The State of Hepatitis B and C in the Mediterranean and Balkan Countries: Report from a Summit Conference

A. Hatzakis,1 P. Van Damme,2 K. Alcorn,3 C. Gore,4 M. Benazzouz,5 S. Berkane,6 M. Buti,7 M. Carballo,8 H. Cortes Martins,9 S. Deuffic-Burban,10,11 A. Dominguez,12 M. Donoghoe,13 A-N. Elzouki,14,15 N. Ben-Alaya Bouaff,16 G. Esmat,17 R. Esteban,18 M. Fabri,19 K. Fenton,20 D. Goldberg,21 I. Goulis,22 T. Hadjichristodoulou,23 T. Hatzigeorgiou,24 O. Hamouda,25 S. Hasurdjievi,26 S. Hughes,24 A. Kautz,26 M. Malik,27 S. Manolakopoulos,28 M. Matiic,29 G. Papatheodoridis,30 R. Peck,31 A. Peterle,24 G. Potamitis,32 D. Prati,33 F. Roudot-Thoraval,34 T. Reic,26 A. Sharara,35 M. Shennak,36 G. Shiha,37 D. Shouval,38 M. Soican,39 H. Thomas,40 M. Thursz,40 M. Tosti,41 C. Trepo,42,43,44 A. Vince,45 E. Vounou,46 L. Wiessing,47 and M. Manns48 1Athens University Medical School, Athens, Greece; 2Viral hepatitis Prevention Board, Vaccine & Infectious Disease Institute, University of Antwerp, Antwerp, Belgium; 3VAM Publications/infohep.org, London, UK; 4Hepatitis C Trust, London, UK; 5Ibn Sina Hospital, Rabat, Morocco; 6Department of Medicine and Gastroenterology, Bologna hospital, Algers, Algeria; 7Department of Internal Medicine, Hospital Universitari Vall d'Hebron, Barcelona, Spain; 8International Center for Migration Health and Development, Geneva, Switzerland; 9Departamento de Doencas Infecciosas, Instituto Nacional de Sâde Dr Ricardo Jorge, Lisbon, Portugal; 10Inserm U995, Université Lille Nord de France, Lille, France; 11TIP-AVENIR Inserm “Modélisation, Aide à la Décision, et Coût-Efficacité en Maladie Infectieuse.” U78, Université Denis Diderot, Paris, France; 12Departamento de Salut Pública, Universitat de Barcelona, CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain; 13World Health Organization Regional Office for Europe, Copenhagen, Denmark; 14Department of Medicine, Hamad General Hospital, HMC, Doha, Qatar; 15Faculty of Medicine, Benghazi University, Benghazi, Libya; 16Observatory of New and Emerging Diseases, Ministry of Health, Tunis, Tunisia; 17Endemic Medicine and Hepatogastroenterology Department, Faculty of Medicine, Cairo University, Cairo, Egypt; 18Internal Medicine and Liver Unit of the Hospital Universitari Vall d’Hebron, Barcelona, Spain; 19Clinic for Infectious Diseases, Clinical Center Vojvodina, Novi Sad, Serbia; 20Health and Wellbeing Directorate, Public Health England, London, UK; 21Group for Blood Borne Viruses, Sexually Transmitted Infections, Vaccine Preventable Diseases and Respiratory Infections, Health Protection Scotland, Glasgow, UK; 224th Department of Medicine, Aristotelian University of Thessaloniki, Thessaloniki, Greece; 23Department of Hygiene and Epidemiology, University of Thessaly, Larissa, Greece; 24European Parliament, Brussels, Belgium; 25Department for Infectious Disease Epidemiology, Robert Koch Institute, Berlin, Germany; 26European Liver Patients Association, Sint Truiden, Belgium; 27Pandemic and Epidemic Disease, World Health Organization Regional Office for the Eastern Mediterranean, Cairo, Egypt; 28Department of Gastroenterology, Athens Medical School, Hippokratio General Hospital, Athens, Greece; 29Clinic for Infectious Diseases and Febrile Illnesses, University Medical Centre Ljubljana, Ljubljana, Slovenia; 302nd Department of Internal Medicine, Athens University Medical School, Athens, Greece; 31World Hepatitis Alliance, Geneva, Switzerland; 32Pancyprian Medical Association, Nicosia, Cyprus; 33Department of Transfusion Medicine and Hematology, Ospedale Alessandro Manzoni, Lecco, Italy; 34Département de Santé Publique, Hôpital Henri Mondor – AP-HP, Université Paris-Est-Créteil, Créteil, France; 35American University Medical Center, Beirut, Lebanon; 36Jordan University Hospital, Amman, Jordan; 37Egyptian Liver Research Institute and Hospital, Cairo, Egypt; 38Liver Unit, Hadassah-Hebrew University Hospital, Jerusalem, Israel; 39National Institute of Public Health, Ljubljana, Slovenia; 40Imperial College, London, UK; 41Istituto Superiore di Sanità, National Centre of Epidemiology, Surveillance and Health Promotion, Rome, Italy; 42Service d’Hépatologie, Hospices Civils de Lyon, Hôpital de la Croix-Rousse, Lyon, France; 43CRLC/INSERM U1052, Lyon, ; 44Université Lyon 1, Lyon; 45Croatian Referral Center for Diagnostics and Treatment of Viral Hepatitis, Zagreb, Croatia; 46Limassol General Hospital, Limassol, Cyprus; 47European Monitoring Centre for Drugs and Drug Addiction, Lisbon, Portugal; and 48Department of Gastroenterology, Hepatology and Endocrinology, Medical School of Hannover, Hannover, Germany

Abbreviations: AIDS, acquired immunodeficiency syndrome; ALT, alanine aminotransferase; CASCADE, Concerted Action on SeroConversion to AIDS and Death in Europe (Collaboration); DAA, directly acting antiviral (drug); DALY, disability-adjusted life year; DDG, Director General for Health and Consumers; EASL, European Association for Study of the Liver; EC DG, Research European Commission Directorate General for Research and Innovation; EMCDDA, European Monitoring Centre for Drugs and Drug Addiction; EMRO, World Health Organization Regional Office for the Eastern Mediterranean; ETV, entecavir; EU, European Union; FYROM, the Former Yugoslav Republic of Macedonia; GDP, gross domestic product; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis delta virus; HIV, human immunodeficiency virus; IDU, injecting drug user; IFN, interferon; MSM, men who have sex with men; NAT, nucleic acid testing; PAT, parenteral antischistosomal therapy; PEG-INF, pegylated interferon; QALY, quality-adjusted life year; STI, sexually transmitted infection; SVR, sustained virological response; TDF, tenofovir; UK, United Kingdom; USA, United States of America; VHPB, Viral Hepatitis Prevention Board; WHO, World Health Organization.

Correspondence: Angelos Hatzakis, Professor of Epidemiology and Preventive Medicine, Head, National Retrovirus Reference Center, Director, Department of Hygiene, Epidemiology and Medical Statistics, Athens University Medical School, 75, Mikras Asias str, Athens 11527, Greece. E-mail: ahatzak@med.uoa.gr
SUMMARY. The burden of disease due to chronic viral hepatitis constitutes a global threat. In many Balkan and Mediterranean countries, the disease burden due to viral hepatitis remains largely unrecognized, including in high-risk groups and migrants, because of a lack of reliable epidemiological data, suggesting the need for better and targeted surveillance for public health gains. In many countries, the burden of chronic liver disease due to hepatitis B and C is increasing due to ageing of unvaccinated populations and migration, and a probable increase in drug injecting. Targeted vaccination strategies for hepatitis B virus (HBV) among risk groups and harm reduction interventions at adequate scale and coverage for injecting drug users are needed. Transmission of HBV and hepatitis C virus (HCV) in healthcare settings and a higher prevalence of HBV and HCV among recipients of blood and blood products in the Balkan and North African countries highlight the need to implement and monitor universal precautions in these settings and use voluntary, nonremunerated, repeat donors. Progress in drug discovery has improved outcomes of treatment for both HBV and HCV, although access is limited by the high costs of these drugs and resources available for health care. Egypt, with the highest burden of hepatitis C in the world, provides treatment through its National Control Strategy. Addressing the burden of viral hepatitis in the Balkan and Mediterranean regions will require national commitments in the form of strategic plans, financial and human resources, normative guidance and technical support from regional agencies and research.

INTRODUCTION

Globally, around 2 billion people have been infected with the hepatitis B virus (HBV), and around 150 million with the hepatitis C virus (HCV) [1]. In 2010, it was estimated that 786 000 deaths worldwide were attributable to hepatitis B and 455 000 to hepatitis C, making hepatitis B the 15th ranked and hepatitis C the 22nd ranked cause of death worldwide [2, 3].

Approximately 14 million people in the World Health Organization (WHO) European Region are estimated to be infected with hepatitis B and 9 million with hepatitis C. Each year, they cause around 36 000 and 86 000 deaths, respectively, with the number of deaths reported to be increasing [4]. The WHO Regional Office for the Eastern Mediterranean Region estimates that 17 million people have chronic HCV infection, and 170 million have chronic HBV infection; each year, around 800 000 new HCV infections and 4.3 million new HBV infections occur in the region [5].

Awareness of the global threat constituted by hepatitis B and C infections led the World Health Assembly in 2010 to pass a resolution urging Member States to take comprehensive action to combat both infections by improvements in screening, vaccination, treatment and prevention. Together with these improvements, rapid progress in drug discovery now affords the prospect of an eventual cure for the majority of people infected with hepatitis C. In 2012, WHO published a Framework for Global Action (see Panel 1) [1].

The Balkan and Mediterranean countries face particular challenges in relation to viral hepatitis due to a legacy of war, displacement and civil unrest in many of these countries. The scale of the public health problem posed by hepatitis B and C remains largely unrecognized due to limited surveillance, poor public awareness and a lack of advocacy in comparison with other infectious diseases. As countries of the Balkans progress towards European Union (EU) accession, and closer trade links develop throughout the Mediterranean region, it is essential for policy makers and stakeholders in the EU to pay greater attention to public health issues in neighbouring states and to support responses to viral hepatitis. Promoting the health of migrants and other marginalized populations, particularly people who inject drugs, will also have a substantial impact on the future burden of chronic liver disease in the EU.

Panel 1: WHO Framework for Global Action on Viral Hepatitis

The Framework for Global Action has four domains:
- Axis one: Increase engagement through awareness, partnerships and mobilizing resources.
- Axis two: Evidence-based policy and data for action.
- Axis three: Prevention of virus transmission by the promotion of vaccination and behavioural and structural interventions.
- Axis four: Screening, care and treatment: develop guidelines and advocate and negotiate for price reductions for treatment, assist countries in developing national strategies.

Following a European Summit Conference on Hepatitis B and C in Europe in 2010, the Hepatitis B and C Public Policy Association organized a meeting in December 2012 for stakeholders in the EU, Balkan and Mediterranean regions.
bringing together expert clinicians, specialists in public health, national policy makers, EU institutions and patient groups from 26 countries to review the current situation and identify opportunities for action. This article summarizes the main findings presented to the conference, the conclusions of its discussions and a Call to Action.

Epidemiology

Prevalence
The prevalence of hepatitis B surface antigen (HBsAg) in the WHO European Region varies from 0.1% in Ireland and the Netherlands to >7% in Eastern Turkey and is higher in south and central Europe (Turkey, Romania, Bulgaria and Greece). Data on prevalence among the general population are lacking in most of the countries, and burden of disease and mortality data are not available for countries with the highest prevalence [6].

The prevalence of HCV antibody ranges from 0.4% in Sweden, Germany and the Netherlands to >2.2% in Italy (although the studies on HCV prevalence in Italy are old and not representative of the general population). The prevalence of HCV in Italy is much higher than that of HBV, probably because of a period of increased iatrogenic transmission in the 1950s [6].

There are large numbers of chronically HBV- and HCV-infected migrants in countries such as Germany, Spain, France, Italy, Greece and the United Kingdom (UK). They remain unidentified, as they and other risk groups are often not included in general population screening studies. A study among immigrants to six EU countries found high rates of HBsAg positivity among migrant populations [7]. In France, the prevalence of anti-HCV is much higher among natives of the Middle East (10.2%) than in the indigenous French population (0.73%) [8]. In Portugal and Greece, both countries with large migrant populations, studies conducted between 2006 and 2008 found high rates of HBsAg among pregnant immigrants and children of migrants [9], and pregnant Albanian and Asian refugees [10,11].

Information on the prevalence of chronic hepatitis B and C infections is lacking in most of the Mediterranean and Balkan states due to limited screening and surveillance (see Tables 1 & 2). With the exception of Croatia [12–14], there is very little information on recent prevalence in high-risk groups such as injecting drug users (IDUs), healthcare workers, men who have sex with men (MSM) and sex workers.

General population prevalence of HBsAg tends to be higher in the Balkan, North African and eastern Mediterranean countries than in northern and central Europe, and similar to prevalence in European Mediterranean countries. Surveys for anti-HCV prevalence carried out in North Africa and the Middle East since 2008 suggest a general population prevalence of 1.69% in Lebanon (presentation by AI Sharara at Hepatitis B and C in the Mediterranean and Balkan countries, December 2012), 1.3% in Libya and 14.7% in Egypt [15,16].

The high prevalence of HCV in Egypt is most likely due to a history of parenteral antischistosomal therapy (PAT) and is perhaps one of the most illustrative examples of iatrogenic transmission. Prevalence is higher in those >30 years, reflecting the exposure index to PAT [17], and is highest in those aged 55–59 years (39.4%) [16].

Prevalence of hepatitis delta virus
The hepatitis delta virus (HDV) is a defective RNA virus that can infect only individuals who have hepatitis B. Coinfection with HBV/HDV causes severe liver disease with rapid progression to cirrhosis and liver decompensation; diagnosis is difficult as there are no specific clinical or histological features.

The prevalence of HDV is declining in some endemic areas but increasing in northern and central Europe because of migration [18]. A study from Hannover in 2006 found a prevalence of anti-HDV/HBsAg positivity of 11.3% among 2354 subjects, of which 26% were from Turkey and 28% from East Europe [19]. Another study from London found a high prevalence among immigrants from southern and eastern Europe (28.1%), Africa (26.8%) and the Middle East (7.3%) [20]. A study from Egypt found that HDV coinfection in HBV carriers is related to severity of liver disease [21]. Improved detection of such cases is needed, as HDV does not respond well to treatment (response rate 20–25%), and relapse rates are high as long as HBsAg is positive.

Burden of chronic liver disease
In many southern European countries, the burden of chronic liver disease due to hepatitis B is increasing due to ageing of unvaccinated populations, and hepatitis C acquired due to injecting drug use. In Italy, although the incidence of both HBV and HCV is decreasing, the burden of associated chronic liver disease due to past epidemics is substantial (330 000) and is highest in the population aged 60 years and above, reflecting vaccination coverage of the population below 31 years (M. Luin Personal communication; Italian Ministry of Health, 2012) [22].

Chronic hepatitis and cirrhosis are among the top ten causes of death in Portugal, but there is no public health programme on liver disease. In Spain, cirrhosis accounted for 17 684–20 897 disability-adjusted life years (DALYs) lost due to HCV-related chronic hepatitis and 5021 DALYs lost due to chronic hepatitis B in 2006. Hepatocellular carcinoma (HCC) due to chronic hepatitis C and B was responsible for 12 005–14 004 DALYs and 2005 DALYs lost, respectively [23].

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### Table 1 Prevalence estimates of hepatitis B surface antigen and antibody against HCV in the non-EU Mediterranean states

<table>
<thead>
<tr>
<th>Country</th>
<th>Population (2011)</th>
<th>HBsAg General population</th>
<th>HCV Ab General population</th>
<th>HBsAg Blood donors</th>
<th>HCV Ab Blood donors</th>
<th>HBsAg Haemodialysis</th>
<th>HCV Ab Haemodialysis</th>
<th>HBsAg Injecting drug users</th>
<th>HCV Ab Injecting drug users</th>
<th>HBsAg Healthcare workers</th>
<th>HCV Ab Healthcare workers</th>
<th>HBsAg Pregnant women</th>
<th>HCV Ab Pregnant women</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Israel</td>
<td>7.7 million</td>
<td>1.96% (2001-2010)</td>
<td>9.9%</td>
<td>0.1% (2011)</td>
<td>0.05% (2011)</td>
<td>1.8% (2000)</td>
<td>0.7% (2008)</td>
<td>5.9% (2008)</td>
<td>24.5% to −30.5% (2008)</td>
<td>0.75–1.5%</td>
<td>3% (2009)</td>
<td>4–5.7% (1996)</td>
<td>0.2–1.7% (1996)</td>
<td></td>
</tr>
<tr>
<td>Jordan</td>
<td>6.5 million</td>
<td>9.9%</td>
<td>0.7 to −1.5%</td>
<td>0.1% (2011)</td>
<td>0.05% (2011)</td>
<td>1.8% (2000)</td>
<td>0.7% (2008)</td>
<td>5.9% (2008)</td>
<td>24.5% to −30.5% (2008)</td>
<td>0.75–1.5%</td>
<td>3% (2009)</td>
<td>4–5.7% (1996)</td>
<td>0.2–1.7% (1996)</td>
<td></td>
</tr>
<tr>
<td>Lebanon</td>
<td>4.2 million</td>
<td>1.6% (2011)</td>
<td>0.2% (2011)</td>
<td>2.2% (2013)</td>
<td>1.3% (2013)</td>
<td>0.75–1.5%</td>
<td>3% (2009)</td>
<td>4–5.7% (1996)</td>
<td>0.2–1.7% (1996)</td>
<td>2.62% (2007)</td>
<td>13% (2005)</td>
<td>1.3% (2005)</td>
<td>1.3% (2005)</td>
<td></td>
</tr>
<tr>
<td>Libya</td>
<td>6 million</td>
<td>0.7% (2007)</td>
<td>0.23% (2007)</td>
<td>2.2% (2013)</td>
<td>1.3% (2013)</td>
<td>0.75–1.5%</td>
<td>3% (2009)</td>
<td>4–5.7% (1996)</td>
<td>0.2–1.7% (1996)</td>
<td>0.7% (2007)</td>
<td>13% (2005)</td>
<td>1.3% (2005)</td>
<td>1.3% (2005)</td>
<td></td>
</tr>
<tr>
<td>Morocco</td>
<td>32.3 million</td>
<td>2.62% (2007)</td>
<td>13% (2005)</td>
<td>0.75–1.5%</td>
<td>3% (2009)</td>
<td>0.75–1.5%</td>
<td>3% (2009)</td>
<td>4–5.7% (1996)</td>
<td>0.2–1.7% (1996)</td>
<td>0.7% (2007)</td>
<td>13% (2005)</td>
<td>1.3% (2005)</td>
<td>1.3% (2005)</td>
<td></td>
</tr>
<tr>
<td>Tunisia</td>
<td>10 million</td>
<td>2.62% (2007)</td>
<td>13% (2005)</td>
<td>0.75–1.5%</td>
<td>3% (2009)</td>
<td>0.75–1.5%</td>
<td>3% (2009)</td>
<td>4–5.7% (1996)</td>
<td>0.2–1.7% (1996)</td>
<td>0.7% (2007)</td>
<td>13% (2005)</td>
<td>1.3% (2005)</td>
<td>1.3% (2005)</td>
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</table>

EU, European Union; HBsAg, hepatitis B surface antigen; HCV Ab, antibody against hepatitis C virus.

Source: Speakers’ presentations at the Conference on Hepatitis B and C in Mediterranean and Balkan countries.
Croatia’s national cancer registry reports a slowly increasing burden of HCC, although the incidence of HCV is declining [24].

In Egypt, mortality due to HCC is increasing. Whereas chronic HCV infection accounted for 65% of HCC in 1995 and chronic HBV infection for 9% [25], in 2010, chronic HCV infection accounted for 94% of HCC and chronic HBV infection for 4% (Gomaa et al., National Liver Institute, unpublished data, 2010). The reason for the declining proportion with chronic hepatitis B could be the increasing effect of vaccination of the population against HBV in childhood.

MAJOR ROUTES OF EXPOSURE AND PRIORITIES FOR PREVENTION

Both hepatitis B and C are bloodborne viruses; hepatitis B can also be transmitted through contact with contaminated body fluids. Transmission may be both perinatal, as from mother to child, and horizontal, as in other cases. The predominant modes of transmission vary across the EU, Balkans, Mediterranean and North African countries, depending on cultural practices, screening for blood and organ donors, prevalence of specific risk behaviours such as injecting drug use, and the extent to which universal precautions against bloodborne virus transmission are consistently implemented.

INJECTING DRUG USE

Sharing of injecting equipment among IDUs accounts for a substantial proportion of transmission of HCV infection (and to a lesser extent of HBV) in European countries. Preliminary data from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in 2010 suggest a possible increase in the seroprevalence of both HBV and HCV among IDUs in some EU and Balkan countries, suggesting inadequate harm reduction interventions for IDUs and/or increasing levels of drug injecting. Data are not available on the magnitude of injecting drug use in the North African countries, probably because of a lack of research into this hidden population.

Levels of HCV antibody prevalence among IDUs in the EU vary widely, ranging from <25% in some studies among IDUs in the Czech Republic, Hungary and Slovenia to >75% in some studies from Belgium, Italy, Portugal and Romania in 2009–2010 [26]. Among young IDUs <25 years, HCV prevalence is increasing in Bulgaria, Cyprus, Greece, Romania and Austria, and among new IDUs in Greece [27, 28].

In the Balkan countries, preliminary unconfirmed data suggest that, among IDUs, the prevalence of HCV is increasing in Bosnia and Herzegovina, Kosovo, the Former Yugoslav Republic of Macedonia (FYROM) and Serbia varying from 24% in Kosovo to >80% in FYROM. In Albania, HCV
prevalence is low (5–9%) but HBV prevalence is very high and increasing (12–18%). Prevalence data are largely lacking for IDUs in North Africa and the Eastern Mediterranean.

**Harm reduction**

Harm reduction interventions to reduce transmission among IDUs are vaccination, needle and syringe programmes (NSPs), opioid substitution therapy (OST) and testing and treatment. Combining or integrating these services could lead to better results, for example, OST and treatment for viral hepatitis. The EMCDDA recommends targeted service delivery designed to meet the needs of drug users [29]. NSPs have been introduced in EU Member States but the scale and coverage are probably not enough to interrupt transmission. An IDU may inject hundreds of times in a year; ideally, this should be with clean injecting equipment each time to stop sharing of injecting equipment. The average number of syringes and needles distributed through specialized programmes per IDU from 2009 to 2010 was the highest in Norway (>300) followed by Luxembourg (>200), but in many countries, it falls far short of what is needed [30].

In the Balkan countries, NSPs and OST are available in Albania, Bosnia and Herzegovina, Macedonia (FYROM), Montenegro and Serbia, although the scale and coverage are low. Kosovo has only one NSP, and OST was introduced in 2012. In many Mediterranean and North African countries, NSPs and OST are not available [31], although OST has been recently introduced in Morocco.

**HEALTHCARE SETTINGS**

Transmission of HBV and HCV in healthcare settings due to poor infection control practices has been observed in many Balkan and Mediterranean countries. High HCV prevalence has been reported in a number of countries, including Bosnia and Egypt, leading to the implementation of dedicated dialysis facilities for chronic HCV patients in the latter country [32,33]. In Italy, according to the estimate of the population attributable risks, dental therapy accounted for 12.9% of HBV infections, and nosocomial exposure for 11.4% of HBV and 48.7% of HCV infections between 2007 and 2011 (Italy’s Integrated Epidemiological System for the Surveillance of Acute Viral Hepatitis [SEI-EVA], 2007–2011, unpublished data). In Spain, outbreaks of HCV infection were reported among 395 persons in diverse healthcare settings from 1996 to 2009 [34]. In another study from Spain, hospital admission accounted for 73% of HCV infections compared with 9% for injecting drug use [35]. There is thus a need to implement and monitor universal precautions across a wide range of healthcare settings in the Balkan and Mediterranean countries.

**Inadequate screening of blood**

Many epidemics of hepatitis C in the Balkan and Mediterranean areas were seen in the aftermath of wars in the past two decades, largely due to inadequate screening of blood donors and rapid demand for blood [36]. In Bosnia, screening for HCV among blood donors was introduced only in 1995 at the end of the war [32]. Although 100% of the blood supply is now screened for HBsAg and anti-HCV, in the North African countries, recipients of blood and blood products have a much higher prevalence of HBV and HCV, as in Egypt and Tunisia [37,38], probably because of the large number of paid, replacement and infected first-time donors. More emphasis is needed on procuring voluntary, nonremunerated, repeat donors.

**Blood, organ and injection safety**

Screening for HBsAg and anti-HCV is highly effective in preventing transmission of bloodborne HBV and HCV, although infection may still be transmitted during the window period. Many countries have implemented HCV RNA and HBV DNA testing and nucleic acid testing (NAT) for blood and organ donors to identify infections in the window period. However, the cost of NAT is very high, and there is insufficient evidence to recommend routine NAT in developing and middle-income countries.

In Europe and the southern Mediterranean countries, blood supply and transplant procedures are very safe. In the Balkans, blood transfusion is generally safe due to mandatory donor screening for HBsAg, HCV and human immunodeficiency virus (HIV). Kosovo, for example, has an HBV prevalence among blood donors of 4.2%, and HCV prevalence of 0.3%, which is similar to that for other South-East European countries [39]. However, a cause for concern is the high percentage of paid donors, as in Albania (23%), and hepatitis B-infected first-time donors, such as in Romania, Bulgaria, Moldova, Serbia and Montenegro, Bosnia and Herzegovina, with the highest percentage in Albania (76.2%). The use of replacement donors ranges from 71.5% in Albania to 96% in Moldova [40]. In addition, national transfusion services are fragmented, resulting in incomplete reporting of data on transfusion safety, haemovigilance and appropriate use of blood.

Globally, about 40–70% of all injections are believed to be unsafe and account for 33% of cases of hepatitis B and 42% of hepatitis C [41]. In Tunisia, intramuscular injections appear to play an important role in the horizontal transmission of HBV via inadequately sterilized syringes used for iatrogenic intramuscular injections in a community with high HBV prevalence [42]. Activities to prevent transmission in healthcare settings must address high rates of reuse of needles and syringes, improper sterilization procedures, financial pressure to reuse needles and syringes, lack of implementation of
universal precautions, low HBV vaccination rates of healthcare workers and the lack of accountability at facility and health system level for failures in infection control. A mathematical model estimated that, in 2004, in the WHO Eastern Mediterranean Region, approximately 2.5 million HBV infections and 645 000 HCV infections could be attributed to unsafe injections annually [43].

**Cosmetic and cultural practices**

Household transmission of hepatitis B (intrafamilial) is a common route of infection in countries such as Tunisia and Jordan due to practices such as scarification, tattooing, circumcision, body piercing and hijama or wet cupping, a form of traditional Arab medicine [44]. In Italy, between 2007 and 2011, 20% of the notified acute hepatitis B and 12.5% of acute hepatitis C infections were attributable to percutaneous exposures during cosmetic procedures (SEIEVA 2007–2011, unpublished data). Better education of those who practise these procedures, screening and observance of universal precautions are needed in these settings.

**Transmission in closed settings**

Prison populations seem to have a much higher prevalence of both HBV and HCV. Prison inmates in Slovenia had a high prevalence of anti-HCV (26%) [45,46], while in Croatia, Italy and Egypt, they had a high prevalence of both HBV and HCV [47–49]. Injecting drug use and tattooing in prisons are likely to contribute to the high prevalence among current and former prisoners.

**SEXUAL EXPOSURE**

In Italy, of the notified acute HBV and HCV infections, 10.3% and 22%, respectively, were attributable to sexual intercourse (SEIEVA 2007–2011, unpublished data).

Evidence is emerging of increasing transmission of HCV among HIV-positive MSM in Europe. Data from 12 cohorts within the Concerted Action on SeroConversion to AIDS and Death in Europe (CASCADE) Collaboration showed that HCV incidence had been increasing among HIV-infected MSM from the mid-1990s, but increased much faster after 2002 [50]. Data on coinfection in the Balkans and southern Mediterranean are lacking.

**PREVENTION**

**Vaccination**

WHO recommends universal vaccination of newborns and catch-up vaccination for those born before the start of universal infant immunization in a country, and for those with risk factors for acquiring hepatitis B, such as IDUs, MSM, sexually transmitted infection (STI) clinic attendees, healthcare workers and those with multiple sex partners.

In 2009, 22 EU countries had universal vaccination programmes, and seven had targeted vaccination programmes. Most countries had selective vaccination programmes for risk groups [51].

Many countries in the Mediterranean region have noted a sharp decline in the number of notified cases of hepatitis B after the introduction of universal vaccination. For example, in Greece, following vaccination programmes, the prevalence of HBsAg has fallen, particularly among migrants and the Muslim minority [52]. In Italy, notifications of acute cases of hepatitis B fell sharply after the start of HBV vaccination in 1992 (SEIEVA 1985–2011, unpublished data). However, cases of hepatitis B were observed among risk groups who should have been vaccinated and were not, such as healthcare workers, household members of HBsAg-positive individuals and IDUs in treatment centres, highlighting the need to specifically target these groups (SEIEVA 2001–2011, unpublished data). Notification of cases of acute hepatitis B among immigrants has also been declining, which could be accounted for by vaccination for hepatitis B in the countries of origin or in Italy, and by herd immunity [SEIEVA 2004–2011, unpublished data].

In Catalonia (Spain), despite the introduction and high coverage of universal vaccination among pre-adolescents since 1991 and infants since 2002, no reduction in the incidence of HBV infection has been observed since 2001. Statistical models suggest that the incidence has increased due to immigration. Vaccination strategies for risk groups should thus be applicable to susceptible immigrants (children and adolescents) from countries with high or intermediate prevalence where hepatitis B vaccination programmes have still not been launched or where coverages are low [53].

Among the Mediterranean and North African countries, Tunisia, Jordan and Egypt reported sharp declines in the incidence of hepatitis B after the introduction of universal vaccination programmes. While most countries have a policy for universal vaccination of newborns, most do not have standardized policies for vaccination of risk groups, and few have catch-up immunization programmes for adolescents. Algeria, Morocco, Tunisia and Israel provide vaccination to healthcare workers (data from presentations at Hepatitis B and C in the Mediterranean and Balkan Countries, December 2012). Libya provides voluntary vaccination to persons from high-risk groups free of charge since 1999 [54,55].

**SCREENING**

Both HBV and HCV are silent diseases with high morbidity and mortality. Screening programmes for early diagnosis, followed by referral to care and treatment, could result in considerable public health gains [6].
The World Health Organization is developing guidelines on screening, treatment and care for viral hepatitis for publication in 2013. At present, high-risk populations such as migrants, IDUs, prisoners, STI clinic attendees and MSM are not screened routinely within the EU or neighbouring countries. A study by WHO EURO among 41 EU countries found that a national policy for screening followed by referral to care was in place in 51% of countries for hepatitis B, and 49% for hepatitis C (WHO/World Hepatitis Alliance/University of Copenhagen. Viral hepatitis: global prevention and control report; preliminary results).

Screening practices are limited in most countries of North Africa and the Middle East, and few countries in the Balkans have yet developed systematic screening practices (see Tables 3 & 4).

There is a lack of evidence on the cost effectiveness of screening, with the exception of screening for HCV among IDUs and migrants in one country and for HBV among pregnant women [6]. A study from the Netherlands demonstrated the cost effectiveness of screening for chronic hepatitis B among migrants \(\text{€9000 per quality-adjusted life year (QALY) gained, 56.}\) The US Preventive Task Force in 2012 recommended screening for HCV infection in adults at high risk, including those with a history of injecting drug use or blood transfusions prior to 1972, and one-time screening for HCV among all those born between 1945 and 1965 [57]. Screening in this population has

---

**Table 3** Comparative HBV and HCV screening policies in the non-EU Mediterranean countries

<table>
<thead>
<tr>
<th>Screening Category</th>
<th>Algeria</th>
<th>Egypt</th>
<th>Israel</th>
<th>Jordan</th>
<th>Lebanon</th>
<th>Libya</th>
<th>Morocco</th>
<th>Tunisia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antenatal screening</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>HBV</td>
<td>HBV</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Blood and organ donors</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Blood transfusion or products prior to 1992 in EU, or any transfusion outside EU</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Clinical signs or laboratory signs (including cirrhosis and HCC)</td>
<td>Both</td>
<td>Both</td>
<td>HCV</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Candidates for chemotherapy or immunosuppressive treatment</td>
<td>Both</td>
<td>Both</td>
<td>HBV</td>
<td>HBV</td>
<td>HBV</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Haemophiliacs who received concentration factors prior to 1987</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>HBV</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>History of shared injecting equipment</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>History of long-term imprisonment</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Hospital surgery patients</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Household contacts</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>HIV</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>IVF candidates</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Men who have sex with men</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Migrants from high prevalence countries</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Military recruits</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Organ or tissue transplants prior to 1992 in EU, or outside EU</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Pre-employment</td>
<td>Both</td>
<td>HCV</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Pregnant women and newborns</td>
<td>Both</td>
<td>HBV</td>
<td>Both</td>
<td>HBV</td>
<td>HBV</td>
<td>HBV</td>
<td>HBV</td>
<td>HBV</td>
</tr>
<tr>
<td>Prenuptial</td>
<td>Both</td>
<td>HBV</td>
<td>Both</td>
<td>HBV</td>
<td>HBV</td>
<td>HBV</td>
<td>HBV</td>
<td>HBV</td>
</tr>
<tr>
<td>STI clinic patients</td>
<td>Both</td>
<td>Both</td>
<td>HBV</td>
<td>Both</td>
<td>Both</td>
<td>HCV</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Traditional medicine exposure</td>
<td>HBV</td>
<td>Both</td>
<td>HBV</td>
<td>Both</td>
<td>Both</td>
<td>HCV</td>
<td>Both</td>
<td>Both</td>
</tr>
<tr>
<td>Unvaccinated healthcare workers</td>
<td>Both</td>
<td>Both</td>
<td>HBV</td>
<td>Both</td>
<td>Both</td>
<td>HBV</td>
<td>Both</td>
<td>HBV</td>
</tr>
<tr>
<td>Occupational exposure and/or carrying out exposure-prone procedures</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>Both</td>
<td>HBV</td>
<td>Both</td>
<td>HBV</td>
</tr>
</tbody>
</table>

EU, European Union; HBV, hepatitis B virus; HCV Ab, hepatitis C virus.

Source: Speakers’ presentations at the Conference on Hepatitis B and C in Mediterranean and Balkan countries.

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been found to be as cost effective as other routine screening programmes [58].

SCREENING FOR MIGRANTS

Bloodborne hepatitis viruses (B, C and D) occur at varying prevalence in all regions of the world. Global population movements caused by economic migration, war and civil unrest are changing the global distribution of viral hepatitis. Migrant populations often represent the ‘overlap’ between viral hepatitis epidemics in the EU and those in their countries of origin in the Balkan and Mediterranean regions.

A recent systematic review and meta-analysis found a high prevalence of chronic hepatitis B infection (7%) among migrants in 110 pooled studies, particularly those from East Asia and sub-Saharan Africa, and among refugees [59]. Similarly, a comparison of hepatitis B prevalence in the three largest migrant populations in six northern European countries showed a five- to forty-fold higher prevalence among these populations when compared with the overall population prevalence [7].

The importance of targeting migrants in surveillance studies cannot be overemphasized. New and undocumented migrants may prefer to stay hidden, and have pressing priorities such as food, shelter, sanitation, and may not opt for detection and treatment of chronic, silent conditions. Language barriers may further limit their access to health care.

A comparison of screening programmes for HBV among migrants in six European countries shows that Germany (20% migrant population) offers screening to the largest number of high-risk groups [7]. The country is examining a number of indicators of migrant health for inclusion in Health Interview and Examination Surveys for children, adolescents and adults.

TREATMENT

Natural history of HBV

HBV causes a chronic disease that can be controlled but not cured. Progression of hepatitis B depends mainly on the age at which the patient becomes infected. The majority of children infected at birth or up to the age of 2 years progress to chronicity, while <5% of adults do. Of those who are chronically infected, 2–10% per year progress to liver cirrhosis and, finally, to decompensation and death. Patients treated before the age of 50 years to effect HBsAg loss have a significantly reduced risk of developing HCC [60]. The risk of progression to HCC is 60 times higher in persons who are HBsAg and hepatitis B e antigen (HBeAg) positive [61].
Hepatitis delta virus: natural history and treatment

Hepatitis delta virus (HDV) makes use of HBsAg to assemble and infect cells and causes progressive, early cirrhosis, mainly in persons who are anti-HBe positive. Low serum HBV DNA and normal ALT levels and absence of specific clinical/histological features make the diagnosis difficult.

There is no definitive therapy for HDV infection at present. The current recommendation is PEG-IFN alpha weekly for 12–18 months, but only about 20–25% of patients respond. HDV may relapse as long as HBsAg is positive; therefore, the only reliable end-point of therapy is clearance of HBsAg.
approved in some countries). SVR rates among IDUs are similar to those in patients with other routes of exposure [76,77]. These drugs have not yet been licensed for use in those with HIV coinfection due to the potential for drug–drug interactions. In the United States of America (USA) and most European countries, current first-line therapy for infection with genotype 1 is a combination of PEG-IFN-α plus ribavirin plus either boceprevir or telaprevir. This combination is effective in both treatment-naïve and treatment-experienced patients, but SVR is higher in treatment-naïve patients. High SVR rates can be achieved even in those with evidence of fibrosis and cirrhosis, but response is poor in prior null responders, especially those with cirrhosis [78]. New drugs under development include other protease inhibitors, the NS5B polymerase and NS5A inhibitors [79]. Preliminary data from investigational studies suggest the potential for cure rates of 80–90% in genotype 1 infection using combinations of DAAs and ribavirin without PEG-IFN, but larger studies will be needed to confirm these results across a wider range of populations [80-82].

CASE STUDY OF TREATMENT SCALE-UP IN THE MEDITERRANEAN REGION: EGYPT

Egypt has the highest HCV prevalence in the world (10%) [83]. Prevalence of chronic HCV infection was strongly age-related in a survey conducted in 2008, reaching 23% in the 50–54 years age group and 25% in the 55–59 years age group [16]. HCV incidence is around 20 times higher than rates observed in European countries and is estimated to lie between 100 000 and 500 000 cases per year [84,85]. Around 67% of seroconverters are under 20 years of age, with HCV-positive family or household members being the strongest predictors of HCV acquisition [84]. Other high-risk groups include healthcare workers [86], prisoners, child recipients of multiple blood transfusions [87] and adult haemodialysis patients [88]. Genotype 4 HCV infection is highly predominant in Egypt [89].

While death rates due to other major cancers have stabilized or fallen since the 1980s, deaths due to HCC have increased from 2.4 per 100 000 in 1987 to 8 per 100 000 in 2010, accounting for 6000–7000 deaths per year (National Cancer Institute, Egypt).

The Egyptian government responded by instituting a National Control Strategy in 2008 to reduce the prevalence of chronic HBV and HCV in the 15–30 years age group by 20% by 2012, treat 20% of all those in need of treatment and ensure that treatment would be available within 100 km of all Egyptians by 2012 [90].

Egypt is the world’s largest provider of treatment for HCV. Treatment is provided through 23 specialist treatment centres, seven of which are each treating more than 2000 patients. The national standard of care is PEG-IFN and ribavirin in patients with F1–F3 fibrosis, costing approximately €2000 for a 48-week course. Around 90% of HCV treatments are funded by the government and, in other cases, discounts of up to 75% are available on treatment costs. The Egyptian government devoted 7% of the health budget to HCV treatment and treated 190 000 patients between 2008 and 2011 (45 000 in 2009, the largest single enrolment to date). Approximately 54% of patients receiving treatment are cured, leaving a substantial pool of patients who require further treatment options. At present, newer HCV treatments remain largely untested in genotype 4 populations (presentation by I. Waked, at Hepatitis B and C in the Mediterranean and Balkan Countries, December 2012).

Modelling suggests that within current financial constraints, ensuring treatment of patients with F4 fibrosis, instead of those with F1 fibrosis, would have the greatest impact on mortality due to HCV in Egypt [91].

ACCESS TO TREATMENT IN THE MEDITERRANEAN AND BALKAN REGIONS

Treatment access is highly variable across the southern European and Mediterranean regions due to the cost of treatment and variations in the resources available for health care. Recent reductions in public spending in many countries, particularly in southern Europe, have resulted in constraints in health services. The cost and availability of treatment in each country is determined by a number of interlocking factors, which throw up discrepancies in treatment access even between countries with similar levels of development. For example, hepatitis C treatment with PEG-IFN is around five to eight times more expensive in Algeria and Morocco than in Egypt, while some antivirals for hepatitis B are more costly in Algeria, Morocco and Israel than in France or Spain (see Table 5). (Data presented by invited speakers from Algeria, Egypt, Israel, Italy, Morocco and Spain, at Hepatitis B and C in the Mediterranean and Balkan Countries, December 2012).

Urgent action is required at EU Commission and Council levels to address the inequalities in access to treatment and arrive at equitable pricing arrangements in the EU and Mediterranean region. A pricing structure that supports national government investments in a comprehensive approach to diagnosis and treatment, for example, by adjusting costs according to the volume of patients treated, requires further discussion. Opportunities to reduce costs through production of generic and biosimilar agents should be examined. The potential benefits of pooled procurement arrangements for drugs and diagnostics also need to be investigated.

RAISING AWARENESS AND POLICY INITIATIVES

Policy developments at the global and regional level have the potential to support countries in developing national plans. Addressing the burden of viral hepatitis in the
Table 5 Costs of treatment for hepatitis B and C in some Mediterranean and Balkan countries

<table>
<thead>
<tr>
<th>Country</th>
<th>GDP per capita, 2011, USD*</th>
<th>HBV drug costs (euro)†</th>
<th>HCV drug costs (euro)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Algeria</td>
<td>$5244</td>
<td>Entecavir: €5788</td>
<td>PEG-IFN alpha-2a/rib: €16 893</td>
</tr>
<tr>
<td>Egypt</td>
<td>$2781</td>
<td>PEG-IFN alpha-2a: €15 893</td>
<td></td>
</tr>
<tr>
<td>France</td>
<td>$42 377</td>
<td>Entecavir: €5812</td>
<td>Peg-IFN/rib: €16 000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tenofovir: €4676</td>
<td>Triple therapy: €16 000 + €27 300 (telaprevir)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PEG-IFN alpha-2a: €9000</td>
<td></td>
</tr>
<tr>
<td>Greece</td>
<td>$25,622</td>
<td>Adefovir: €4225</td>
<td>Peg-IFN/rib: €10 680-€13 812</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Entecavir: €3895</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lamivudine: €400</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PEG-IFN alpha-2a: €6840</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tenofovir: €3928</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tenofovir: €2858</td>
<td></td>
</tr>
<tr>
<td>Israel</td>
<td>$31,282</td>
<td>Adefovir: €1925</td>
<td>PEG-IFN: €9010</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Entecavir: €6646</td>
<td>Ribavirin: €5308</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lamivudine: €1657</td>
<td>Telaprevir: €55 300</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PEG-IFN alpha-2a: €5544-9010</td>
<td>Boceprevir: €20 165</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Telbivudine: €3795</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tenofovir: €4266</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>$36,103</td>
<td>Entecavir: €5000</td>
<td>PEG-IFN/rib: €12 000-€18 000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PEG-IFN alpha-2a: €9000</td>
<td>DAA: €12 000-€50 000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tenofovir: €3000</td>
<td>PEG-IFN/rib: €12 000</td>
</tr>
<tr>
<td>Morocco</td>
<td>$3054</td>
<td>Adefovir: €2940</td>
<td>Protease inhibitor: €27 300</td>
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<td></td>
<td>Entecavir: €5760</td>
<td>PEG-IFN/rib: €12 000</td>
</tr>
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<td></td>
<td></td>
<td>IFN: €3264</td>
<td>protease inhibitor: €27 300</td>
</tr>
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<td>Lamivudine: €1524</td>
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<td></td>
<td>PEG-IFN: €12 000</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Telbivudine: €1920</td>
<td></td>
</tr>
<tr>
<td>Serbia</td>
<td>$6310</td>
<td>Lamivudine: €600</td>
<td>PEG-IFN/rib: €3500-7000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tenofovir: €3600</td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>$31943</td>
<td>Adefovir: €4894</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Entecavir: €4745</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Telbivudine: €4745</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tenofovir: €3474</td>
<td></td>
</tr>
</tbody>
</table>

†Source: Country representative presentations, Conference on Hepatitis B and C in the Mediterranean and Balkan Countries.
‡Ibid.

Balkan and Mediterranean regions will require national commitments in the form of strategic plans, financial and human resources, as well as normative guidance and technical support from regional agencies. Some of the key lessons from successful national programme development are outlined in Panel 3.

### PANEL 2: FACTORS INFLUENCING TREATMENT ACCESS AT NATIONAL LEVEL

- Gross domestic product (GDP) and overall resources for health.
- Membership of the EU. Countries in the EU are bound to a reference pricing system for medicines, which imposes high drug prices on recent EU entrants relative to GDP.
- Speed of reimbursement approval for new medicines.
- National treatment guidelines.
- Expanded access arrangements organized by pharmaceutical companies.
- Prices negotiated with pharmaceutical companies relative to volumes.
- Differential pricing policies of pharmaceutical companies.
There is also a need for expanded investment in research into viral hepatitis. Up-to-date information on the epidemiology and burden of disease attributable to hepatitis B and C is critical for the development of appropriate policy at national and EU levels. New opportunities for EU funding may emerge in Horizon 2020, the EU Framework Programme for Research and Innovation, 2014–2020, subject to agreement on the proposed budget of €80 billion. Prioritization of disease-specific research calls within the Horizon 2020 framework will depend on the identification of gaps in knowledge. WHO is working to develop a public health research agenda for viral hepatitis.

World Hepatitis Day (28 July) is an official WHO disease awareness day and provides an important opportunity to raise awareness through educational and screening activities at the national level. It also provides a platform for civil society and professional lobbying of government. Government support for World Hepatitis Day would be an important step in raising awareness and challenging the stigma of viral hepatitis.

CONCLUSIONS

There has been welcome progress towards developing European-level and international strategic approaches to viral hepatitis. These include general surveillance and risk group-specific monitoring (ECDC and EMCDDA), research (EC DG Research and DG Health) and the development of guidance (WHO, ECDC, Viral Hepatitis Prevention Board [VHPB] and EMCDDA). Nevertheless, the growing burden of liver disease caused by viral hepatitis requires further urgent action at European and international levels. Viral hepatitis is now estimated to cause more deaths than HIV in the WHO European region. Concerted action is required to achieve universal access to prevention, care and treatment for viral hepatitis. Recent improvements in the treatment for viral hepatitis, and the future promise of new therapies that could cure the majority of people with HCV infection, could remain out of reach for the majority of people with viral hepatitis in southern Europe and the Mediterranean region without actions on the part of governments, normative authorities, pharmaceutical companies and advocates to promote and expand access.

An extension of screening for hepatitis B and C, according to the respective local epidemiology, will be required to reduce the future burden of liver disease in the Balkan and Mediterranean countries as most people with viral hepatitis do not know they have been infected. Undiagnosed people cannot benefit from treatment. Migrant populations and people who inject drugs in Balkan and the Mediterranean countries are at high risk of viral hepatitis and liver disease and require diagnosis, prevention measures (including vaccination and harm reduction) and treatment.

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Keith Alcorn is Senior Editor at NAM Publications, which has received educational grants from Boehringer Ingelheim, Janssen, Merck and Roche for work relating to hepatitis C or hepatitis C/HIV coinfection.

M Benazzouz has no conflict of interests.

Saadi Berkane has received fees for serving as speaker, consultant and advisory board member from Bristol-Myers Squibb, Roche, Merck and Janssen.

Maria Buti has received fees as a speaker for Bristol-Myers Squibb (BMS), Merck, Gilead and Janssen.

Manuel Carballo has no conflict of interests.

Helena Cortes Martins has no conflict of interests.

Angela Dominguez Garcia has no conflict of interests.

Martin Donoghoe has no conflict of interests.

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Abdul Naser Elzouki has no conflict of interests.

Nissaf Ben-Alaya-Bouaifi has no conflict of interests.

Gamal Esmat has no conflict of interests.

Rafael Esteban has received fees as a speaker or adviser for MSD, Janssen, BMS, Gilead, Abbott, Novartis and GlaxoSmithKline.

Milotka Fabri has no conflict of interests.

Kevin Fenton has no conflict of interests.

David Goldberg has received consultancy fees from Merck and Janssen for epidemiological/public health work associated with hepatitis C virus (HCV) over the past 4 years. He has also served on the advisory boards for these 2 companies but at no time has he advised on anything related to specific products.

Charles Gore is CEO of The Hepatitis C Trust, which has received grants from Roche, MSD, Boehringer Ingelheim, Janssen, Gilead and BMS (never amounting to more than 25% of the Trust’s income), and is the unremunerated President of the World Hepatitis Alliance, which has received educational grants from Roche, BMS, Merck, Janssen, Novartis, Boehringer Ingelheim, Gilead, Achillion, Abbvie/Abbott and GSK. He has received no personal payments at all.

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Osama Hamouda has no conflict of interests.

T Hadjichristoloudou has no conflict of interests.

Angelos Hatzakis has served on advisory boards for Gilead and has received travel grants and research grants from Gilead. He is Co-Chair of the Hepatitis B and C Public Policy Association, which is supported by grants from Gilead, Bristol-Myers Squibb, Janssen and MSD.

Stanimir Hasurdjievi is a patient representative and advocate and in these capacities has participated and held presentations on behalf of the following organizations: European Liver Patients’ Association (ELPA) (Executive Director) and Bulgarian National Patients’ Organization (NPO) (Chairperson). As nongovernmental not-for-profit organizations ELPA and NPO receive unconditional financial support from their benefactors. While representing either organization before third parties, Mr. Hasurdjievi has not received any specific fees apart from coverage of travel and accommodation. Mr. Hasurdjievi has also served on advisory boards for HCAB, ECAB and the Bulgarian National Health Insurance Fund as a patient representative. Neither of those mentioned bodies has paid any speaker fees.

Raquel J.J. Peck is the International Relations Director of the World Hepatitis Alliance and a secondee to the Global Hepatitis Programme (GHP) at the World Health Organization. As a nongovernmental, not-for-profit organization, the World Hepatitis Alliance has received educational, unrestricted grants from Roche, BMS, Merck, Janssen, Novartis, Boehringer Ingelheim, Gilead, Achillion, Abbvie/Abbott and GSK. She has not received personal payments. Regarding her position at the GHP, there are no conflict of interests to report.

Achim Kautz has no conflict of interests.

Mamunur Malik has no conflict of interests.

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Spilios Manolakopoulos has served as an advisory board member and speaker for Gilead, BMS, Novartis, Roche and Merck and has received research grants from BMS but not for this study.

Mojca Matičič has received travel grants and speaker fees from Bayer, Berlin Chemie, Gilead, GSK, Janssen, MSD, Roche and Schering Plough.

George Papaioedhodidis has received fees for serving as a speaker, consultant and an advisory board member for Abbott, Boehringer, BMS, Gilead, Janssen, Merck, Novartis and Roche and has received research support from BMS, Gilead and Roche.

George Potamitis has no conflict of interests.

Daniele Prati has received research grants and fees for serving as a speaker, consultant and an advisory board member for Abbott, Roche, Gilead, BMS and Novartis.

Tatjana Reic has no conflict of interests.

Ala I. Sharara has no conflict of interests.

Mustafa Shennak has no conflict of interests.

Gamal Shihab has no conflict of interests.

Daniel Shouval is a member of the advisory board of Scigen, Israel, expert advisory board of Jansen European and
recipient of speaker fees. He also served as speaker for Biotest, Germany, DiaSorin Israel, and GSK, Belgium.

Maja Soćan has no conflict of interests.

Mark Thursz has received fees for serving as a speaker, consultant and an advisory board member for BMS, Gilead, Janssen and Abbott within the past three years.

Elena Tosti has no conflict of interests.

Christian Trépo has served on advisory boards for Roche, Schering Plough, MSD, Gilead and Flamel and received research grants from Janssen, Roche, MSD and Flamel.

Pierre Van Damme is full professor at the University of Antwerp and full-time personnel member of the University. Pierre Van Damme is head of the Vaccine and Infectious Disease Institute at the University of Antwerp, which is a WHO collaborating centre for the prevention and control of infectious diseases. He acts as chief and principal investigator for vaccine trials conducted on behalf of the University of Antwerp, for which the University obtains research grants from vaccine manufacturers. He is the executive secretary of the Viral Hepatitis Prevention Board (VHPB): the executive VHPB secretariat benefits from being seated at the Centre for the Evaluation of Vaccination (CEV) of the University of Antwerp, where it has the infrastructure and administrative services of the University at its disposal. VHPB is supported by unrestricted grants from the vaccine industry (GSK Biologicals, Sanofi Pasteur MSD, Sanofi Pasteur and Merck), several universities in Europe and other institutions (www.vhpb.org). He receives no personal remuneration for this work.

Adriana Vince has received fees for serving as a speaker for MSD, Janssen, Novartis and Roche and as an advisory board member for MSD.

Emmelia Vounou has no conflict of interests.

Lucas Wisessing has no conflict of interests.

Notes:

1 WHO Eastern Mediterranean region comprises Afghanistan, Bahrain, Djibouti, Egypt, Islamic Republic of Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Occupied Palestinian territory, Oman, Pakistan, Qatar, Saudi Arabia, Somalia, South Sudan, Sudan, Syrian Arab Republic, Tunisia, United Arab Emirates, Yemen.

2 In this report, ‘Mediterranean’ refers to countries bordering the Mediterranean, and ‘Balkans’ refers to non-European Union countries in south-eastern Europe.

3 Participating countries in the Conference were: Albania, Algeria, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Egypt, France, Former Yugoslav Republic of Macedonia (FYROM), Greece, Israel, Italy, Jordan, Lebanon, Libya, Malta, Montenegro, Portugal, Romania, Serbia, Slovenia, Spain, Syria, Tunisia, United Kingdom and United States, with representatives from European Centre for Disease Control and Prevention (ECDC), European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), European Commission, European Parliament, WHO, WHO EMRO, WHO Regional Office for Europe and the Viral Hepatitis Prevention Board (VHPB).

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APPENDIX CALL TO ACTION
This Call to Action is endorsed by:
Takis Hatzigeorgiou MEP
Stephen Hughes MEP
Alojz Peterle MEP
Viral Hepatitis Prevention Board
European Association for the Study of the Liver
European Liver Patients Association
World Hepatitis Alliance
International Centre for Health, Migration and Development
Hepatitis B and C Public Policy Association.

The conference on Hepatitis B and C in Mediterranean and Balkan countries has united a range of stakeholders to urge the formulation and implementation of effective policies and targeted actions by national governments, healthcare providers and civil society in the fight against hepatitis B and C.

The conference commends previous work in the domain of hepatitis B and C in particular, to the 63rd World Health Assembly’s resolution on Viral Hepatitis of May 2010, the Call to Action launched at the European Parliament in 2006, the European Parliament’s Written Declaration on Hepatitis C in 2007, the Call to Action launched at the Brussels Conference on Hepatitis B and C in Europe in 2010 and the WHO Prevention and Control of Viral Hepatitis Infection: Framework for Global Action, launched in July 2012.

The Steering Group of the Conference on Hepatitis B and Hepatitis C in Mediterranean and Balkan Countries, together with its partner associations, calls on the countries of these regions to create national viral hepatitis strategies and action plans and, in particular, to
1. Involve all sectors of society in the fight against hepatitis B and C.
2. Place the fight against hepatitis B and C within a Right to Health framework.
3. Actively participate in World Hepatitis Day.
4. Improve awareness of the health and economic impact of hepatitis B and C.
5. Strengthen surveillance of hepatitis B and C.
6. Build intercountry research capacities dedicated to hepatitis B and C.
7. Make prevention and control of hepatitis B and C a key part of public health action.
8. Invest in better case detection and treatment programmes in primary health care.
9. Develop outreach programmes to ensure more voluntary counselling and testing.
10. Explore innovative ways of reaching all vulnerable groups, including migrants.
12. Create community-based programmes to support people living with viral hepatitis.

WHO’s Global Hepatitis Programme launched on World Hepatitis Day 2012 the Prevention and Control of Viral Hepatitis Infection: Framework for Global Action. This sets out four axes for action:
1. Partnership, mobilization and communication.
2. Data for policy and action.

Axis 1

1. Involve all sectors of society in the fight against hepatitis B and C
   • organize technically backed briefings for senior policy makers in all government sectors
   • work with all stakeholders to mobilize the necessary funding to implement the action plan
   • involve nongovernmental organizations representing key risk groups in decision making.
2. Place the fight against hepatitis B and C in a Right to Health framework
   • adopt and use human rights approaches that have been developed in HIV/AIDS
   • link human rights approach to public health principles and health benefits
   • ensure that those living with hepatitis B and C are aware of their rights.
3. Actively participate in World Hepatitis Day
   • work with experts, civil society and healthcare providers to raise hepatitis awareness
   • create public health campaigns around the impact of hepatitis B and C on health
   • take all necessary measures, including legislation, to tackle stigma and discrimination.

Axis 2

4. Improve awareness of the health and economic impact of hepatitis B and C
   • develop robust national databases on hepatitis B and C and liver cancer
   • emphasize hepatitis B and C in all medical and nursing education curricula
   • make policy makers more aware of the economic impact of untreated hepatitis B and C.
5. Strengthen the surveillance of hepatitis B and C in all countries in these regions
   • promote routine centralized hepatitis reporting with standardized case definitions
   • promote national and intercountry use of standard routine surveillance protocols
   • monitor and evaluate the effectiveness of prevention and control interventions.
6. Build intercountry research capacities dedicated to hepatitis B and C
promote and fund research on epidemiology and factors affecting hepatitis B and C
promote and fund research on ways of preventing and managing hepatitis B and C
promote and fund collaborative intercountry research using common protocols.

Axes 3 and 4

7. Make prevention of hepatitis B and C a central part of public health action
   ● ensure high coverage of universal neonatal HBV vaccination, especially birth dose
   ● ensure HBV vaccination of healthcare workers and other risk groups
   ● develop tailored initiatives for injecting drug users and other special risk groups.

8. Invest in better case detection and treatment programmes in primary health care
   ● develop protocols on case detection and contact prevention for PHC
   ● develop special training programmes for PHC staff based on standardized new protocols
   ● ensure referral for people who need to be seen at a secondary or tertiary level.

9. Develop outreach programmes to ensure more voluntary counselling and testing
   ● develop/adapt voluntary counselling and testing (VCT) protocols and train national staff
   ● identify ways of encouraging/incentivizing high-risk people to be tested, including screening
   ● ensure that policies on hepatitis B and C VCT include access to and retention in treatment.

10. Explore innovative ways of reaching all vulnerable and underserved groups
    ● identify the most vulnerable groups and their barriers to health care, including migrants
    ● give special attention to groups with highest rates of transmission and burden of disease
    ● ensure equity of access to hepatitis prevention and control measures.

11. Ensure universal access to treatment
    ● strengthen treatment policies and health systems capacities in treatment
    ● adopt international guidelines and recommendations on treatment
    ● train healthcare providers in hepatitis B and C management.

12. Create community-based programmes for people living with viral hepatitis
    ● assess the needs of people living with hepatitis B and C, especially vulnerable groups
    ● train and support community-based groups to improve ‘living with hepatitis B and C’
    ● ensure the integration of community-based groups into the national action plan.

1 Of particular note are:
    ● The 63rd World Health Assembly Resolution on Viral Hepatitis, adopted on 21 May 2010;
    ● MEP Thomas Ulmer’s Call to Action on Hepatitis B launched at the European Parliament in 2006, and the European Parliament’s Written Declaration on Hepatitis C requesting i.a. a Council Recommendation to promote screening for Hepatitis;
    ● The European Parliament Report of April 2010 on the European Commission’s Communication on Action Against Cancer, which ‘Urges that... the prevention and control of diseases which can develop into cancer, for instance primary and secondary prevention of viral hepatitis and treatment where appropriate, should be addressed by the Cancer Partnership and in future EU initiatives, such as a revised Council recommendation on cancer screening’;
    ● The inclusion of Hepatitis B and C in the surveillance and monitoring programmes of the European Centre for Disease Prevention and Control (ECDC) and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA);
    ● The joint ‘ECDC and EMCDDA guidance. Prevention and control of infectious diseases among people who inject drugs, EMCDDA/ECDC, Stockholm, October 2011’;
    ● Work currently undertaken by the European Association for Disease of the Liver (EASL), the European Liver Patient Association (ELPA) and the Viral Hepatitis Prevention Board (VHPB).