more implementation studies of screening strategies among risk populations that includes both HBV and HCV, especially among migrants from endemic countries.
2. We need more examples of workplace-based outreach HBV/HCV screening among migrants to determine that, as in our experience, this model of screening is acceptable to the target population, is feasible, has utility and is supported by employers.
3. Future screening studies should adopt the good practices in linkage to care described in this thesis, elsewhere (3) and as part of HEPscreen (37, 61-64) to minimise attrition and maximise health impact.
4. There is a need for a standardised reporting framework for screening interventions to set out the key outcomes. This should include as a minimum: uptake, prevalence, costs per person screened, costs per case and proportion of cases reaching the various stages of care (progress through the cascade).
5. Screening interventions should provide, where required, additional social and administrative support to integrate migrants living with high levels of socio-economic vulnerability into society and the health care system.

B) Cost-effectiveness

6. Cost-effectiveness modelling studies should recalibrate the key parameters of uptake, attrition and intervention costs (specifically running screening interventions) using 'real world' measures using, for instance, those in Chapter 6.
7. In future modelling studies, the intervention costs related to screening should encompass staff time, consumables and logistical resources (as well as the commonly included costs related only to blood/serum sample-taking and serological testing) required to recruit/bring people to health services for screening.
8. There is a need for more cost-effectiveness studies of screening and treatment for HCV but focused only on interferon-free DAAs. Most of the CEAs of screening and treatment conducted prior to the availability of interferon-free DAAs for HCV treatment arguably are redundant.

C) Epidemiology

9. The development and consistent application of an EU/EEA or international standard for the design and quality assessment of seroprevalence studies to inform pooling and/or statistical comparison of data across studies and populations would greatly improve understanding of prevalence across countries and populations.

10. Future seroprevalence studies of HCV should measure both anti-HCV and HCV RNA to ensure data relate to viraemic chronic infections and not simply report evidence of anti-HCV exposure or a resolved infection.

D) National policy

11. Countries should (continue to) invest in harm reduction strategies and services to prevent IDU-acquired HBV/HCV. Injecting drug use should be seen primarily from the policy perspective of protecting and promoting public health (and not criminalisation).

12. Countries where general population anti-HCV prevalence is estimated to be high should explore the feasibility and utility (and costs) of birth cohort screening among people born 1945-1965. Much can be learned from studies in the United States (31, 41, 74, 75) and France.(76) Birth cohort (HCV) screening has been demonstrated to be good value for money.(41)

13. Low HBsAg prevalence, Northern/Western European Union Member States should focus (non-antenatal) screening efforts on migrants born in HBV endemic countries.

Recommendations and Implications for EU Policy:

This research took place within and across the EU/EEA landscape and the included studies were funded through EU Agencies. This perspective and experience has generated some wider policy implications and insights. These recommendations seek to influence the continuation of EU funding for research and action around the key themes and topics explored in this thesis.

1. The European Medicines Agency and other joint medical procurement mechanisms should utilise the combined purchasing power of the EU to negotiate better value access to interferon-free DAA regimens.

2. Chronic viral hepatitis infection should be explicitly mentioned as a priority area for action as part of a future EU Cross Border Threats framework for action.

3. Future and existing EU Frameworks, Agencies and other policy mechanisms should aim to build the epidemiological capacity in middle income MS specifically in Central and Eastern Europe where there are gaps in data and a likely high burden of CHB/CHC.

4. The EU should, on humanitarian grounds, reduce systemic barriers to health care for undocumented migrants, asylum seekers and other vulnerable populations. Universal access to health care should also be considered as a cornerstone of a successful Cross Border Threats programme.

5. EU level funding for public health projects, especially those that aim to develop tools for practice/a toolkit such as HEPscreen, should provide a follow up tranche of budget and funded staff time for dissemination and awareness raising. This funding should

only be available following completion of the tools/toolkit to ensure it is ring-fenced for dissemination of practice-focused outcomes. This could improve adoption and use of tools/toolkits produced as part of EU health funding.

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SUMMARY

This thesis focuses on chronic viral hepatitis infection in the EU/EEA through work conducted as part of the EU Health Programme funded HEPscreen project and two large scale systematic reviews and meta-analysis/epidemiological analysis in collaboration with the European Centre for Disease Control (ECDC). The strategic aim of this work is to inform future efforts towards the WHO-led goal to eliminate chronic viral hepatitis as a health threat in Europe by 2030. Whilst progress has been made and incident infections are declining in most EU/EEA countries, there is much to do to achieve this ambitious goal within this narrow timeframe. The research is focused around the first three strategic pillars of the WHO elimination strategy: 1) the who and where; 2) the what; and 3) the how. There are two broad aims:

1. To understand the epidemiology of chronic viral hepatitis in the general population and among key risk groups in the EU/EEA;
2. To understand the health system conditions and screening interventions that effectively reach, diagnose and retain at-risk migrants in health care for viral hepatitis.

In **Chapter 1**, provides an introduction to the aetiology, sequelae, transmission routes, global epidemiology and broader public health context of how we can eliminate hepatitis B (HBV) and C (HCV) virus infections. HBV and HCV are remarkably successful blood-borne infections transmitted through contact with infected blood/blood products and other bodily fluids (although latterly more for HBV than for HCV). Infections can spontaneously resolve and lead to immunity or they can fail to resolve and progress to chronic infection. Chronic infections can, if left untreated, progress over decades to serious liver disease specifically fibrosis, cirrhosis and hepatocellular carcinoma (HCC).

However, we have the ability to prevent both incident cases (via primary prevention measures) and to address the burden of chronic infection (through screening and treatment). Chapter 1 explains how patchy implementation of primary prevention in some parts of the world and at historic periods has led to an unequal global distribution of HBV and HCV as well as to a birth cohort effect in most middle and high-income countries. We also elucidate the different drivers of infection for the two viruses and from region to region. Perinatal transmission is responsible for around a third of chronic hepatitis B (CHB) cases and is thus the key driver of infection in HBV endemic areas. Interrupting transmission through antenatal screening, maternal antiviral treatment (to reduce viral load) and birth dose vaccination is crucial to control the spread of HBV. In low prevalence areas, most HBV transmission is via risk behaviour, specifically unprotected sexual contact or sharing

drug injecting equipment with HBsAg carriers. Risk group vaccination and harm reduction interventions are therefore key primary prevention measures. Past/current shared injecting drug practices are also key driver of HCV infection, placing people who inject(ed) drugs (PWID) at increased risk of both HBV and HCV infection. Prior to the introduction of stringent hospital and health care infection control measures (in the late 1980s/early 1990s in most high income countries), including blood/blood product screening, both HBV and HCV were also acquired via unscreened blood transfusions and contaminated percutaneous medical equipment. However, in many resource-poor countries, transmission via the use of unsafe medical tools remains a key driver of incident infections.

Encouragingly, prevalence of both HBsAg and anti-HCV/HCV RNA has decreased over time in most countries. Many countries now face a dichotomy: a declining incidence of new infections due to the success of primary prevention alongside a projected increase in chronic viral hepatitis-related mortality due to ageing and disease progression in the most affected birth cohort (born 1945-1965).

Expanded scope in antiviral treatment has the potential to suppress viral replication, halt disease progression and even cure chronic (HCV) infection. These potential public health benefits of effective treatment can only be realised by finding (through screening), retaining in care and treating people with a chronic hepatitis B/C infection. Our understanding of transmission risks allows us to define key risk groups for case finding (screening). In low prevalence middle and high-income countries, migrants born in endemic countries are one population subgroup in which the likelihood of being chronically infected is higher. Migrants born in HBV endemic countries may have been exposed to HBV perinatally or parenterally as children (and therefore may be at high risk of CHB infection). Migrants from HCV endemic countries are suspected to be at risk of CHC infection due to nosocomial/ iatrogenic exposure where health care infection control practices are substandard.

Drawing on a range of methodological techniques from epidemiology, public health and the social sciences, this thesis seeks to answer the following three research questions:

1. To what extent are migrants from endemic countries a risk group for chronic hepatitis B and C in Europe?
2. What can be learned from different migrant-focused models of HBV/HCV screening?
3. What are the key conditions to maximise the impact public health of HBV/HCV screening among migrants?

We begin in **Chapter 2** with a systematic review and meta-analysis to retrieve, analyse and describe prevalence estimates for the general population and in two low risk populations often used as a proxy for the general population (first time blood donors and pregnant women). We found considerable heterogeneity in HBsAg/anti-HCV prevalence and in the availability and quality of data across the EU/EEA. The findings from this study can assist Member States in elimination planning and progress monitoring as well as to highlight priority areas for epidemiological capacity-building. We show in this study how HBsAg/anti-HCV prevalence increases in an Eastern and Southern direction in the EU/EEA. We also show how using the prevalence in first time blood donors or pregnant women is an unreliable proxy for the general population due to inherent bias in these selective groups.

We further expand on the work to understand the epidemiology of chronic HBV/HCV infection in the EU/EEA in **Chapter 3**, turning here to the prevalence in three key behavioural risk groups: men who have sex with men (MSM), PWID and people incarcerated in prison. Data were gathered via a systematic review and meta-analysis (for MSM and people in prison) and via an epidemiological analysis of data systematically collected by the European Monitoring Centre for Drug Dependency and Addiction (EMCDDA). This study found that PWID and people in prison are the priority populations for CHB/CHC screening and treatment in most EU/EEA countries given the high prevalence of infection and dynamic interaction between the two sub-populations. We aimed, as in Chapter 2, to control for key sources of selection bias for each population via the development of study quality assessment frameworks. This systematic study found a paucity of studies across the three risk groups, especially high quality studies with a low risk of bias. This underlines the need for epidemiological capacity building across the EU/EEA to enable and equip Member States to measure and monitor the prevalence in key risk populations.

We turn in **Chapters 4 and 5** to the burden of chronic viral hepatitis among migrants from endemic countries to the EU/EEA. We conducted a systematic review and epidemiological analysis to estimate the burden of CHB (**Chapter 4**) and CHC (**Chapter 5**) attributable to migrants to all 31 EU/EEA Member State and across the EU/EEA as a whole. We searched for systematic reviews of the prevalence of virological markers of chronic infection to develop a global, national prevalence data set. We then retrieved demographic information on population size of all 31 EU/EEA Member State, and on the size and country of birth of all (registered) migrants to each EU/EEA Member State. We then developed estimates for the number of (potential) cases of CHB and CHC in both the general population in each (and across all) EU/EEA Member State and among migrants from endemic countries. We found that migrants from endemic countries account for around 10% of the EU/EEA population but are disproportionately affected by CHB/CHC, accounting for a quarter of all (estimated) CHB infections and 14% of all CHC infections. We also found that in low prevalence Northern/

Western EU/EEA Member States, migrants from endemic countries account for almost all estimated CHB infections and from a third to a half of all CHC infections. To validate the use of country of birth prevalence as a proxy for migrants, we also compared the prevalence found in studies among migrants (living in EU/EEA Member States and representative of the general population) with the prevalence retrieved for the corresponding country of birth. This analysis showed that, whilst there are limited data points for the prevalence in migrants, country of birth prevalence can be used as a proxy for the prevalence in migrants.

Chapters 2-5 aim to answer research question 1. In **Part 2**, we turn to questions 2 and 3 and focus on 'the how' of secondary prevention. **Chapters 6 - 13** describe the key scientific work conducted as part of the EU Health Programme funded project *HEPscreen: screening for chronic viral hepatitis among migrants in Europe*. This consortium project funded during 2011-2014 aimed to define the tools and conditions for effective screening and linkage to care for chronic viral hepatitis among migrants in Europe. Alongside the scientific output reported in this thesis, we also translated and synthesised the knowledge and findings gathered into a practical online toolkit aimed at supporting policy makers, public health practitioners and clinicians to implement and evaluate the impact of screening among migrants from endemic countries. This toolkit is available in multiple EU languages at http://www.hepscreen.eu and is an accessible repository of good practices consisting of epidemiological tools, practical checklists, animated videos to improve knowledge and awareness, and short documentary videos of models of good practice screening to assist in replication.

Chapter 6 describes the six screening pilot studies that were at the core of the HEPscreen project. In this study, we report on the implementation, outcomes and costs of six models of screening for CHB/CHC among migrants. We pilot tested two *outreach screening models* (one in community locations in Barcelona, Spain; one in workplaces in Grampian, Scotland), *an opportunistic model* (also in Barcelona) and *an invitation-based model* (in London, the UK) both in primary care, and *two extension models* (adding HBV/HCV screening to university-based tuberculosis screening in Grampian, Scotland; extending antenatal HBV screening to include HCV in Budapest/Pest County, Hungary). We collected and compared data on cascade of care outcomes, screening uptake, prevalence and costs. Five of the six screening models were completed, screening 1203 people for HBV and HCV. Uptake varied from 33% in workplace outreach screening to 78% in opportunistic screening in primary care. The invitation-based model in primary care ceased prematurely due to low uptake (2.3%). Attrition was seen in the community outreach where testing was not offered at the first point of contact. The highest HBsAg prevalence (12.9%) was detected among South-East Asian migrants. The highest anti-HCV prevalence was found in migrants from Central (10.3%) and South (8.3%) Asia, and Eastern Europe (5.3%). Costs per person screened ranged

from €48 (tuberculosis screening extension model) to €111 (community outreach model). We conclude that at-risk migrants can be effectively reached via screening models in health care and community settings. Uptake in community-based outreach screening may be improved by offering testing at the first point of contact. HBV/HCV screening should prioritise migrants born in intermediate/high prevalence countries to maximise public health impact.

Chapters 7 to 13 focus on understanding the health system conditions that facilitate implementation of screening among migrants. **Chapter 7** describes a systematic literature search for guidelines related to screening, counselling, clinical management and treatment for chronic viral hepatitis. We further supplemented this search with a survey among policy makers and clinicians to identify guidelines not retrieved by the search. The online survey retrieved 40 national guidelines in addition to the 12 retrieved by the systematic scientific database search. This study suggests that scientific databases are not the most important source to disseminate good practice guidelines to clinicians.

Language barriers are the focus of **Chapter 8**. Via an online survey among clinicians involved in screening and/or clinical management and treatment of viral hepatitis, we investigate the availability of interpreters and translated materials for chronic viral hepatitis patients in the six HEPscreen study countries (Germany, Hungary, Italy, the Netherlands, Spain and the United Kingdom). We also investigate how far clinicians feel that language barriers explain three scenarios: why screening is not offered to culturally and linguistically diverse (CALD) migrants with country of birth-related risk factors; why the uptake of screening is low among at-risk CALD migrants; and why CALD migrants with evidence of a chronic viral hepatitis infection do not reach secondary care for clinical investigation and treatment. We found that support to overcome language barriers (interpreters/translated materials) is more common in the 'difference-sensitive' health systems of the Netherlands, Spain and the UK and less common in the 'difference-blind' health systems of Germany, Hungary and Italy. We also found that in 'difference-blind' countries, where migrants are (largely) expected to assimilate to the language and culture of the host country, clinicians disagree that language barriers explain the three scenarios despite the reported infrequent availability of services that overcome language barriers. This finding highlights that wider social and cultural norms and values around assimilation (the expectation that migrants adapt to the host country) exists in health care. Conversely, in 'difference-sensitive' health systems, clinicians agree that language barriers are important explanations for the three scenarios despite the frequent availability of interpreters and translated materials.

We turn to pre-test information prior to HBV/HCV screening among migrants in **Chapter 9**. We set out via a systematic literature search, content analysis and a DELPHI-inspired online survey among clinicians to add explore and expand the concept of pre-test information before HBV/HCV screening. The study first defines the objectives and discussion topics of pre-test information before HBV/HCV screening as reported in good practice guidelines retrieved via the search and content analysis. Secondly, we explored clinicians' perceptions of the objectives of pre-test information and the importance of each discussion topic towards achieving each objective. Finally, we consolidate findings into a consensus on the desirable and feasible aspects of pre-test information – what can be delivered topic-wise that assures key objectives (securing informed choice, achieving a high uptake, reducing stigma and improving knowledge) when time in health care encounters is limited. We then further synthesise these findings (as an annex to the study) into a practical 'pre-test information' checklist aimed at clinicians offering screening among migrants. The checklist outlines the priority discussion topics if time is limited as well as which topics can increase feelings of stigma, fear and shame among at-risk migrants offered screening.

Chapters 10 to 13 focus on current pathways for patients with evidence of chronic viral hepatitis infection in referral, clinical management and access to treatment in the six HEPscreen countries. All four studies utilise online survey methodology among practising clinicians, with Chapters 12 and 13 specifically focused among secondary care specialists (in infectious diseases, gastroenterology or hepatology). In **Chapter 10**, we explore current practices in referral of patients with evidence of a CHB/CHC infection and findings allude to the existence of complex and unclear referral pathways within countries and to the variability in the role of primary care. Secondary care specialists report variably or rarely receiving patients with evidence of a CHB/CHC infection from services likely to be involved in screening such as antenatal care, sexual health services and harm reduction/PWID testing facilities/services in Germany, Hungary, Italy and the Netherlands. Most commonly across all six study countries is the referral from or via GPs to specialist care, highlighting the pivotal 'gate-keeper' role of GP services in these countries but especially so in Spain, the Netherlands and the UK. Findings from this study suggest that strengthening and systematising referral between screening/diagnosing services and clinical management/treatment services is a key part improving progression through a cascade of care.

We build on these findings in **Chapter 11**, focusing on the role of the GP in screening and clinical management for CHB/CHC, with data gathered also via an online survey among GPs and specialists in secondary care. We first focus on how common it is for GPs to offer screening to key risk groups including migrants born in endemic countries, PWID, MSM, sex workers and people with abnormal liver function tests. Results show variability in the offer of screening across all groups across all countries. Most relevant for this thesis

is the finding that HBV/HCV screening among migrants born in endemic countries is not systematically offered by GPs in any of the six study countries. We suggest that systematising and expanding the offer of HBV/HCV screening to migrants from endemic areas by GPs can contribute significantly to increasing the diagnosed fraction and can be achieved via electronic patient prompts, invitation-based screening using country of birth selection criteria and interventions to improve GP knowledge and awareness.

In **Chapter 12**, we set out to determine if restrictions in access to antiviral treatment for CHB/CHC exist for six vulnerable populations: undocumented migrants, asylum seekers, people without health insurance, people with only state insurance, PWID and people abusing alcohol. We used a four point Likert scale (complete, significant, some or no restriction) to measure clinicians' perceptions of restrictions in their country. Most notable was the discordance of opinion about restrictions within countries, especially for groups for whom the health care system defines access to treatment, such as undocumented migrants, asylum seekers and people without health insurance. This study adopts a health system perspective and the six countries in our study represent different types: in Germany and the Netherlands, a Bismarkian system exists where state insurance is crucial for access to health care. It is, therefore, not surprising that we do observe some or significant restrictions in access to treatment among people without health insurance. Italy, Spain and the UK operate a Beveridge-style system where health care coverage is free and universal, and funded through collective national insurance payments. This universalism is mirrored in responses from Italy where no or only some restrictions exist for all six patient/population groups. It is, however, somewhat surprising that restriction to treatment among those without health insurance is reported in Spain and the UK where insurance is not expected to play a role. However, both systems require registration to receive social support and access to health care would be limited without this registration, not because patients do not have health insurance coverage per se but because those without (state) insurance cover are effectively considered undocumented migrants or persons for whom health care entitlement is uncertain. Hungary operates a hybrid of a Semashko-style Soviet system and a Bismarckian-influenced model where individual (social) health insurance coverage is key to access but the legacy of out-of- pocket payments remains. Most restrictions are reported in Hungary, especially among undocumented migrants, asylum seekers and people without insurance.

Chapter 13 examines access to antiviral treatment options in the six countries. We investigate via a three point Likert scale (no, some, complete) the level of restriction for each treatment option approved for use in Europe (by the European Medicines Agency) up to summer of 2014. We deployed two surveys – one in 2012 and a follow up in 2015 about interferon-free direct acting antivirals (DAAs) (sofosbuvir, simeprevir, declatasvir and simeprevir/ledipasvir) approved in 2014. We find that most options for CHB treatment are widely available for

use by specialists in all six countries. This further strengthens the rationale for expanding access to HBV screening. For HCV treatment, clinical and health system factors restrict and ration the use of the latest antiviral innovations in Hungary, Italy, the Netherlands, Spain, and the UK. The latest innovations in HCV treatment appear to be limited to certain hospitals but, most significantly, to patients with advanced disease, specifically F3/4 cirrhosis. While these patients are most urgently in need of treatment, to maximise the health gains from secondary prevention, highly effective DAAs would need to become available for patients without cirrhosis.

Finally we discuss the three research questions and the research, policy and practice implications arising out of this thesis in **Chapter 14.** We open the discussion on research question one with three conceptualisations of to what 'extent' migrants born in endemic countries are a key risk group: 1) 'extent' in terms of relative magnitude; 2) 'extent' in terms of relative prevalence and 3) 'extent' seen through the lens of distributional justice. We conclude based on these conceptualisations that migrants from endemic countries are the key risk group for HBV in most low prevalence, high income Member States in the North and West of the EU/EEA. We draw a slightly more nuanced conclusion for HCV: migrants from endemic countries are one key risk group based on their higher prevalence (compared to the host population) and relatively high contribution (in relation to population size). However, PWID and people (formerly) incarcerated in prison are the key HCV risk group due to the very high (>50%) prevalence in these two populations. What this epidemiology underlines is the need for a more sensitive approach to the discussion of risk factors when offering screening to migrants from endemic countries and specifically to avoid stigmatisation of (people with) viral hepatitis infection through avoiding emphasis on illicit drug use, sexual contact and criminality as the source of infection.

We synthesize the learning from the HEPscreen Project in discussion of research question 2 summarising five key learning points for effective HBV/HCV screening among migrants:

1. A simple care pathway;
2. Involvement of/partnership with secondary care to facilitate referral;
3. Offering on site screening with awareness-raising/pre-test information;
4. The availability of interpreters/translated materials to reduce language barriers;
5. The use at the planning stage of country of birth prevalence and demographic information to define the migrant communities at highest risk of chronic viral hepatitis infection.

There is an urgent need for more implementation studies of screening among migrants, specifically studies that compare different models of screening and report outcomes and costs across the cascade of care.

The discussion turns to the question of how to maximise the impact of screening among and linkage to care of at-risk migrant groups (research question 3). We elucidate two key conditions required for maximise impact:

1. Good data across the cascade of care;
2. Scaling up key interventions and good practices as part of a strategic approach.

Good data across the cascade of care are necessary to understand (national) progress towards elimination. We refer to the WHO led elimination strategy and action plan, specifically the key indicator set, as important strategic tools and frameworks available to assist countries/regions in data collection and elimination planning. Scaling up good practices in designing and delivering screening to at-risk migrants as part of a strategic approach improves population health and makes effective use of scarce health care resources.

The key term here is strategic – the notion of making effective use of existing resources; of mapping existing interventions and looking both for gaps in provision and for unexplored synergy; of building partnerships between layers and levels within health systems; of adopting project management techniques when implementing multiple interventions within a defined area/for a defined population; appropriately targeting interventions; of using evidence to guide intervention/project development; of prudent financial planning to maximise delivery and minimise waste; and of including evaluation in the cycle of intervention/strategy development and implementation.

We conclude the discussion by summarising a series of recommendations – for research and practice, for national policy and for EU policy.

SAMENVATTING

Dit proefschrift gaat over chronische virale hepatitis infecties in de EU/EER en beschrijft werk uitgevoerd in het kader van het door het EU Health Programme gefinancierde HEPscreen project, en twee grootschalige systematische reviews en meta-analyse/epidemiologische analyse voor het European Centre for Disease Control (ECDC). Het strategische doel van dit werk is om richting te geven aan de toekomstige inspanningen om het door de World Health Organisation (WHO) gestelde doel, om chronische virale hepatitis als een bedreiging voor de gezondheid in Europa te elimineren voor 2030, te bereiken. Hoewel er vooruitgang is geboekt en het aantal nieuwe infecties daalt in de meeste EU/EER-landen, is er nog veel te doen om dit ambitieuze doel te bereiken in dit smalle tijdsbestek. Het onderzoek is gericht op de eerste drie strategische pijlers van de eliminatie strategie van de WHO: 1) 'het wie en waar'; 2) 'het wat'; en 3) 'het hoe'. Er zijn twee overkoepelende doelen:

1. Inzicht krijgen in de epidemiologie van chronische virale hepatitis in de algemene bevolking en onder belangrijke risicogroepen in de EU/EER;
2. Inzicht krijgen in de gezondheidszorg organisatorische voorwaarden en screeningsinterventies die migranten met virale hepatitis effectief bereiken, diagnosticeren en in zorg houden.

Hoofdstuk 1 geeft een inleiding op de etiologie, de gevolgen, de transmissie routes, wereldwijde epidemiologie en bredere volksgezondheid context van de manier waarop we hepatitis B (HBV) en C (HCV) virusinfecties kunnen elimineren. HBV en HCV zijn opmerkelijk besmettelijke infecties die kunnen worden overgedragen door contact met besmet bloed/bloedproducten en andere lichaamsvloeistoffen (hoewel dit laatste meer voor HBV dan HCV). Infecties kunnen spontaan herstellen en leiden tot immuniteit of ze kunnen overgaan in een chronische infectie. Chronische infecties kunnen, indien onbehandeld, na tientallen jaren ernstige leverziekten zoals cirrose en hepatocellulair carcinoom (HCC) veroorzaken.

We hebben echter de mogelijkheid om zowel nieuwe gevallen te voorkomen (via primaire preventiemaatregelen) als ook de ziektelast van chronische infectie aan te pakken (door screening en behandeling). In hoofdstuk 1 wordt uitgelegd hoe gebrekkige implementatie van primaire preventie in sommige delen van de wereld en in specifieke periodes heeft geleid tot een ongelijke wereldwijde verdeling van HBV en HCV, evenals een geboortecohort effect in de meeste midden en hoog inkomen landen. We verhelderen ook de verschillende onderliggende factoren voor de verspreiding van de twee virussen en van regio tot regio. Perinatale transmissie is verantwoordelijk voor ongeveer een derde van de chronische hepatitis B (CHB) en is de belangrijkste drijvende kracht in HBV endemische gebieden. Het onderbreken van transmissie door prenatale screening en antivirale behandeling tijdens de

zwangerschap (waardoor de viral load afneemt) en een geboortedosis vaccinatie is cruciaal om de verspreiding van HBV tegen te gaan. In lage prevalentie gebieden vindt de meeste HBV transmissie plaats via risicogedrag zoals onbeschermd seksueel contact of het delen van drug injectiemateriaal met HBsAg dragers. Risicogroep vaccinatie en harm reduction zijn dan ook belangrijke primaire preventie maatregelen. (Ex)druggebruik is ook een belangrijke oorzaak van HCV-infectie, wat mensen die drugs injecteren (PWID) een verhoogd risico geeft op zowel HBV als HCV-infectie. Voorafgaand aan de invoering van strenge controle maatregelen (o.a. bloed/bloedproduct screening) in het ziekenhuis en de gezondheidszorg (in de late 1980/begin jaren 1990 in de meeste rijke landen), werden zowel HBV en HCV ook overgedragen via ongescreende bloedtransfusies en besmet percutane medische apparatuur. In vele resource-arme landen, blijft transmissie via het gebruik van onveilige medische hulpmiddelen een belangrijke motor bij het ontstaan van nieuwe infecties.

Het is bemoedigend dat de prevalentie van zowel HBsAg als anti-HCV/HCV RNA in de loop der tijd is verminderd in de meeste landen. Veel landen staan nu voor een dichotomie: een dalende incidentie van nieuwe infecties als gevolg van het succes van de primaire preventie en tegelijkertijd een verwachte toename van chronische virale hepatitis gerelateerde sterfte als gevolg van de vergrijzing en de progressie van de ziekte in het zwaarst getroffen geboortecohort (geboren 1945-1965).

Verbeterde antivirale behandeling heeft het vermogen om virale replicatie te onderdrukken, progressie van de ziekte te stoppen en zelfs chronische (HCV) infectie te genezen. Deze potentiële voordelen voor de volksgezondheid van een effectieve behandeling kunnen alleen worden gerealiseerd door het opsporen (via screening), in zorg brengen en het behandelen van mensen met een chronische hepatitis B/C-infectie. Ons begrip van transmissie risico's stelt ons in staat om belangrijke risicogroepen voor case-bevinding (screening) te definiëren. In midden en hoge-inkomenslanden met een lage prevalentie zijn migranten geboren in endemische landen een bevolkingsgroep waarin de kans om chronisch geïnfecteerd te zijn hoger is. Migranten geboren in HBV endemische landen kunnen perinataal of parenteraal zijn blootgesteld aan HBV als kinderen (en hebben daarom een hoog risico op CHB infectie). Migranten uit HCV endemische landen kunnen risico op CHC infectie hebben gelopen als gevolg van nosocomiale/iatrogene blootstelling, daar waar de gezondheidszorg infectie controle praktijken ondermaats zijn.

Op basis van een aantal methodologische technieken uit de epidemiologie, volksgezondheid en de sociale wetenschappen, wil dit proefschrift de volgende drie onderzoeksvragen beantwoorden:

1. In welke mate zijn migranten uit endemische landen een risicogroep voor chronische hepatitis B en C in Europa?
2. Wat kan geleerd worden uit verschillende op migranten gerichte modellen voor HBV/HCV screening?
3. Wat zijn de belangrijkste voorwaarden om de volksgezondheid impact van HBV/HCV-screening onder migranten te maximaliseren?

In **hoofdstuk 2** worden met een systematische review en meta-prevalentie schattingen voor de algemene bevolking en twee laag risico populaties die vaak gebruikt worden als een proxy voor de algemene bevolking (bloed donoren en zwangere vrouwen) verzameld, geanalyseerd en beschreven. Wij vonden een aanzienlijke heterogeniteit in HBsAg/anti-HCV-prevalentie en in de beschikbaarheid en de kwaliteit van de gegevens in de hele EU/EER. De bevindingen van deze studie kunnen EU/EER-lidstaat helpen bij de eliminatie planning en voortgangsbewaking alsmede gebieden voor epidemiologische capaciteitsopbouw te prioriteren. Wij tonen in deze studie aan hoe HBsAg/anti-HCV-prevalentie toeneemt in een oostelijk en zuidelijk richting in de EU/EER. Wij laten ook zien dat de prevalentie in de bloed donoren en zwangere vrouwen een onbetrouwbare proxy is voor de algemene bevolking als gevolg van inherente bias in deze selectieve groepen.

In **hoofdstuk 3** draait het om de prevalentie in drie belangrijke gedragsgebonden risicogroepen: mannen die seks hebben met mannen, injecterende druggebruikers (PWID) en gedetineerden. De gegevens werden verzameld via een systematische review en meta-analyse (MSM en gedetineerden) en via een epidemiologische analyse van gegevens die systematisch worden verzameld door het European Monitoring Centre for Drug Dependency and Addiction (EMCDDA). Deze studie bleek dat PWID en gedetineerden de prioriteit populaties zijn voor CHB/CHC screening en behandeling in de meeste EU/EER-landen, gezien de hoge prevalentie van infectie en dynamische interactie tussen de twee subpopulaties. Wij streven ernaar, zoals in hoofdstuk 2, voor belangrijke bronnen van selectiebias voor elke populatie te corrigeren via de ontwikkeling van studiekwaliteitsbeoordelingsraamwerken. Deze systematische studie vond een gebrek aan studies over de drie risicogroepen, vooral van studies van hoge kwaliteit met een laag risico op bias. Dit onderstreept de noodzaak voor epidemiologische capaciteitsopbouw in de hele EU/EER om EU/EER-lidstaten in staat te stellen om de prevalentie in de verschillende risicogroepen te meten te monitoren.

Wij richten ons in **hoofdstukken 4 en 5** op de ziektelast van chronische virale hepatitis onder migranten uit endemische landen in de EU/EER. Wij voerden een systematische review en epidemiologische analyse om het aandeel van migranten aan de ziektelast van CHB (hoofdstuk 4) en CHC (hoofdstuk 5) te schatten migranten voor alle 31 EU/EER-lidstaten en in de hele EU/EER als geheel. Wij hebben gezocht naar systematische reviews van de

prevalentie van virologische markers van chronische infectie om een nationale prevalentie dataset te ontwikkelen voor alle landen in de wereld. Vervolgens hebben we demografische informatie over de omvang van de populatie van alle 31 EU/EER-lidstaten verzameld, en van de grootte en het land van geboorte van alle (geregistreerde) migranten in elke EU/EER-lidstaat. Vervolgens hebben we het aantal (potentiële) gevallen van CHB en CHC geschat, zowel in de algemene bevolking in elke EU/EER-lidstaten (en in totaal) en onder migranten uit endemische landen. Wij vonden dat migranten uit endemische landen ongeveer 10% van de EU/EER-bevolking uitmaken, maar dat ze onevenredig worden getroffen door CHB/CHC aangezien een kwart van de (geschatte) CHB infecties en 14% van alle CHC infecties bij migranten gevonden wordt. Wij vonden ook dat in lage prevalentie landen in het noorden en westen van de EU/EER, migranten uit endemische landen bijna alle geschatte CHB infecties en tussen een derde tot de helft van alle CHC infecties vertegenwoordigen. Om de validiteit van het gebruik van de prevalentie in het geboorteland als een proxy voor de prevalentie onder migranten te toetsen, hebben we deze waar beschikbaar vergeleken. Deze analyse toonde aan dat, hoewel er beperkte data zijn over de prevalentie onder migranten, de prevalentie in het geboorteland kan worden gebruikt als een proxy voor de prevalentie onder migranten.

In de hoofdstukken 2-5 wordt vraagstelling 1 beantwoord. In **deel 2**, richten we ons op de vragen 2 en 3 en ligt de focus op 'het hoe' van secundaire preventie. **Hoofdstukken 6 - 13** beschrijven het wetenschappelijke werk dat is uitgevoerd als onderdeel van het EU-gezondheidsprogramma gefinancierde project *HEPscreen: screening voor chronische virale hepatitis onder migranten in Europa*. Dit consortiumproject, met looptijd 2011-2014, had als doel de instrumenten en voorwaarden te definiëren voor effectieve screening en toe geleiding tot zorg voor chronische virale hepatitis onder migranten in Europa. Naast de wetenschappelijke output die in dit proefschrift wordt beschreven, hebben we ook de kennis en de bevindingen verzameld en gesynthetiseerd in een praktische online toolkit, gericht op het ondersteunen van beleidsmakers, volksgezondheidsprofessionals en clinici om de impact van screening onder migranten uit endemische landen te implementeren en te evalueren. Deze toolkit is beschikbaar in meerdere talen via http://www.hepscreen.eu en is een toegankelijke verzameling van goede praktijkvoorbeelden, bestaande uit epidemiologische instrumenten, praktische checklists, animatiefilmpjes om de kennis en het bewustzijn te verbeteren, en korte documentaire video's van screeningsprojecten in de praktijk om implementatie te vergemakkelijken.

Hoofdstuk 6 beschrijft de zes pilot screeningprojecten die de kern van de HEPscreen project vormden. In deze studie rapporteren we over de uitvoering, de resultaten en de kosten van de zes manieren van screening voor CHB/CHC onder migranten. Er zijn twee *outreach screening modellen* getest (één in de gemeenschap locaties in Barcelona, Spanje,

één in werkplaatsen in Grampian, Schotland), een *opportunistisch model* (ook in Barcelona) en een *model met persoonlijke uitnodiging* (in Londen, het Verenigd Koninkrijk), beide in de eerste lijn, en twee *uitbreidingsmodellen* (toevoegen van HBV/HCV screening aan tuberculosescreening in Grampian, Schotland; uitbreiding van de prenatale HBV-screening met HCV in Budapest/Pest regio, Hongarije). Wij verzamelden en vergeleken gegevens op uitkomsten in de cascade van de zorg, screening deelname, prevalentie en kosten. Vijf van de zes screeningsmodellen werden voltooid, waarbij 1203 mensen voor HBV en HCV werden gescreend. De deelname varieerde van 33% in de screening op de werkplek tot 78% bij opportunistische screening in de eerstelijn. Het op uitnodiging-gebaseerde model vanuit de huisarts stopte voortijdig door een lage deelname (2,3%). Uitval werd gezien in de gemeenschap-outreach waar het testen niet bij het eerste contactpunt werd aangeboden. De hoogste HBsAg prevalentie (12,9%) werd gevonden onder Zuidoost-Aziatische migranten. De hoogste anti-HCV prevalentie werd gevonden onder migranten uit Centraal (10,3%) en Zuid (8,3%) Azië en Oost-Europa (5,3%). Kosten per gescreend persoon varieerde van €48 (tuberculose screening uitbreidingsmodel) tot €111 (gemeenschap-outreach model). Wij concluderen dat een migranten met een verhoogd risico effectief via screening modellen kunnen worden bereikt in de gezondheidszorg en maatschappelijke instellingen. Deelname in gemeenschap-outreach screening kan worden verbeterd door het aanbieden van testen bij het eerste contactpunt. HBV/HCV screening moet prioriteit geven aan migranten geboren in intermediaire/hoge prevalentie landen om te impact op de volksgezondheid te maximaliseren.

Hoofdstukken 7 - 13 richten zich op het begrijpen van de aspecten van het gezondheidszorgsysteem die de implementatie van screening onder migranten bevorderen. **Hoofdstuk 7** beschrijft een systematisch literatuuronderzoek naar richtlijnen met betrekking tot screening, counseling, patiëntmanagement en de behandeling van chronische virale hepatitis. Wij hebben deze zoekopdracht verder aangevuld met een onderzoek onder beleidsmakers en clinici om richtlijnen te identificeren die niet met de zoekopdracht zijn gevonden. De online-enquête identificeerde 40 nationale richtlijnen in aanvulling op de 12 die waren gevonden in het systematische literatuuronderzoek. Deze studie suggereert dat wetenschappelijke databanken niet de belangrijkste bron zijn om goede praktijkrichtlijnen onder clinici te verspreiden.

Taalbarrières zijn de focus van **hoofdstuk 8**. Via een online enquête onder clinici die betrokken zijn bij het screenen en/of patiëntmanagement en de behandeling van virale hepatitis, onderzoeken we de beschikbaarheid van tolken en vertaalde materialen voor chronische virale hepatitis patiënten in de zes HEPscreen studie landen (Duitsland, Hongarije, Italië, Nederland, Spanje en het Verenigd Koninkrijk). Wij onderzoeken ook in hoe verre clinici vinden dat taalbarrières drie scenario's verklaren: waarom screening

niet aan cultureel en taalkundig diverse (CALD) migranten met aan het geboorteland-gerelateerde risicofactoren wordt aangeboden; waarom de deelname aan screening laag is bij CALD-migranten; en waarom CALD migranten een chronische virale hepatitis infectie de secondaire zorg niet bereiken voor klinisch onderzoek en behandeling. Wij vonden dat ondersteuning bij het overwinnen van taalbarrières (tolken/vertaald materiaal) vaker beschikbaar is in de 'verschil-gevoelige' gezondheidsstelsels van Nederland, Spanje en het Verenigd Koninkrijk en minder vaak in de 'verschil-blinde' gezondheidsstelsels van Duitsland, Hongarije en Italië. Wij vonden ook dat in 'verschil-blinde' landen, waar migranten (grotendeels) verwacht worden te assimileren aan de taal en cultuur van het gastland, clinici er niet mee eens zijn dat taalbarrières een rol spelen in de drie scenario's, ondanks de gerapporteerde sporadische beschikbaarheid van diensten om taalbarrières te overkomen. Deze bevinding wijst erop dat de bredere sociale en culturele normen en waarden rond assimilatie (de verwachting dat migranten zich aanpassen aan het gastland) ook bestaat in de gezondheidszorg. Omgekeerd, zijn clinici in 'verschil-gevoelige' gezondheidszorgsystemen het erover eens dat taalbarrières belangrijke verklaringen zijn voor de drie scenario's, ondanks de veelvuldige beschikbaarheid van tolken en vertaalde materialen.

In **hoofdstuk 9** gaan we in op pre-test counseling voorafgaand aan HBV/HCV screening onder migranten. Via een systematisch literatuuronderzoek, inhoudsanalyse en een DELPHI geïnspireerde online enquête onder clinici is het concept van pre-test counseling voor HBV/HCV screening verkend en uitgebreid. We rapporteren over de wenselijkheid en haalbaarheid van aspecten van pre-test counseling - wat kan worden per onderwerp worden meegenomen dat de belangrijkste doelstellingen veiligstelt (geïnformeerde keuze, het bereiken van een hoge deelname, een vermindering van stigmatisering en verbetering van kennis) wanneer de tijd in de gezondheidszorg beperkt is. Wij hebben deze bevindingen vervolgens verder gesynthetiseerd (als bijlage bij de studie) in een praktische 'pre-test counseling' checklist gericht op clinici die screening onder migranten aanbieden. De checklist schetst welke gespreksonderwerpen prioriteit hebben als tijd beperkt is, en welke onderwerpen gevoelens van stigmatisering, angst en schaamte kunnen verhogen onder migranten die screening aangeboden krijgen.

Hoofdstukken 10 - 13 richten zich op de huidige trajecten voor patiënten met chronische virale hepatitis-infectie bij doorverwijzing, klinische behandeling en toegang tot behandeling in de zes HEPscreen landen. Alle vier studies maken gebruik van online enquêtes onder clinici, waarbij hoofdstuk 12 en 13 specifiek gericht zijn op specialisten in de tweede lijn (in infectieziekten, gastro-enterologie en hepatologie). In **hoofdstuk 10** onderzoeken we de huidige praktijken in de verwijzing van patiënten met bewijs van een CHB/CHC infectie. De bevindingen suggereren het bestaan van complexe en

onduidelijke verwijstrajecten binnen landen en variabiliteit in de rol van de eerstelijns gezondheidszorg. Secondaire zorg specialisten melden wisselend of zelden patiënten met CHB/CHC besmetting te ontvangen vanuit diensten die zijn betrokken bij screening, zoals antenatale zorg, seksuele gezondheid en harm reduction/PWID testfaciliteiten/services in Duitsland, Hongarije, Italië en Nederland. Het meest gebruikelijk in alle zes studie landen is de verwijzing vanuit de huisarts naar specialistische zorg, wat de cruciale 'poortwachter' rol van de huisartsen in deze landen onderstreept, vooral in Spanje, Nederland en het Verenigd Koninkrijk. Bevindingen uit deze studie suggereren dat de versterking en systematisering van doorverwijzing van screening/diagnosticerende diensten naar klinische behandeling/ behandelde diensten is een belangrijk onderdeel is bij het verbeteren van de doorstroom in de cascade van de zorg.

Wij bouwen voort op deze bevindingen in **hoofdstuk 11**, met de nadruk op de rol van de huisarts in screening en klinische behandeling voor CHB/CHC, met gegevens verzameld via een online enquête onder huisartsen en specialisten in de secondaire zorg. Wij richten ons eerst op hoe gebruikelijk het is voor huisartsen om de belangrijkste risicogroepen, zoals migranten geboren in endemische landen bieden, pwid, MSM, sekswerkers en mensen met abnormale lever functies te screenen. De resultaten tonen variatie aan in het aanbod van screening in alle groepen in alle landen. Het meest relevant voor dit proefschrift is de bevinding dat HBV/HCV screening voor migranten geboren in endemische landen niet systematisch wordt aangeboden door huisartsen in de zes studie landen. Wij stellen voor dat systematiseren en het uitbreiden van het aanbod van HBV/HCV screening voor migranten uit endemische gebieden door huisartsen aanzienlijk kan bijdragen aan het verhogen van de gediagnosticeerde fractie en kan worden bereikt via prompts in het elektronisch patiëntendossier, screening-uitnodiging op basis van het geboorteland en interventies om kennis en bewustzijn van de huisarts te verbeteren.

In **hoofdstuk 12**, pogen we te bepalen of er beperkingen in de toegang tot antivirale behandeling voor CHB/CHC bestaan voor zes kwetsbare groepen: ongedocumenteerde migranten, asielzoekers, mensen zonder ziektekostenverzekering, mensen met alleen een overheidsverzekering, PWID en mensen die misbruik maken van alcohol. Wij gebruikten een vier-punt Likert-schaal (totale, significante, enkele of geen beperking) om percepties van beperking onder clinici te meten in hun land. Het meest opvallend was de discordantie van meningen over beperkingen binnen landen, in het bijzonder voor groepen voor wie de gezondheidszorg toegang tot behandeling bepaalt, zoals ongedocumenteerde migranten, asielzoekers en mensen zonder ziektekostenverzekering. Deze studie hanteert een gezondheidszorgstelsel perspectief en de zes landen in onze studie vertegenwoordigen verschillende types: Duitsland en Nederland hebben een Bismarkian systeem waarin een zorgverzekering van cruciaal belang is voor de toegang tot de gezondheidszorg. Het is

dan ook niet verwonderlijk dat we enkele of belangrijke beperkingen in de toegang tot behandeling waarnemen onder mensen zonder ziektekostenverzekering. Italië, Spanje en het Verenigd Koninkrijk hebben een Beveridge-stijl systeem waar de dekking van de gezondheidszorg gratis en universeel is en gefinancierd wordt door middel van collectieve nationale verzekering uitkeringen. Dit universalisme wordt weerspiegeld in de reacties van respondenten uit Italië, waar geen of enkele beperkingen bestaan voor alle zes patiëntengroepen. Het is echter enigszins verrassend dat restrictie op de behandeling onder degenen zonder ziektekostenverzekering werd gemeld in Spanje en het Verenigd Koninkrijk, waar de zorgverzekering niet wordt verwacht een rol te spelen. Echter, beide systemen vereisen registratie voor het ontvangen van sociale steun en toegang tot gezondheidszorg zou worden beperkt zonder registratie, niet omdat patiënten geen ziektekostenverzekering hebben per se, maar omdat mensen zonder verzekering effectief gezien beschouwd worden als gedocumenteerde migranten of personen voor wie recht op verzekerde zorg onzeker is. Hongarije hanteert een hybride van een Semashko-stijl Sovjet-systeem en een Bismarckiaanse - beïnvloed model waarin individuele (sociale) ziektekostenverzekering de sleutel is tot toegang, maar de erfenis van out-of-pocket betalingen blijft. De meeste beperkingen worden gerapporteerd in Hongarije, vooral onder ongedocumenteerde migranten, asielzoekers en mensen zonder verzekering.

Hoofdstuk 13 onderzoekt de toegang tot antivirale behandeling opties in de zes landen. Wij onderzoeken via een drie-punt Likert-schaal (geen, sommige, volledig) het niveau van de beperking voor elke behandeling optie die is goedgekeurd voor gebruik in Europa (door de European Medicines Agency) tot en met de zomer van 2014. Wij hebben twee onderzoeken ingezet - een in 2012 en een follow-up in 2015 over interferon-vrij direct werkende antivirale DAAs (sofosbuvir, simeprevir, declatasvir en simeprevir/ledipasvir) goedgekeurd in 2014. Wij vonden dat de meeste opties voor CHB-behandeling op grote schaal beschikbaar zijn voor gebruik door specialisten in alle zes landen. Dit versterkt verder de onderbouwing voor uitbreiding van de toegang tot HBV screening. Voor HCV behandeling, beperken klinische en gezondheidszorg factoren het gebruik van de nieuwste antivirale innovaties in Hongarije, Italië, Nederland, Spanje en het Verenigd Koninkrijk. De laatste innovaties in HCV-behandeling lijken beperkt te zijn tot bepaalde ziekenhuizen, maar vooral voor patiënten met geavanceerde ziekte, met name F3/4 cirrose. Hoewel deze patiënten het meest dringend behoefte hebben aan behandeling, om de gezondheid voordelen van secundaire preventie te maximaliseren, zouden de zeer effectieve DAAs ook beschikbaar moeten zijn voor patiënten worden zonder cirrose.

Tot slot bespreken we de drie onderzoeksvragen en de onderzoek, beleid en praktijk implicaties die voortkomen uit dit proefschrift in **hoofdstuk 14**. Wij openen de discussie over onderzoeksvraag één met drie conceptualiseringen van in welke 'omvang' migranten

geboren in endemische landen een belangrijke risicofactor groep zijn: 1) 'omvang' qua relatieve grootte; 2) 'omvang' in termen van relatieve prevalentie en 3) 'omvang' gezien door de lens van herverdelende rechtvaardigheid. Wij concluderen op basis van de verschillende conceptualiseringen dat migranten uit endemische landen de belangrijkste risicogroep zijn voor HBV in de meeste lage prevalentie, hoog inkomen lidstaten in het noorden en westen van de EU/EER. Wij trekken een iets genuanceerder conclusie over HCV: migranten uit endemische landen zijn een belangrijke risicogroep op basis van de hogere prevalentie (vergeleken met de (algemene) bevolking) en relatief grote aandeel (met betrekking tot populatiegrootte). Echter, PWID en (ex)gedetineerden zijn de belangrijkste HCV risicogroep als gevolg van de zeer hoog (> 50%) prevalentie in deze twee populaties. Wat de epidemiologie onderstreept is de noodzaak van een gevoeliger benadering van risicofactoren bij het aanbieden screening aan migranten uit endemische landen, specifiek wat betreft het voorkomen van stigmatisering van (mensen) met virale hepatitis door het vermijden van nadruk op illegaal drugsgebruik, seksueel contact en criminaliteit als bron van besmetting.

We synthetiseren de lessen uit het HEPscreen Project bij het bespreken van onderzoeksvraag 2 en vaten de vijf belangrijke leerpunten voor een effectieve HBV/HCV screening bij migranten samen:

1. een eenvoudige zorgpad;
2. betrekken van/samenwerken met de tweedelijnszorg om verwijzing te vergemakkelijken;
3. het aanbieden van screening op locatie met bewustwordings/pre-test informatie;
4. beschikbaarheid van tolken/vertaalde materialen om taalbarrières op te heffen;
5. in het planningsstadium gebruik maken van de prevalentie in het geboorteland en demografische informatie om de migrantengemeenschappen met het grootste risico op chronische virale hepatitis infectie vast te stellen.

Er is een dringende behoefte aan meer implementatie studies naar screening onder migranten, in het bijzonder studies die verschillende modellen van screening vergelijken en de resultaten en de kosten over de cascade van zorg beschrijven.

De discussie richt zich op de vraag hoe de impact van screening en toegeleiding tot zorg van migrantengroepen met een verhoogd risico te maximaliseren is (onderzoeksvraag 3). Wij verhelderen twee belangrijke voorwaarden voor een optimale impact:

1. goede gegevens over de gehele cascade van de zorg;

2. het opschalen van de belangrijkste interventies en goede praktijken in het kader van een strategische aanpak.

Goede gegevens over de verschillende fases in de cascade van de zorg zijn nodig om (nationale) vooruitgang richting eliminatie te monitoren Wij verwijzen naar de eliminatie strategie en het actieplan van de WHO, met name de essentiële indicator set, als belangrijke strategische tools en frameworks die beschikbaar zijn voor landen/regio's als hulp bij het verzamelen van gegevens en de eliminatie planning. Opschaling van goede praktijken in het ontwerpen en aanbieden van screening aan risicogroepen migranten in het kader van een strategische aanpak verbetert de gezondheid van de bevolking en maakt effectief gebruik van schaarse middelen de gezondheidszorg.

De belangrijkste term hier is strategisch - het idee van het effectief gebruik maken van bestaande middelen; het in kaart brengen van bestaande interventies en op zoek gaan naar tekortkomingen in de dienstverlening en naar onontdekte synergie; van het opbouwen van partnerschappen tussen de lagen en niveaus binnen gezondheidssystemen; het gebruik van project management technieken bij de implementeren van verschillende interventies; het op de passende doelgroep richten van interventies; het gebruik maken van wetenschappelijk bewijs bij de interventie/projectontwikkeling; van een zorgvuldige financiële planning om de uitvoering te maximaliseren en verspilling te minimaliseren; en het opnemen van een evaluatie in de cyclus van de interventie/strategieontwikkeling en implementatie.

De discussie wordt afgesloten met een reeks aanbevelingen - voor onderzoek en praktijk, voor nationaal beleid en voor het EU-beleid. Deze zijn hieronder weergegeven:

Aanbevelingen voor toekomstig onderzoek en praktijk

A) Screening

1. Er is duidelijk en dringend behoefte aan meer implementatie studies van screening strategieën in risico populaties die zowel HBV als HCV bevatten, vooral onder migranten uit endemische landen.

2. Wij hebben meer voorbeelden nodig van workplace-based outreach HBV/HCV-screening onder migranten om te bepalen of, zoals in onze ervaring, dit screeningsmodel aanvaardbaar is voor de doelgroep, haalbaar is, nut heeft en wordt ondersteund door werkgevers.

3. Toekomstige screening studies moeten de goede praktijken voor toegeleiding tot zorg beschreven in dit proefschrift, elders (1) en als onderdeel van HEPscreen (2-6) gebruiken om het uitval te minimaliseren en het de gezondheid impact te maximaliseren.

4. Er is behoefte aan een gestandaardiseerd rapportagekader voor de belangrijkste resultaten van screening interventies. Dit zou minimaal moeten omvatten: deelname, prevalentie, kosten per persoon die wordt gescreend, kosten per opgespoord geval en het aantal gevallen dat de verschillende stadia van zorg bereikt (voortgang door het continuum).

5. Screening interventies moeten, waar nodig, bijkomende sociale en administratieve ondersteuning bieden aan sociaal-economische kwetsbare migranten om integratie in de samenleving en het gezondheidszorgsysteem te bevorderen.

B) Kosten efficiëntie

6. Kosteneffectiviteit modelstudies moeten de belangrijkste parameters met betrekking tot deelname, uitval en interventie kosten (in het bijzonder het uitvoeren van screening interventies) opnieuw kalibreren op basis van 'echte wereld' uitkomsten met behulp van bijvoorbeeld die uit hoofdstuk 6.

7. In toekomstige modelleringsstudies moeten de interventiekosten van screening de personeelskosten, verbruiksgoederen en logistieke middelen omvatten (evenals de vaak opgenomen kosten die alleen betrekking hebben op bloed/serummonstering en serologisch testen) die nodig zijn om mensen te werven/brengen naar gezondheidsdiensten voor screening.

8. Er is behoefte aan meer kosten-effectiviteitsstudies van screening en behandeling voor HCV maar alleen gericht op interferon-vrije DAA's. De meeste van de KEA's van screening en behandeling die zijn uitgevoerd voorafgaand aan de beschikbaarheid van interferonvrije DAA's voor HCV-behandeling, zijn waarschijnlijk overbodig.

C) Epidemiologie

9. De ontwikkeling en consistente toepassing van een EU/EER of internationale standaard voor het ontwerp en de kwaliteitsbeoordeling van seroprevalentiestudies om pooling en/of statistische vergelijking van gegevens tussen studies en populaties te ondersteunen zou inzicht in de prevalentie tussen landen en bevolkingsgroepen sterk verbeteren.

10. Toekomstige seroprevalentie onderzoeken naar HCV moeten tenminste HCV RNA meten om ervoor te zorgen dat de gegevens betrekking hebben op viraemische chronische infecties en niet alleen op blootstelling aan HCV of geklaarde infectie .

D) Nationaal beleid

11. Landen moeten (blijven) investeren in harm reduction strategieën en diensten om te IDU-verworven HBV/HCV te voorkomen. Injecterend drugsgebruik moet in de eerste plaats worden gezien vanuit het beleidsperspectief van de bescherming en bevordering van de volksgezondheid (en niet vanuit criminalisering).

12. Landen waar de anti-HCV-prevalentie in de algemene bevolking hoog wordt geschat, moeten de haalbaarheid en het nut (en kosten) van geboortecohort screening onderzoeken onder mensen geboren in de periode 1945-1965. Er is veel te leren van studies in de Verenigde Staten (7-10) en Frankrijk.(11) Van geboorte-cohort (HCV) screening is aangetoond dat het waar voor het geld is.(9)

13. Noord/West-Europese EU-Lidstaten met een lage HBsAg prevalentie moeten zich richten op (niet-prenatale) screening van migranten geboren in HBV endemische landen.

Aanbevelingen en implicaties voor het EU-beleid:

Dit onderzoek vond plaats in het gebied van de EU/EER en de studies die hierin werden opgenomen, werden gefinancierd via EU-agentschappen. Dit perspectief en de opgedane ervaring heeft geleid tot een aantal bredere beleidsimplicaties en inzichten. Deze aanbevelingen hebben tot doel de voortzetting van EU-financiering voor onderzoek en actie rond kernthema's en onderwerpen in dit proefschrift te beïnvloeden.

1. De European Medicines Agency en andere gezamenlijke medische aanbestedingsmechanismen moeten de gecombineerde koopkracht van de EU te gebruiken om te onderhandelen over een betere prijs voor toegang tot interferon-vrije DAA regimes.

2. Chronische virale hepatitis-infectie moeten expliciet worden genoemd als een van de prioriteiten voor actie in het kader van een toekomstig EU-Cross Border Threats actiekader.

3. Toekomstige en bestaande EU-Frameworks, agentschappen en andere beleidsmechanismen moeten erop gericht zijn de epidemiologische capaciteit in het midden inkomen Lidstaten met name in Centraal- en Oost-Europa op te bouwen waar er lacunes zijn in data en een waarschijnlijke hoge last van CHB/CHC.

4. De EU zou, op humanitaire gronden, systemische belemmeringen tot zorg moeten verminderen voor ongedocumenteerde migranten, asielzoekers en andere kwetsbare groepen. Universele toegang tot gezondheidszorg moet ook worden beschouwd als een hoeksteen van een succesvol Cross Border Threats programma.

5. EU financiering voor volksgezondheid projecten, vooral degenen die gericht zijn op de ontwikkeling van een toolkit/instrumenten voor de praktijk zoals HEPscreen, moeten een follow-up tranche van de begroting en gefinancierde personeelsinzet bieden voor de verspreiding en bewustwording. Deze financiering moet alleen beschikbaar zijn na de voltooiing van de instrumenten/toolkit om te zorgen dat het geoormerkt is voor de verspreiding van praktijkgerichte resultaten. Dit kan de goedkeuring en het gebruik van instrumenten/toolkits geproduceerd als onderdeel van EU health financiering verbeteren.

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ABOUT THE AUTHOR

Abby Falla was born on 9th April 1982 in Singapore. Abby grew up near Manchester in the north of England, the United Kingdom. She completed her secondary education at Priestnall High School in 1998 and her post-16 education at the Ridge Danyers College in 2001. In 2001, Abby began her undergraduate degree in Social and Political Science at the University of Sheffield. This cemented her interest in political philosophy and social justice, and awoke her interest health inequalities.

Abby graduated with Honors (degree class 2: 1) in 2004 and began her career in public health in 2005 when she joined Manchester Joint Health Unit, a local government-based policy, strategy and intervention development unit focused on reducing health inequalities. Abby was awarded Young Employee of the Year 2008 and gained a Master of Science in Public and Environmental Health from the University of Salford in 2010. In 2011, Abby moved to the Netherlands and shifted her public health career focus to scientific research.

Abby has been working as a PhD Researcher since December 2011, jointly affiliated to the Department of Public Health, Erasmus University Medical Centre and to Rotterdam-Rijnmond Municipal Health Service (GGD Rotterdam-Rijnmond) as part of an academic collaboration (CEPHIR). As part of her PhD trajectory, Abby completed a second MSc. in Public Health with the Netherlands Institute for Health Sciences (NIHES) in 2014.

At the core of Abby's PhD is the scientific output from *HEPscreen: Screening for chronic viral hepatitis among migrants in the EU*, an 11 partner consortium project across six EU countries funded by the EU Health Programme in 2011-2014. Abby led the development of the HEPscreen Toolkit (www.hepscreen.eu), an extensive online repository of specially created or collated tools to assist practitioners and policy makers in designing and delivering HBV/HCV screening among migrants. Alongside this, Abby worked on three systematic reviews/meta-analyses: two funded by the ECDC focused on the epidemiology of chronic viral hepatitis in Europe and one funded by the WHO focused on the macro-economic impact of non-communicable diseases.

Abby lives in Amsterdam with her husband Matt Webster and son Otis, together with their two cats Presto and Daisy.

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Falla AM, Veldhuijzen IK, Ahmad AA, Levi M, Richardus JH. Indications, options and restrictions for treatment of chronic hepatitis B and C in the UK, Germany, the Netherlands, Hungary, Italy and Spain.

Other publications

Chaker L*, **Falla AM***, van der Lee SJ*, Muka T, Imo D, Jaspers L, Colpani V, Mendis S, Chowdhury R, Bramer WM, Pazoki R, Franco OH. The global impact of non-communicable diseases on macro-economic productivity: a systematic review. *European Journal of Epidemiology* 2015; 30(5): 357-395.

Muka T*, Imo D*, Jaspers L, Colpani V, Chaker L, van der Lee SJ, Mendis S, Chowdhury R, Bramer WM, **Falla AM**, Pazoki R, Franco, OH. The global impact of non-communicable diseases on healthcare spending and national income: a systematic review. *European Journal of Epidemiology* 2015; 30(4): 251-277.

Jaspers L*, Colpani V*, Chaker L, van der Lee SJ, Muka T, Imo D, Mendis S, Chowdhury R, Bramer WM, **Falla AM**, Pazoki R, Franco, OH. The global impact of non-communicable diseases on households and impoverishment: a systematic review." *European Journal of Epidemiology* 2015; **30**(3): 163-188.

*denotes joint 1st authorship due to equal contribution

PHD PORTFOLIO

Summary of PhD training and teaching

Name PhD student:	Abigail M. Falla	PhD period:	2011 - 2012
Erasmus MC Department:	Public Health	Promotor(s):	Prof. Dr. Jan Hendrik Richardus
Research School:	NIHES	Supervisor:	Dr. Irene K. Veldhuijzen

1. PhD training	Year	Workload (Hours/ECTS)
General courses		
Research Integrity	2014	8 hours
Masters of Science specialisation Public Health: Netherlands Institute for Health Sciences	2012-2014	70 ECTS
Core Courses:		
Bio-statistical Methods I: Basic Principles	2013	5.7 ECTS
Bio-statistical Methods II: Classical Regression Models	2013	4.3 ECTS
Public Health Research: from Epidemiology to Health		
(a) Analysis of Population Health	2012	1.9 ECTS
(b) Analysis of Determinants	2012	1.9 ECTS
(c) Intervention Development	2012	1.9 ECTS
International Comparison of Health Care Systems	2012	1.4 ECTS
Advanced courses:		
Epidemiology of Infectious Diseases	2013	1.4 ECTS
Planning and Evaluation of Screening	2013	1.4 ECTS
Principles of Epidemiologic Data-analysis	2013	0.7 ECTS
Health Services: Research and Practice	2014	0.9 ECTS
Erasmus Summer Programme		
Principles of Research in Medicine	2012	0.7 ECTS
Methods of Public Health Research	2012	0.7 ECTS
Primary and Secondary Prevention Research	2012	0.7 ECTS
Social Epidemiology	2012	0.7 ECTS
Introduction to Global Public Health	2012	0.7 ECTS
Methods of Health Services Research	2012	0.7 ECTS
History of Epidemiologic Ideas	2013	0.7 ECTS
Clinical Decision Analysis	2013	0.7 ECTS
Health Economics	2013	0.7 ECTS
Principles of Genetic Epidemiology	2013	0.7 ECTS
Causal Inference	2014	0.7 ECTS
Topics in Meta-analysis	2014	0.7 ECTS
Seminars and workshops		
EUPHA Migrant and Ethnic Minority Health, Granada	2014	0.8 ECTS

1. PhD training	Year	Workload (Hours/ECTS)
Presentations		
European Association for the Study of the Liver (EASL) Annual Conference, Amsterdam, Netherlands (Poster)	2013	0.2 ECTS
Holland Fuse: "How to get practice into science?", Noordwijkhout, Netherlands (Elevator Pitch)	2013	0.4 ECTS
European Public Health Association (EUPHA) Annual Conference, Brussels (Poster)	2013	0.2 ECTS
European Public Health Association (EUPHA) Annual Conference, Brussels (Oral Poster Presentation)	2013	0.3 ECTS
EUPHA Migrant and Ethnic Minority Health, Granada, Spain (Poster)	2014	0.2 ECTS
EUPHA Migrant and Ethnic Minority Health, Granada, Spain (Oral Poster Presentation)	2014	0.3 ECTS
HEPscreen Final Conference (project summary presentation), (Satellite to HepHIV in Europe) Barcelona, Spain	2014	0.5 ECTS
(Inter)national conferences		
European Association for the Study of the Liver (EASL) Annual Conference	2013	1 ECTS
Holland Fuse: "How to get practice into science?", Noordwijkhout, Netherlands	2013	1 ECTS
European Public Health Association (EUPHA) Annual Conference, Brussels, Belgium	2013	1 ECTS
EUPHA Migrant and Ethnic Minority Health, Granada, Spain	2014	1 ECTS
HepHIV in Europe, Barcelona, Spain	2014	1 ECTS
HEPscreen Final Conference	2014	1 ECTS
Supervising Master's theses		
VUMC MSc. thesis supervision	2014	100 hours