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Historical epidemiology of hepatitis C virus (HCV) in select countries – volume 2

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SUMMARY. Chronic hepatitis C virus (HCV) infection is a leading cause of liver related morbidity and mortality. In many countries, there is a lack of comprehensive epidemiological data that are crucial in implementing disease control measures as new treatment options become available. Published literature, unpublished data and expert consensus were used to determine key parameters, including prevalence, viremia, genotype and the number of patients diagnosed and treated. In this study of 15 countries, viremic prevalence ranged from 0.13% in the Netherlands to 2.91% in Russia. The largest viremic populations were in India (8 666 000 cases) and Russia (4 162 000 cases). In most countries, males had a higher rate of infections, likely due to higher rates of injection drug use (IDU). Estimates characterizing the infected population are critical to focus screening and treatment efforts as new therapeutic options become available.

Keywords: diagnosis, disease burden, epidemiology, HCV, hepatitis C, incidence, mortality, prevalence, treatment.

INTRODUCTION

The epidemiology of hepatitis C virus (HCV) infection remains poorly understood in many countries. At the same time, HCV-related mortality continues to increase as the infected population ages [1] and HCV-related morbidity is forecasted to increase as the infected population advances to late-stage liver diseases [2–4].

Abbreviations: CHS, Clalit Health Services; G, Genotype; HCV, hepatitis C virus; HPSC, Health Protection Surveillance Centre; IDU, injection drug use; MELD, Model for End Stage Liver Disease; Peg-IFN, Pegylated interferon; RBV, ribavirin; RNA, ribonucleic acid; THL, National Institute for Health and Welfare; UN, United Nations.

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In 2010, the World Health Assembly adopted resolution WHA 63.18 that recognized viral hepatitis as a global public health problem [5]. By 2014, the World Health Organization adopted resolution WHA76.6 asking countries to develop comprehensive national hepatitis strategies [6]. However, countries require reliable data and an understanding of the disease dynamics to develop robust strategies.

A number of studies have characterized HCV infection rates across different countries/regions [7–12], but they have typically focused on quantifying the anti-HCV infections. This study is a continuation of a project to quantify HCV epidemiology in countries around the world in a systematic manner.

The aim of this study was to develop consensus estimates, using the best available published and unpublished data, for the total number of viremic infections [HCV ribonucleic acid (RNA) positive], the total number of viremic-diagnosed individuals, the number of viremic newly diagnosed, annual number of treated patients and the number of liver transplants attributed to HCV in each country. The countries were selected based on the availability of published data and the willingness to collaborate. Other countries are being analysed and will be published separately.

METHODOLOGY

A systematic review of the literature was conducted to identify studies reporting the total number of HCV cases diagnosed, treated and cured. The review encompassed all studies between January 1990 and July 2013. Indexed articles were found by searching PubMed and Embase. Non-indexed sources were identified through individual countries' ministry of health websites and international agencies' reports. In addition, an expert panel in each country provided proceedings of local conferences, unpublished data and data from large liver centres that could be extrapolated to the national level.

Face-to-face meetings were conducted to review findings and analyses with the expert panel. When no input data were available, analogues (data from countries with a similar healthcare practice and/or risk factors) or expert inputs were used. Ranges were used to capture uncertainty in inputs, with wider ranges implying greater uncertainty.

Viremic infections represented current RNA-positive HCV, or chronic HCV infections. The term viremic was used throughout this study to highlight the presence of HCV. The term incidence was used for new HCV infections (acute or infections among immigrants entering the country) per calendar year and not newly diagnosed. Care was taken to collect and list the year of the reported collection since the data were reported over a wide range of years. As shown in the next publication in this supplement [13], a modelling approach was used to estimate the HCV-infected populations (viremic, diagnosed and treated) in 2013. Unless stated, population data were obtained from the United Nations' (UN) population database by age, gender and five-year age cohort [14].

The annual number of liver transplants was gathered from national or international databases and adjusted for the proportion attributed to HCV. The number of antibody positive and RNA-positive-diagnosed cases was gathered from national databases, use of analogues or expert panel input. It were explicitly stated when published or official data were not available. In countries where HCV was a notifiable infection and a reliable annual number of newly diagnosed cases was reported, the total diagnosed cases was calculated by summing data from all years after taking into consideration the mortality among the diagnosed cases. In countries where the number of total and newly diagnosed cases was not available, expert panel input was used. Diagnosis rates from the known countries (analogues) were provided to the expert panel, and the panel selected one or more countries that had similar profiles. It was assumed that the viremic rate among the diagnosed population was the same as the total infected population, and the same viremic rate was used to estimate the number of viremic-diagnosed individuals.

Two methods were used to estimate the total number of treated HCV patients. In countries where reliable national data were available, the reported numbers were used. In other countries, the annual number of units of Pegylated-Interferon (Peg-IFN) or ribavirin (RBV) sold, as reported by IMS Health [15], were converted to treated patients using the average number of units per patient. The number of treated patients was calculated using the genotype distribution of the infected population (assumed the genotype distribution of the treated population was the same as the overall population), the duration of treatment for each genotype, the number of Peg-IFN or RBV units per week and the per cent of patients who completed their treatment (80% in most countries unless stated otherwise). The annual number of units was adjusted using inputs from the expert panel to account for uses other than HCV as well as potential under-reporting.

RESULTS

The results of the literature review, including estimates of antibody and viremic prevalence, genotype and viremic diagnosis, as well as annual treatment and liver transplants are shown in Table 1. Figure 1 shows the age and gender distribution of the HCV-infected population collected for each country.

Argentina

HCV-infected population

HCV epidemiology data are sparse in Argentina. The prevalence of anti-HCV in adults (individuals aged ≥20 years) was estimated at 1.50% based on expert consensus, with lower

Table 1 Hepatitis C virus (HCV) epidemiology by country

	Argentina	Finland	Greece	India	Ireland	Israel	Luxembourg	Mexico
Country's Population (000)	41 500	5600	11 400	1 275 100	4500	6500	500	100 000
Year	2013	2012	2012	2013	2010	2004	2013	2000
HCV Antibody Positive (000)								
Total Cases	428 (133 - 829)	27 (21 - 34)	168 (91 - 245)	10 730 (6376 - 19 127)	40 (26 - 66)	145 (67 - 156)	4.0 (2.3 - 4.6)	950 (750 - 1090)
Prevalence	1.0% (0.3% - 2.0%)	0.5% (0.4% - 0.6%)	1.5% (0.8% - 2.1%)	0.8% (0.5% - 1.5%)	0.9% (0.6% - 1.5%)	2.0% (0.9% - 2.1%)	0.7% (0.4% - 0.9%)	1.0% (0.8% - 1.1%)
Year of Estimate	2013	2012	2012	2013	2010	2010	2013	2000
Viremic Infections (000)								
Total Viremic Cases	342 (133 - 664)	22 (16 - 27)	134 (73 - 196)	8666 (5150 - 15 449)	30 (20 - 50)	110 (50 - 118)	3.1 (1.8 - 3.6)	619 (750 - 1090)
Viremic Prevalence	0.8% (0.3% - 1.6%)	0.4% (0.3% - 0.5%)	1.2% (0.6% - 1.7%)	0.7% (0.4% - 1.2%)	0.7% (0.4% - 1.1%)	1.5% (0.7% - 1.6%)	0.6% (0.3% - 0.7%)	0.6% (0.8% - 1.1%)
Viremic Rate (%)	80%	80%	80%	81%	75%	76%	77%	65%
Year of Estimate	2013	2012	2012	2013	2010	2010	2013	2000
Genotypes (%)								
1a	20%	-	-	9%	42%	12%	-	18%
1b	38%	-	-	16%	14%	57%	-	31%
1 Other	1%	32%	45%	3%	-	-	55%	20%
1	59%	32%	45%	28%	56%	69%	55%	69%
2	22%	16%	7%	-	4%	8%	4%	21%
3	18%	46%	34%	64%	39%	20%	34%	7%
4	1%	6%	14%	7%	1%	3%	6%	0%
5	-	-	-	0%	-	-	0%	0%
6	-	-	-	-	-	-	-	0%
Other	-	-	-	-	-	-	-	2%
Year of Estimate	2010	2013	1997-2006	2012	2010	2004	2013	2002-2009
Diagnosed (Viremic)								
Total Cases	112 300	16 400	32 000	408 300	9900	22 000	2600	155 800
Annual Newly Diagnosed	4900	900	4000	52 600	800	2200	100	14 700
Year of Estimate	2010	2013	2011	2012	2010	2010	2013	2011
Treated								
Annual Number Treated	200	300	1970	15 000	400	1010	100	3100
Year of Estimate	2011	2011	2011	2011	2011	2011	2011	2011
Liver Transplants								
Total Liver Transplants	329	56	57	375	61	75	10	101
HCV Liver Transplants	74	6	9	109	12	26	1	32
% due to HCV	22%	11%	16%	29%	20%	35%	13%	32%
Year of Estimate	2013	2011	2011	2011	2011	2011	2011	2011

(continued)

Table 1 *(continued)*

	Mongolia	Netherlands	New Zealand	Norway	Poland	Russia	Slovak Republic	South Africa
Country's Population (000)	2900	16 500	4500	5000	38 300	143 000	5500	50 100
Year	2013	2009	2013	2012	2009	2010	2011	2010
HCV Antibody Positive (000)								
Total Cases	290 (250 - 460)	29 (9 - 50)	65 (35 - 94)	27 (22 - 35)	286 (197 - 380)	5861 (4930 - 6620)	68 (39 - 88)	562 (320 - 810)
Prevalence	10.0% (8.7% - 15.6%)	0.18% (0.06% - 0.30%)	1.5% (0.8% - 2.1%)	0.6% (0.5% - 0.7%)	0.8% (0.5% - 1.0%)	4.1% (3.5% - 4.6%)	1.2% (0.7% - 1.6%)	1.1% (0.6% - 1.6%)
Year of Estimate	2013	2009	2013	2012	2009	2010	2011	2010
Viremic Infections (000)								
Total Viremic Cases	200 (179 - 320)	22 (7 - 37)	50 (27 - 72)	22 (18 - 28)	200 (138 - 266)	4162 (3500 - 4700)	33 (19 - 44)	432 (246 - 623)
Viremic Prevalence	6.8% (6.1% - 10.9%)	0.13% (0.04% - 0.22%)	1.1% (0.6% - 1.6%)	0.4% (0.4% - 0.6%)	0.5% (0.4% - 0.7%)	2.9% (2.5% - 3.3%)	0.6% (0.4% - 0.8%)	0.9% (0.5% - 1.2%)
Viremic Rate (%)	70%	74%	76%	80%	70%	71%	49%	77%
Year of Estimate	2013	2009	2013	2012	2009	2010	2011	2010
Genotypes (%)								
1a	-	-	44%	18%	2%	2%	1%	2%
1b	99%	-	11%	18%	77%	53%	69%	22%
1 Other	-	49%	-	4%	-	-	20%	7%
1	99%	49%	55%	40%	79%	55%	90%	32%
2	1%	10%	7%	9%	0%	8%	2%	1%
3	-	29%	35%	50%	14%	36%	7%	13%
4	-	11%	-	1%	5%	-	1%	12%
5	-	-	-	-	-	-	-	36%
6	-	-	1%	-	0%	-	1%	-
Other	-	1%	2%	-	2%	-	1%	7%
Year of Estimate	2004	2002-2005	2013	2001	2003-2012	2012	2003-2007	2010-2012
Diagnosed (Viremic)								
Total Cases	60 000	12 000	20 000	12 000	30 200	1 789 500	3400	54 600
Annual Newly Diagnosed	1300	700	900	1100	3000	55 900	300	2600
Year of Estimate	2013	2013	2013	2012	2012	2012	2012	2013
Treated								
Annual Number Treated	200	900	900	600	2100	5500	300	100
Year of Estimate	2011	2011	2013	2011	2011	2011	2011	2011
Liver Transplants								
Total Liver Transplants	8	135	36	110	300	204	21	31
HCV Liver Transplants	3	16	13	25	83	66	5	2
% due to HCV	38%	12%	36%	23%	28%	32%	23%	5%
Year of Estimate	2013	2011	2013	2013	2011	2011	2011	2011

HCV antibody prevalence – prevalence of past or active HCV infection, viremic prevalence – prevalence of active HCV infections, viremic rate – per cent of past or active infections who have an active infection, viremic-diagnosed – the number individuals diagnosed with an active infection, annual newly diagnosed – the number of active HCV infections diagnosed for the first time

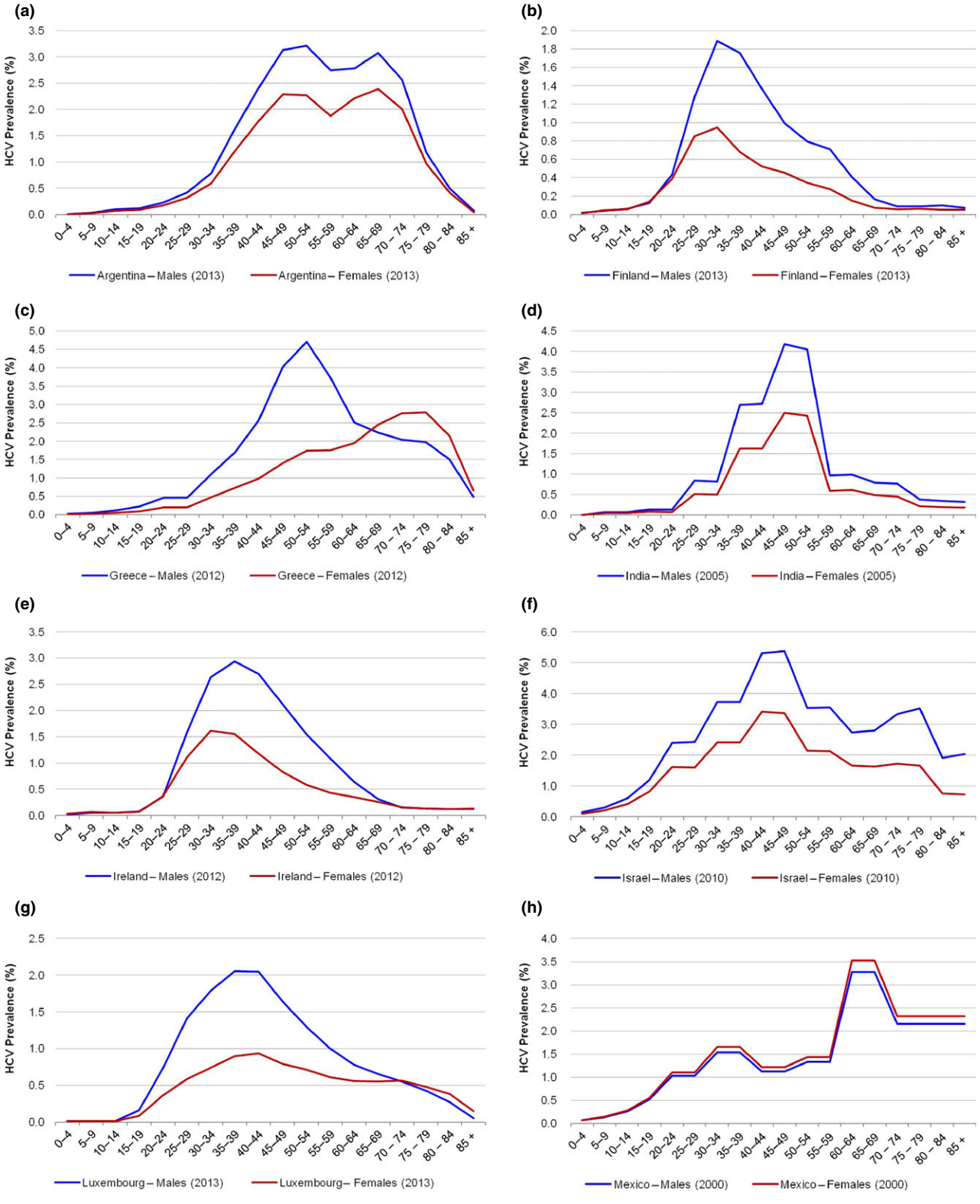
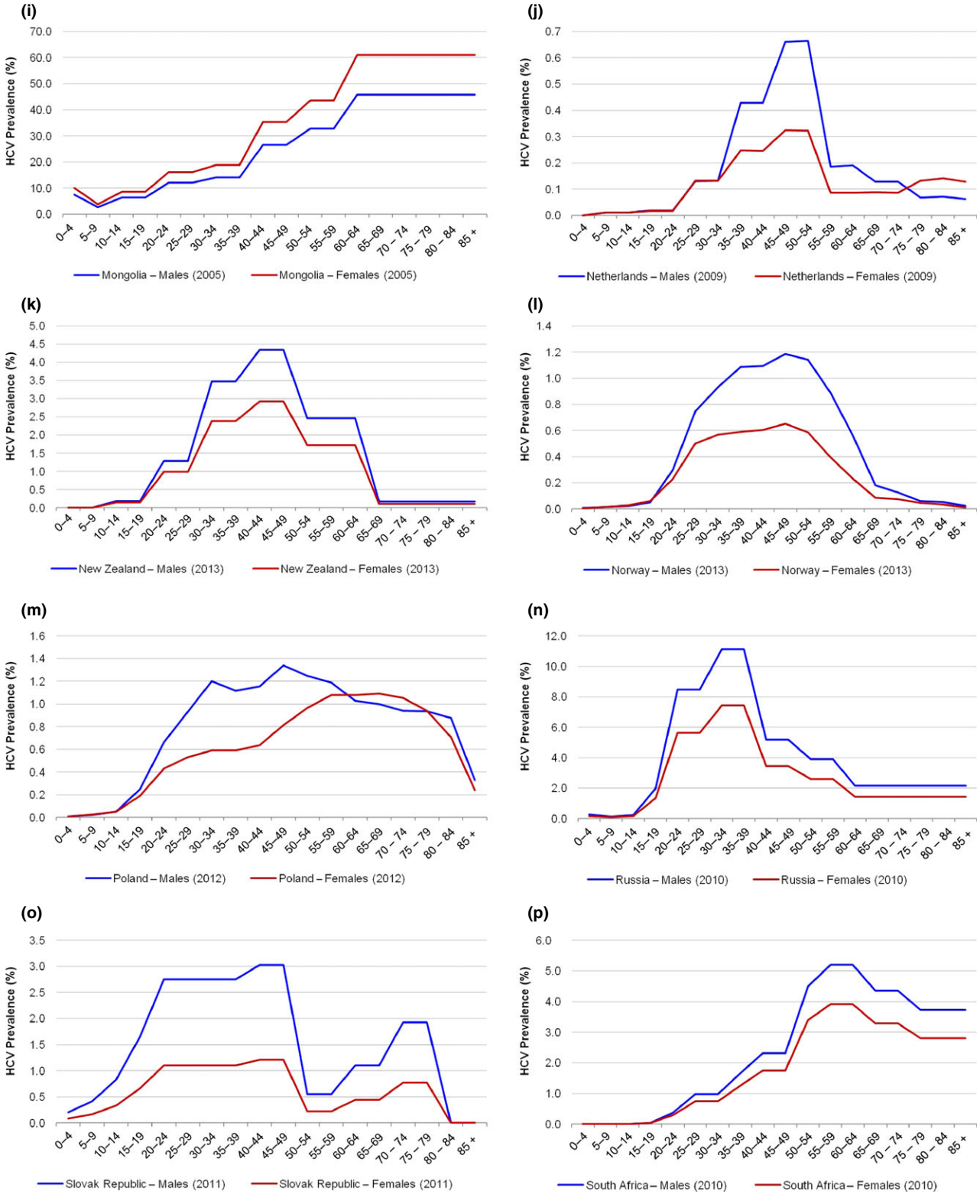


Fig. 1 Viremic hepatitis C virus (HCV) prevalence by age and gender.

prevalence among younger individuals. A viremic rate of 80% was applied [16]. The total viremic population in 2013 was estimated at 342 000 individuals, corresponding to viremic prevalence of 0.83%. For the age and gender distribution of the infected population, a hybrid distribution was constructed using notification data for HCV infection [17]



for individuals aged 0–59 years and transplant data [18] organized by age and gender for individuals aged ≥60 years. The notified and transplanted populations were aged to the year 2013, accounting for mortality and cured patients. The genotype distribution of the prevalent population was estimated using data from a population of over 200 treated patients [19], while the distribution of G1 subtypes was based on sentinel unit data [20].

Diagnosed
Estimates of the diagnosed population were based upon data for positive blood donations from the Pan American Health Organization [12]. The annual number of notifications was scaled up to account for diagnosis in other venues. There were an estimated 112 300 previously diagnosed cases in 2010 and 4900 newly diagnosed cases.

Treated
It was estimated that 200 patients annually were treated based on expert consensus and IMS data for standard units of Peg-IFN sold after adjustment to account for under-reporting.

Liver transplants
In 2013, there were 329 liver transplants performed in Argentina; 74 (22.4%) were attributable to HCV. The annual number of liver transplants was available from a national organ registry for the years 1999 to 2013 [18]. The proportion of liver transplants attributable to HCV was reported as 22.0% before the adoption of the Model for End Stage Liver Disease (MELD)-based allocation and 22.4% after MELD allocation [21].

Finland

HCV-infected population
There are no studies reporting anti-HCV prevalence in the general population in Finland. Thus, in 2012 expert consensus estimated the anti-HCV prevalence in the general population to be 0.49% using the known number of diagnosed cases in the country. The viremic rate was estimated to be 79.5% using a Norwegian study [22], corresponding to a viremic prevalence of 0.39% in 2012 with 21 800 infected individuals. The age and gender distribution was developed using diagnosed data from the National Institute for Health and Welfare (THL) [23]. The number of RNA-positive-diagnosed cases was available from 1995 to 2013. The diagnosed population was adjusted for mortality and cured, by year, and was aged to 2013. It was assumed that the age and gender distribution of the diagnosed population was reflective of the current distribution in Finland.

Diagnosed
The THL reported 16 400 patients living with a diagnosis [23] in 2013. There were 930 individuals newly diagnosed during the same year.

Treated
According to a panel of experts, 300–400 individuals were treated per year from 2008 to 2012.

Liver transplants
Liver transplant data were available through Scandiatransplant. In 2011, there were 56 liver transplants performed in Finland [24]. It was estimated that 1–6 liver transplants per year were attributable to HCV.

Greece

HCV-infected population
Estimates for prevalence were based upon data reported from a 2012 nationally representative phone survey conducted among Greek adults 18–70 years of age [25]. Prevalence rates were age-standardized and corrected for high-risk populations not included in the survey. The age-adjusted anti-HCV prevalence was 1.79%. When taking into account high-risk individuals, an anti-HCV prevalence of 1.87% was estimated for 2011. Assuming that the prevalence among individuals 0–17 years is 0.10%, the total prevalence was estimated at 1.47%. There are no robust studies to estimate the prevalence of HCV-RNA in Greece. A viremic rate of 80% was applied to this analysis [26], corresponding to a viremic prevalence of 1.18% (134 000 viremic infections) in 2011.

For the age and gender distribution of the infected population, data were available by birth year from more than 1200 patients participating in clinical trials or observational studies from multiple sites across Greece [27]. The population was adjusted for mortality and cure, and aged to 2012. The genotype distribution was developed using data from the nationwide HEPNET-GREECE cohort study which included patients from 20 centres from 1997 to 2006 [28].

Diagnosed
In 2011, it was estimated that 32 000 cases had been diagnosed. In the same year, it was estimated that 4000 individuals were newly diagnosed per year.

Treated
According to a previous study [25], 58% of diagnosed chronic HCV patients have ever been treated. This corresponds to approximately 15 700 treated patients through 2011. The same study and IMS data were used to estimate 1970 patients treated in 2011.

Liver transplants
Liver transplant data were available through the Hellenic Transplant Organization. In 2011, there were 57 liver transplants for Greek patients, and in 2013, there were 54 (25 performed in Greece and 29 performed abroad) [29]. It is estimated that 16.0% of transplants were attributable to HCV [29].

India

HCV-infected population
The anti-HCV seroprevalence was estimated at 0.84% in 2013. This estimate was calculated using a weighted aver-

age of published estimates from nonblood donor and nontribal population studies [30–39]. An anti-HCV range of 0.5%–1.5% was chosen from a consensus document published by the HCV Taskforce of the Indian National Association for the Study of the Liver (personal communication with P. Puri 2014). A viremic rate of 80.8% [30] was used, corresponding to 0.68% (0.40%–1.21%) viremic prevalence in 2012. A 2005 age distribution was chosen from a study of volunteer blood donors, in which seroprevalence was highest among individuals 41–50 years of age, and males were more commonly infected than females (M:F ratio – 1.64:1.00) [40].

The genotype distribution was obtained from a subtyping analysis of 398 patients (personal communication with Samir Shah, 2014). Genotypes 3 and 1 accounted for 64% and 28% of HCV infections, respectively, with 16% (of all infections) genotype 1b. Genotype 4a accounted for the remaining 7% of infections, with <1% genotype 5.

Diagnosed

There were an estimated 408 300 previously diagnosed viremic infections by 2012. This estimate was generated using blood bank reports and linear extrapolations. The number of HCV-positive blood units from 2004 to 2008 were used to estimate the number of HCV positive units in 2003, 2005–2007 and 2009–2012 [41,42]. It was then assumed that for every diagnosis in blood banks, two other cases were diagnosed among physicians or hospitals. The total number of diagnosed cases from blood banks was multiplied by a factor of 2 to account for diagnoses occurring outside of the blood supply system and adjusted for viremia using the above viremic rate. In 2012, there were an estimated 52 600 new viremic diagnoses.

Treated

IMS data were used to estimate 15 000 patients were treated annually in 2011.

Liver transplants

Liver transplant data from 1998 to 2013 were extrapolated using published literature [43] and expert feedback. The first liver transplant occurred in 1998, and by 2007, a total of 343 transplants had been performed in India [43]. Following 2007, the number of transplants annually began to increase rapidly, with 300 transplants in 2009 and 800–900 in 2013 (Expert consensus). An estimated 40% of transplants were attributable to HCV [44], and expert consensus suggests that approximately 50% of transplants were performed on patients from other countries. In 2011, an estimated 375 transplants were performed, with 109 (29%) attributable to HCV.

Ireland

HCV-infected population

The viremic population was estimated at 29 700 individuals at the end of 2009 [45] corresponding to viremic prevalence of 0.67%. With a viremic rate of 75% [45], anti-HCV prevalence was estimated at 0.89%, or 39 700 cases. Age and gender specific newly diagnosed cases from 2004–2006 to 2008–2012 were reported by the Health Protection Surveillance Centre (HPSC) [46]. These data were used to estimate the age distribution of the prevalent population in 2013 after accounting for mortality and cured patients. The genotype distribution of the prevalent population is based upon a study of samples collected between 1989 and 2004 in Ireland [45], while the distribution of G1 subtypes were from clinical data.

Diagnosed

Based on a national study, there were estimated to be 9900 viremic individuals in Ireland who are living with a diagnosis as of 2010 [45]. In 2012, 820 viremic individuals were newly diagnosed, based on the 1036 notifications reported by HPSC [47], with adjustment for viremia and application of the previously published under-reporting factor (100/95) [45].

Treated

In 2011, it is estimated that 360 patients were treated in Ireland, using IMS data for units of Peg-IFN sold in Ireland, after accounting for under-reporting.

Liver transplants

Annual liver transplants and the proportion attributable to HCV are collected through the Liver Transplant Unit at St. Vincent's University Hospital in Dublin. Between 2000 and 2013, there were 111 liver transplants performed in Ireland for HCV liver-related disease [48]. In 2011, 12 HCV-related liver transplants were conducted.

Israel

HCV-infected population

The anti-HCV seroprevalence was estimated at 1.96% in 2010. This estimate was calculated using unpublished data from Clalit Health Services (CHS), as described in Cornberg 2011 [10]. A viremic rate of 75.5% was used [49], corresponding to a 1.48% viremic prevalence, or approximately 109 800 viremic cases in 2010. The age and gender distribution were derived from CHS lab data for 15 300 patients [10,49].

The predominant HCV genotype in Israel is genotype 1 (69%), followed by genotype 3 (20%) [10,49].

Diagnosed
CHS data were used to estimate the total number of diagnosed cases after taking into consideration that CHS covers ~60% of the population. It was estimated that 21 960 viremic individuals were diagnosed, and 2200 viremic cases are newly diagnosed annually.

Treated
Expert consensus estimated that 1010 individuals received treatment in 2011.

Liver transplants
Liver transplant data from 2003 to 2013 were available from the Ministry of Health [50], and transplant data prior to 2003 were extrapolated to achieve 769 transplants from 1991 to 2011, as suggested in a recent study [51]. During the same time, expert consensus suggests that approximately 100 transplants were performed abroad. An estimated 35% of transplants were attributable to HCV, using published studies [51] and expert consensus to account for transplants performed outside of Israel.

Luxembourg

HCV-infected population
The anti-HCV prevalence in 2013 was estimated at 0.7% in the general population, based on two databases and the consensus of an expert panel. The National Health Laboratory (LNS) database has records of 2205 cases from 1990 to 2013, with 94% confirmed chronic HCV (n = 2062) [52]. Additionally, the Centre Hospitalier of Luxembourg (CHL) database has records for 2141 cases from 2002 to 2013, with 93% confirmed chronic HCV (n = 1988) [53]. A viremic rate of 77% was calculated after removing cured patients from database estimates. This viremic rate corresponded to 3080 viremic cases in 2013.

The age and gender distribution of the infected population was estimated using CHL and LNS databases [52,53] and accounting for mortality and cure. Using this method, in 2013 the median age was 35–39 years, with a 2:1 ratio of males to females.

The genotype distribution was obtained through an analysis of 1368 patients in the CHL cohort [54]. Genotypes 1 (55.3%) and 3 (33.6%) predominated, followed by genotypes 4 (6.4%), 2 (4.3%) and 5 (0.4%) [54].

Diagnosed
CHL and LNS databases were used to estimate the number of individuals living with an HCV diagnosis in 2013 [52,53]. A diagnosis rate of 84% was calculated, corresponding to 2590 diagnosed viremic infections, with approximately 100 new viremic cases diagnosed annually.

Treated
In 2013, approximately 100 patients were treated, based on IMS data for standard units of Peg-IFN sold [15] and an adjustment factor for use of Peg-IFN for other indications (32%). Additionally, it was assumed that 26 cases were treated in prisons in 2010, an increase from 10 cases in 2004.

Liver transplants
The number of liver transplants from 2003 to 2012 was available through Eurotransplant [55]. As little data were available on the per cent of transplants attributable to HCV in Luxembourg, a Belgian analog of 12.6% was used [56].

Mexico

HCV-infected population
The estimate for anti-HCV prevalence in the general Mexican population was derived from data obtained from the 2000 National Health Survey [57]. This study reported an anti-HCV prevalence of 1.40% (95% CI: 1.1–1.6%) in the adult population (>20 years of age). It was estimated that the anti-HCV prevalence in the entire population was 0.95% [12]. The age and gender distribution was developed using the age and gender distribution from the National Health Survey analysis with an exponential decrease, by 5-year cohort, for individuals <20 years of age. The viremic rate, 65.2%, was derived from an analysis of individuals participating in general screening programs conducted by the Mexican Liver Foundation from 2007 to 2013. This led to a viremic prevalence of 0.62% (619 000 cases) in 2000. A weighted average of three studies totalling more than 11 000 patients from multiple regions was used for the genotype distribution [58–60].

Diagnosed
Using blood donation screening by the Centro Nacional de la Trasfusion Sanguinea and unpublished general screening data from the Mexican Liver Foundation, it was estimated that 155 800 of the infected population was living with a diagnosis 2011 [61–64]. In 2011, 14 700 individuals were newly diagnosed.

Treated
Using unpublished data from the Mexican Social Security Institute, it was estimated that 3110 patients were treated in 2011.

Liver transplants
Liver transplant data were available through the Centro Nacional de Trasplantes. In 2011, there were 101 liver transplants performed in Mexico, and in 2013, there were 149 transplants [65]. It was estimated that 31.8% of liver transplants per year were attributable to HCV [66–69].

Mongolia

HCV-infected population

Based on expert consensus, the prevalent viremic population in 2013 was estimated at 200 000 individuals, equivalent to 6.8% prevalence. An overall viremic rate of 70% was estimated, resulting in an anti-HCV prevalence of 9.8% (285 700 cases). The high estimate for prevalence came from a study in the general population [70], while the low prevalence estimate was based upon a study of blood donors [71]. For the age and gender distribution of the infected population, published estimates by age and gender were applied [70]. The genotype distribution of the prevalent population was estimated using data from 167 RNA samples collected throughout the country [70].

Diagnosed

Based on expert consensus, there were an estimated 60 000 previously diagnosed cases and 1300 newly diagnosed cases in 2013.

Treated

It was estimated that 200 patients annually were treated based on expert consensus and IMS data for standard units of Peg-IFN sold after adjustment to account for under-reporting.

Liver transplants

In 2013, there were an estimated eight liver transplants in Mongolia; three (38%) were estimated to be attributable to HCV.

The Netherlands

HCV-infected population

The most recent HCV estimate among the Dutch general population, as well as specific risk groups, reports an anti-HCV prevalence of 0.22% (0.07–0.37%) among 15- to 79-year-olds in 2009 [72]. When applied to the entire population, this estimate corresponds to an anti-HCV prevalence of 0.18%. The viremic rate was estimated to be 74% [73], corresponding to a viremic prevalence of 0.13% in 2009 and 21 800 infected individuals. There were no reliable age and gender distributions available for The Netherlands but the median age was reported at 54 years old in 2006-2007 [74] similar to the United States. In addition, the United States and Dutch gender ratios were considered comparable as well as the timing of the peak infections [72,75]. The Dutch age and gender distributions were established using the United States as an analog [75]. The genotype distribution was established using data from an analysis of patient data collected between 2002 and 2005 from 53 hospitals in 11 of the 12 Dutch provinces [76].

Diagnosed

Based on expert consensus, there were estimated to be 12 000 viremic individuals in the Netherlands with a known diagnosis of chronic HCV in 2013. It was estimated that each year 650 viremic individuals were newly diagnosed.

Treated

In 2013, 880 patients were treated for chronic (or acute) HCV infection in the Netherlands [77].

Liver transplants

Liver transplant data were available through the Eurotransplant Statistics Report Library. In 2011, there were 135 liver transplants performed in the Netherlands, increasing to 142 in 2013 [78]. It is estimated that 12% of liver transplants per year are attributable to HCV [79].

New Zealand

HCV-infected population

In New Zealand, the viremic population was estimated at 50 000 individuals in 2013, corresponding to viremic prevalence of 1.11% [80]. A viremic rate of 76.5% was applied, based on clinic data collected from patients in New Zealand [81], resulting in an anti-HCV prevalence of 1.45%. The age and gender distribution of the infected population was based on demographic data collected through March 2014 from over 1000 HCV individuals attending an HCV clinic [81]. The genotype distribution of the prevalent population was based upon New Zealand clinic data [82].

Diagnosed

Based on expert consensus, 40% of the viremic population was previously diagnosed in 2013 (20 000 individuals). Based on the ratio of newly to previously diagnosed in Australia [83,84], it was estimated that 910 cases were newly diagnosed in 2013.

Treated

In 2013, it is estimated that 900 patients were treated in New Zealand, based on expert consensus and IMS data for standard units of Peg-IFN sold in New Zealand, which were adjusted for under-reporting. Approximately 50% of patients were treated with Peg-IFN and RBV (reimbursed by the government) and the remaining 50% of patients were treated within clinical trials.

Liver transplants

In 2013, there were 36 liver transplants performed in New Zealand of whom 24 were in adults. Thirteen transplants were attributable to HCV (54% of all adult transplants). The total number of annual liver transplants was available from transplant registry reports for the years 1997 to 2012 [85]. The proportion of all liver transplants attribut-

able to HCV varied by years and was estimated at 38% for all years [85].

Norway

HCV-infected population

The anti-HCV prevalence in 2012 was estimated at 0.55% in the general population, based on notification data and consensus from local experts. A viremic rate of 79.5% was chosen, corresponding to 21 800 viremic cases in 2012 [22]. The age and gender distribution of the infected population was estimated using annual notification data (1990–2013) aged to 2013 accounting for mortality, cure and spontaneous clearance [86]. Using this method, in 2013, 54% of the population was between 40 and 55 years of age. By comparison, 54% of notifications were between 30 and 50 years of age in 2013. A 2003 study of the general population found the highest prevalence in individuals between 40 and 45 years of age, suggesting a 2013 average age of 50–55 [22].

The genotype distribution was predominantly genotype 3 (50%) and genotype 1 (40%), with 9% genotype 2 and 1% genotype 4 (personal communication with Olav Dalgard, 2013). A genotype 1a/1b split was obtained from a 2003 study [22] and applied to the distribution presented above.

Diagnosed

Notification data from 1990 to 2013, as reported to the Norwegian Surveillance System for Communicable Diseases (MSIS), were aged to 2013 accounting for mortality, cure and spontaneous clearance rates [86]. An estimated 12 000 viremic-infected patients were living with a diagnosis in 2013, with approximately 1090 new viremic infections diagnosed in 2013 [86].

Treated

In 2013, approximately 605 patients were treated, based on Ribavirin user data collected by the Norwegian Prescription Registry [87]. Ribavirin user data from 2004 to 2013 were calibrated in 2010 to IMS data for standard units of Peg-IFN sold to account for duplication of use across years.

Liver transplants

The number of liver transplants from 1999 to 2012 was available through Scandiatransplant [88]. Among 110 transplanted in 2013, approximately 22.7% of those who received a liver transplant were anti-HCV positive (personal communication with Olav Dalgard, 2014). Prior to 2008, the number transplanted with anti-HCV (1984–1994, 2.1%; 1995–2004, 6.9%; 2005–2008, 11.2%) were calculated using the frequency of diagnoses in liver transplants and assuming that 40% of hepatocellular carcinoma was attributable to HCV [89,90].

Poland

HCV-infected population

There are a number of studies reporting anti-HCV prevalence in Poland [91–101]. The largest study determined a viremic (RNA positive) rate of 0.60% [91]. However, it also determined an antibody positive prevalence of 1.94%. A more recent study found an antibody prevalence of 1.91% with a single ELISA test and 0.86% with confirmatory tests [92]. Thus, in 2009, the anti-HCV prevalence in the adult population (18+) in Poland was estimated to be 0.86%, with an estimated prevalence of 0.72% for all ages. The viremic prevalence was estimated to be 0.60% in adults. For this analysis, it was estimated that there were 200 000 viremic infections in 2009 (for all ages), corresponding to a prevalence of 0.52%.

The age and gender distribution was developed using diagnosed data from 1999 to 2012 from the National Institute of Public Health–National Institute of Hygiene (NIPH–NIH) [102]. The number of RNA-positive-diagnosed cases was available from 1999 to 2012. The diagnosed population was adjusted for mortality and cured, by year, and was aged to 2012. It was assumed that the age and gender distribution of the diagnosed population was reflective of the current distribution in Poland.

Diagnosed

At the end of 2012, there were 30 200 patients living with a diagnosis and 2290 individuals were newly diagnosed [102]. For this analysis, 3000 newly diagnosed were assumed per year, beginning in 2012.

Treated

An average number of 3470 individuals were treated per year from 2008 to 2012, with 2100 treated in 2011. In the light of increased triple therapy treatment for previously warehoused patients, the total number of treated patients increased to 4040 for the first time in 2013. It was anticipated that the number of treated patients would decrease to the 2008–2012 average with an estimated 3500 individuals treated in 2014.

Liver transplants

Liver transplant data were available through Poltransplant, the Center for Organizational and Coordination for Transplantation. In 2011, there were 300 liver transplants performed in Poland, increasing to 318 transplants in 2013 [103]. It was estimated that 28% of transplants were attributable to HCV [104].

Russia

HCV-infected population

The estimate for prevalence in the general Russian population was derived from a general consensus of 4.1% in

2010 reported in multiple sources [8,105,106]. Applying a viremic rate of 71% [107], the viremic prevalence in 2010 was estimated at 2.91%, corresponding to 4 162 000 infections. The age and gender distribution was developed using the age distribution and gender ratio of infection presented previously [108]. The genotype distribution was developed using data from a regional registry of more than 40 000 patients with chronic viral hepatitis [108].

Diagnosed
Using unpublished data and an analysis of regional registries conducted by the Russian National Reference Center for Viral Hepatitis, approximately 43% of the infected population in 2012 had received anti-HCV testing [109]. In 2012, 55 900 chronic individuals were newly diagnosed (unpublished data).

Treated
Using regional registries, it was estimated that 5500 patients were treated in 2011.

Liver transplants
Liver transplant data were available through the Russian transplant society [110,111]. In 2011, there were 204 liver transplants performed in Russia [110]. It was estimated that 32% of liver transplants per year were attributable to HCV [112,113].

Slovak Republic

HCV-infected population
The estimate for prevalence in the general Slovak population came from an unpublished analysis of 4596 individuals across all regions in the Slovak Republic from 2010 to 2011 (EPID Study). This study reported an anti-HCV prevalence of 1.40% among adults with a viremic rate of 49.2%, corresponding to a viremic prevalence of 0.70%. The anti-HCV prevalence among all ages was estimated at 1.24% with a viremic prevalence of 0.61% corresponding to 33 400 viremic infections.

The age and gender distribution was developed using the age and gender distribution from the same analysis. A previous analysis of data collected from 1997 to 2002 reported similar results [114]. Among randomly sampled individuals over 15 years of age, there was an anti-HCV prevalence of 1.52%, a viremic rate of 43.6% and a viremic prevalence of 0.67%.

Diagnosed
According to expert consensus, approximately 10% of the infected population were patients living with a diagnosis in 2012. Between 2006 and 2012, an average of 270 individuals yearly were newly diagnosed [115].

Treated
It was estimated by expert consensus that 320 patients were treated in 2011.

Liver transplants
Liver transplant data were available through the Slovak Centre of Organ Transplantation as reported by the International Registry in Organ Donation and Transplantation. In 2011, there were 21 liver transplants performed in the Slovak Republic [116]. It was estimated that 23% of liver transplants per year were attributable to HCV [117]; however, there is evidence that transplantation due to HCV is increasing with 12 of 13 transplants being attributed to chronic HCV infection to date in 2014 (unpublished data).

South Africa

HCV-infected population
The burden of chronic HCV disease in South Africa is largely unknown and epidemiological data describing the characteristics of the disease are limited. It has been estimated that the prevalence of anti-HCV ranges from 1.4% to 1.8% among blood donors and healthcare workers [118]. For this analysis, an anti-HCV prevalence estimate of 1.7% in 2009 was applied for the adult population [119], which corresponded to 1.12% among all ages when a lower prevalence among children was taken into consideration. Applying a viremic rate of 76.9% (consensus estimate), the viremic prevalence was estimated at 0.86%, corresponding to 432 000 infections among all ages.

The age and gender distribution was developed using the age distribution and gender ratio of infection from specimens received by the National Institute of Communicable Diseases (NICD) from 2010 to 2012 [118]. The genotype distribution was developed using specimens available for analysis from the NICD sample [118].

Diagnosed
From 2008 to 2013, it was estimated that 10 000 individuals were diagnosed through the national healthcare system and that 54 600 individuals were living with a diagnosis in 2013.

Treated
According to the panel of experts, an estimated 100 patients were treated in 2011.

Liver transplants
Liver transplant data were available through the Organ Donor Foundation. In 2011, there were 31 adult liver transplants performed in South Africa [120]. It was estimated that 5% of liver transplants per year are attributable to HCV.

DISCUSSION

The goal of this analysis was to develop consensus estimates of the HCV epidemiology using best available published and unpublished data. The analysis was supported by an exhaustive literature search to identify relevant published studies in each country. The results were then reviewed with a panel of experts in each country, which provided hospital level and other unpublished data.

The data presented here can be used by researchers for a number of different purposes – modelling HCV disease burden, exploring the impact of immigration on HCV infections and determining potential response rate of therapies that vary by genotype. The next manuscript in this supplement will describe how these data can be used to project HCV disease progression using a mathematical model [13]. However, the topic of immigration as a source of new HCV infections has been one of growing interest [121]. The breakout of prevalence by age and gender (Fig. 1) should provide sufficient detail to inform estimates of HCV infections for people moving across borders. It is interesting to note that HCV prevalence in most countries drops in individuals aged 30–35 (Fig. 1), the average age of immigrants to most countries. Exceptions are found in countries where injection drug use (IDU) is the main source of new HCV infections – Finland, Ireland, Luxembourg, Norway, Poland, Russia and Slovak Republic. Although HCV prevalence among 30- to 35-year-olds is high in these countries, the IDU population with an HCV infection is an unlikely source of new immigrants. Thus, care should be taken in using the data presented here without adjustments.

A number of countries had centralized registries for diagnosed HCV cases – Finland, Ireland, Norway and Poland. Additionally, Luxembourg is in the planning stages for a centralized registry. Although Israel does not have a central registry for HCV, one national healthcare provider, CHS, covers over 60% of the population and retains detailed data. Russia has regional registries, and work is underway to consolidate data across the country. Greece recently used an innovative technique of using a randomized national phone survey to quantify the diagnosis rate in the country [25]. Although the method has some limitations, it does provide a quick technique to quantify diagnosis rates in countries where central registries are not available.

Great care was taken to combine data, analysis and expert panel consensus to provide the best available data. However, there were a number of limitations with this analysis. In some countries, very little data were available and the consensus numbers reported here may not be representative of the true state of HCV infection in the country. This highlights the need for more robust epidemiology studies to quantify HCV in the general population while considering the urban, rural and marginalized populations (IDU, people in institutions, etc.).

In countries where registries or epidemiology studies were available, it was assumed that the reported numbers are representative of the countries' HCV-infected population. Data reported to the registries could have a selection bias as testing and reporting may not be uniform across all subpopulations. In addition, viremic rate and genotype distribution were typically based on studies with relatively small sample sizes. Data from multiple studies were compared to minimize bias, but it is worth noting that both variables can change over time due to treatment rate and immigration.

The number of treated patients was estimated based on the drug sales when a central registry was not available. There was considerable variation in the number of treated patients across countries (Table 1). The use of drug sales data has a number of limitations including under-reporting, the use of drugs in multiple indications and the need to incorporate average adherence and genotype distribution. An effort was made to deal with these limitations using expert panels. In countries where drug sales data were not available or where data are limited, the expert panel estimates were used which may over or under-estimate the total number of treated patients in the country.

This analysis highlights the need for more robust HCV epidemiology analyses that take into consideration the general population and subpopulations that may not be captured in a national study. The data required for a detailed analysis of HCV disease burden include anti-HCV and viremic prevalence, the number previously and newly diagnosed, the annual number of treated patients and the genotype distribution. Ideally, future studies will be conducted in multiple regions of the country to provide accurate national estimates as well as variations across different geographies.

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