

Historical epidemiology of hepatitis C virus (HCV) in selected countries

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SUMMARY. Chronic infection with hepatitis C virus (HCV) is a leading indicator for liver disease. New treatment options are becoming available, and there is a need to characterize the epidemiology and disease burden of HCV. Data for prevalence, viremia, genotype, diagnosis and treatment were obtained through literature searches and expert consensus for 16 countries. For some countries, data from centralized registries were used to estimate diagnosis and treatment rates. Data for the number of liver transplants and the proportion attributable to HCV were obtained from centralized databases. Viremic prevalence estimates varied widely between countries, ranging from 0.3% in Austria, England and Germany to 8.5% in Egypt. The largest viremic popula-

tions were in Egypt, with 6 358 000 cases in 2008 and Brazil with 2 106 000 cases in 2007. The age distribution of cases differed between countries. In most countries, prevalence rates were higher among males, reflecting higher rates of injection drug use. Diagnosis, treatment and transplant levels also differed considerably between countries. Reliable estimates characterizing HCV-infected populations are critical for addressing HCV-related morbidity and mortality. There is a need to quantify the burden of chronic HCV infection at the national level.

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

INTRODUCTION

Hepatitis C viral (HCV) infection is a major public health burden in many countries [1], and a number of new treatment options will become available in the coming years that promise convenience (oral therapies) with a higher efficacy (cure rates >90%), a shorter duration of treatment

(12–24 weeks) and fewer side effects and contraindications as compared to the current standard of care. In the light of these options, clinicians and government agencies will require reliable data to evaluate how to utilize these therapies most efficiently. A number of studies have characterized HCV infection rates across different countries [2–6], but they have typically focused on quantifying the total

Abbreviations: BASL, Belgium Association for the Study of Liver; CHC, chronic hepatitis C; DAA, direct-acting antiviral agent; G, Genotype; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IDU, injection drug use; INE, National Institute of Statistics; IRODaT, International Registry on Organ Donation and Transplantation; PEG-IFN, Pegylated interferon; PHAC, Public Health Agency of Canada; PI, protease inhibitor; RBV, ribavirin; RNA, ribonucleic acid; RVR, rapid viral response; SVR, sustained viral response; UN, United Nations.

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number of HCV infections. In addition, as described below, many countries have published national data in local or regional journals, but they typically focus on one aspect of HCV epidemiology.

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 positive or chronic HCV cases), 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 of the expert panel to meet. 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. Nonindexed 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 and government reports.

Face-to-face meetings were conducted to review findings and analyses with the expert panel. When no input data were available, it was explicitly stated, and 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 HCV or chronic HCV infections. The term viremic was used throughout this study to highlight the presence of HCV virus. The term chronic hepatitis C (CHC) was also used to represent viremic infections. The term incidence was used for new HCV infections and not newly diagnosed.

Unless stated, population data were obtained from the United Nations (UN) population database by age, gender and 5-year age cohort [7]. Population data for the following countries were collected as listed:

Egypt – Population estimates came from the UN database for 1950–2005 and future >2013 [7]. For the years 2006–2012, population data came from the Egyptian Central Agency for Public Mobilization and Statistics [8]. Age and gender distribution in 2012 was used for future years.

England – Population estimates were calculated as a per cent of the total UK population, obtained by 5-year age

and gender cohorts from the UN population database [7]. The per cent of the UK population residing in England in 1991, 2001 and 2011 was obtained from the Office of National Statistics [9].

Portugal – Data for 1950–1969 were obtained from the UN population database [7]. For 1970–1975, median population values from the UN and the Instituto Nacional de Estatística (INE) were used to ensure a smooth transition between the two data sets [10,11]. For 1976 onward, INE population data were applied exclusively.

Spain – The National Statistics Institute of Spain, Instituto Nacional de Estadística (INE) and the UN population database were used [12,13]. INE provided historical data describing the time period from 1970 to 2011. Population estimates for 1950–1969 and 2012–2100 were obtained from the UN World Population Prospects and trended according to the figures provided by INE.

Sweden – Population data were obtained from the UN population database, with validation of data from Swedish Population Registry at Statistics Sweden [14].

Switzerland – Population data were from the Swiss Federal Office of Statistics and the UN population database [7,15].

Turkey – Population data were obtained from the Turkish Statistical Institute [16,17].

The annual number of liver transplants was gathered from national or international databases and adjusted for the percentage 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. When published or official data were not available, it was explicitly stated. In most cases, the national databases reported antibody-positive infections, and a separate analysis was used to estimate per cent viremic. In countries where HCV was a notifiable infection and a reliable annual number of newly diagnosed cases were reported, the total diagnosed cases were 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

Table 1 HCV epidemiology by country

	Australia	Austria	Belgium	Brazil	Canada	Czech Republic	Denmark	Egypt
Country's population (000)	22 900	8 300	10 100	189 600	33 400	10 600	5500	75 200
Year	2012	2008	1994	2007	2011	2012	2007	2008
HCV antibody positive (000)								
Total cases	308 (277–339)	38 (8–60)	88 (12–114)	2616 (2332–3000)	330 (210–460)	60 (21–74)	34 (27–35)	9387 (8449–10 326)
Prevalence	1.3% (1.2–1.5%)	0.5% (0.1–0.7%)	0.9% (0.1–1.1%)	1.4% (1.2–1.6%)	1.0% (0.6–1.3%)	0.6% (0.2–0.7%)	0.6% (0.5–0.6%)	12.5% (11.2–13.7%)
Year of estimate	2012	2008	1994	2007	2011	2012	2007	2008
Viremic infections (000)								
Total viremic cases	230 (207–253)	28 (6–44)	70 (10–91)	2106 (1877–2415)	254 (161–354)	42 (15–52)	21 (17–22)	6358 (5722–6994)
Viremic prevalence	1.0% (0.9–1.1%)	0.3% (0.1–0.5%)	0.7% (0.1–0.9%)	1.1% (1.0–1.3%)	0.7% (0.5–1.0%)	0.4% (0.1–0.5%)	0.4% (0.3–0.4%)	8.5% (7.6–9.3%)
Viremic rate (%)	75	74	80	81	77	70	62	68
Year of estimate	2012	2008	1994	2007	2011	2012	2007	2008
Genotypes (%)								
1a	20	20	–	31	37	8	34	–
1b	17	52	50	33	21	27	12	4
1 Other	17	–	9	0.4	6	31	–	6
1	55	72	59	65	64	66	46	10
2	5	5	6	5	14	1	8	–
3	37	19	19	30	20	31	43	–
4	2	4	14	0.1	0.3	2	3	90
5	–	–	2	0.2	–	–	–	–
6	2	–	–	–	–	–	–	–
Other	–	–	–	–	1	–	–	–
Year of estimate	–	2012	1994, 2004	1995–2000, 2002–2006	1998–2004	2012	2012	–
Diagnosed (viremic)								
Total cases	185 000	9700	22 900	300 000	176 400	13 000	11 600	871 700
Annual newly diagnosed	11 300	600	2900	10 000	7600	800	700	125 000
Year of estimate	2010	2012	2010	2013	2013	2012	2010	2013
Treated								
Annual number treated	3900	1100	710	11 700	3600	880	105	65 000
Year of estimate	2011	2011	2011	2011	2013	2011	2011	2011
Liver transplants								
Total liver transplants	194	128	299	1494	482	89	51	230
HCV liver transplants	69	28	38	448	160	14	5	213
% due to HCV	36	22	13	30	33	16	10	93
Year of estimate	2011	2011	2011	2011	2011	2011	2011	2011

Table 1 (continued)

	England	France	Germany	Portugal	Spain	Sweden	Switzerland	Turkey
Country's population (000)	50 700	60 600	82 000	10 000	46 800	9500	7100	70 600
Year	2005	2004	2012	1995	2012	2012	1998	2009
HCV antibody positive (000)								
Total cases	221 (153–286)	394 (277–490)	410 (246–738)	152 (117–195)	702 (526–877)	53 (45–66)	110 (57–128)	667 (500–833)
Prevalence	0.4% (0.3–0.6%)	0.7% (0.5–0.8%)	0.5% (0.3–0.9%)	1.5% (1.2–1.9%)	1.5% (1.1–1.9%)	0.6% (0.5–0.7%)	1.6% (0.8–1.8%)	0.9% (0.7–1.1%)
Year of estimate	2005	2004	2012	1995	2012	2012	1998	2009
Viremic infections (000)								
Total viremic cases	152 (105–197)	256 (180–319)	275 (165–494)	115 (89–148)	481 (361–602)	41 (35–51)	88 (45–102)	547 (410–683)
Viremic prevalence	0.3% (0.2–0.4%)	0.4% (0.3–0.5%)	0.3% (0.2–0.6%)	1.1% (0.9–1.5%)	1.0% (0.8–1.3%)	0.4% (0.4–0.5%)	1.2% (0.6–1.4%)	0.8% (0.6–0.9%)
Viremic rate (%)	69	65	67	76	69	77	80	82
Year of estimate	2005	2004	2012	1995	2002	2012	1998	2009
Genotypes (%)								
1a	23	15	25	14	26	40	26	8
1b	12	30	33	44	44	10	26	84
1 Other	11	15	4	–	–	–	–	–
1	44	60	63	58	69	50	52	92
2	5	9	6	2	3	20	9	2
3	47	20	27	28	20	30	29	5
4	4	9	3	9	8	–	10	1
5	–	2	–	0.2	–	–	–	–
6	–	0.2	–	–	–	–	–	–
Other	–	–	–	3	–	–	–	–
Year of estimate	2007–2010	2001–2007	2003–2011	2002–2008	1996–2004	2012	1994, 2012	2012
Diagnosed (viremic)								
Total cases	46 200	133 600	160 000	40 600	167 300	32 900	32 900	81 900
Annual newly diagnosed	5600	9000	4000	1300	15 300	1500	1100	5500
Year of estimate	2010	2010	2012	2013	2010	2013	2012	2012
Treated								
Annual number treated	5400	10 100	12 700	1200	9800	1100	1100	4200
Year of estimate	2011	2011	2011	2011	2011	2011	2011	2011
Liver transplants								
Total liver transplants	572	1164	1199	219	1137	156	109	904
HCV liver transplants	103	274	272	51	359	35	23	154
% due to HCV	15	24	23	23	32	22	21	17
Year of estimate	2011	2011	2011	2011	2011	2011	2011	2011

IMS Health [18], was 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), 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 also adjusted to account for uses in HCV and any under-reporting using inputs from the expert panel.

RESULTS

Australia

HCV-infected population

The total viremic HCV population in 2012 was estimated at 230 000 (207 000–253 000) with a viremic prevalence rate of 1.0% (0.9–1.1%) [19] (Table 1). Low and high estimates for viremic HCV prevalence were assumed to be equal to 90% and 110% of the total estimated viremic population. Viremia was estimated at 74.6% [20]. Anti-HCV prevalence was estimated at 1.3% (1.2–1.5%), equivalent to 308 000 (277 000–339 000) anti-HCV positive individuals. For the age and gender distribution of the infected population (Fig. 1), notification data for HCV infection (newly acquired and unspecified) from 1995 to 2013 were utilized to calculate age- and gender-specific HCV detection rates by 5-year age group. It was assumed that all individuals diagnosed after 2010 were alive in 2013. For other years, it was assumed that diagnosed cases aged ≥ 70 (1995), ≥ 75 (1996–2000), ≥ 80 (2001–2005), ≥ 85 years (2006–2010) were lost to mortality [21]. The genotype (G) distribution of the prevalent population was estimated using data from an Australian surveillance system [22], and validated using data from a published study [23] (Table 1).

Diagnosed

In 2010, it was estimated that there were 185 000 viremic individuals who were living with a known HCV diagnosis [20]. There were 11 300 newly diagnosed individuals in 2010 according to the national surveillance system [21].

Treated

The number of treated patients in 2011 was estimated at 3900 using the units of PEG-IFN sold [18]. During the 2000s, PEGIFN and RBV treatment was the standard of care for chronic HCV and in the Australian context led to a sustained viral response (SVR) in around 50% for people with HCV G1 and 70% for HCV G2/3 [22]. However, treatment uptake remained low (2000–4000 people per year; 1–2% of chronic HCV population), even following the removal of mandatory pre-treatment liver biopsy in 2006

and broadening of inclusion criteria to include all fibrosis stages and normal alanine aminotransferase levels [24].

Liver transplants

In 2011, there were 194 liver transplants performed in Australia. Thirty-six percent (69 transplants) were attributable to HCV. The total number of annual liver transplants was available from a national organ registry for the years 1985–2012 [25]. The number of liver transplants attributable to HCV as a primary indication, and the number of cases attributable to HCC as a primary indication, and the number of cases attribute to HCC with HCV as a secondary indication were reported annually by the Kirby Institute [19].

Austria

In 2008, there were an estimated 38 000 (8000–60 000) anti-HCV individuals, with an anti-HCV prevalence rate of 0.5% (0.1–0.7%) [2,26]. With a viremic rate of 73.9%, there were approximately 28 000 (6000–44 000) viremic individuals, corresponding to a viremic prevalence rate of 0.3% (0.1–0.5%) [2,26]. The base and low estimates were obtained through a recent WHO review of the European Region, which noted an anti-HCV prevalence estimate of 0.1% among first-time blood donors and calculated a 0.5% anti-HCV prevalence among the general population [2]. The base was imputed from blood donor studies, using a ratio of general population prevalence to blood donor prevalence, from countries with studies from both populations [2]. A high prevalence of 0.7% was chosen from Straus 2003 [26]. A representative Austrian HCV age and gender distribution was not available, but the expert panel estimated that similar to US, the peak in HCV infections fell between 50 and 59 years old with more infected males than females (Fig. 1). The 2004 genotype distribution of the infected population (Table 1) was estimated using findings from centres in Innsbruck and Graz (personal communication with Wolfgang Vogel and Rudolf Stauber, 2013), as well as Linz (1992–2006 database) [27]. The prominent genotypes are G1b (52%), G1a (20%) and G3 (19%), with G2 (5%), G4 (4%) and G6 (0.1%) accounting for <10% of all cases combined [26,27].

Diagnosed

An estimated 9700 individuals with viremic HCV (36%) were living with a positive diagnosis in 2012, and since 2003, an average of 600 new viremic diagnoses have been reported annually [27,29,30]. Published studies noted that 10 607 unique cases of HCV were reported through the National Hospital Discharge Register (HDR) over eight years (1993–2000) [26]. From 2000 forward, notification data from the Austrian Federal Ministry of Health [29,30], adjusted with a viremic rate of 73.9% [2], were summed and adjusted annually for mortality and cured.

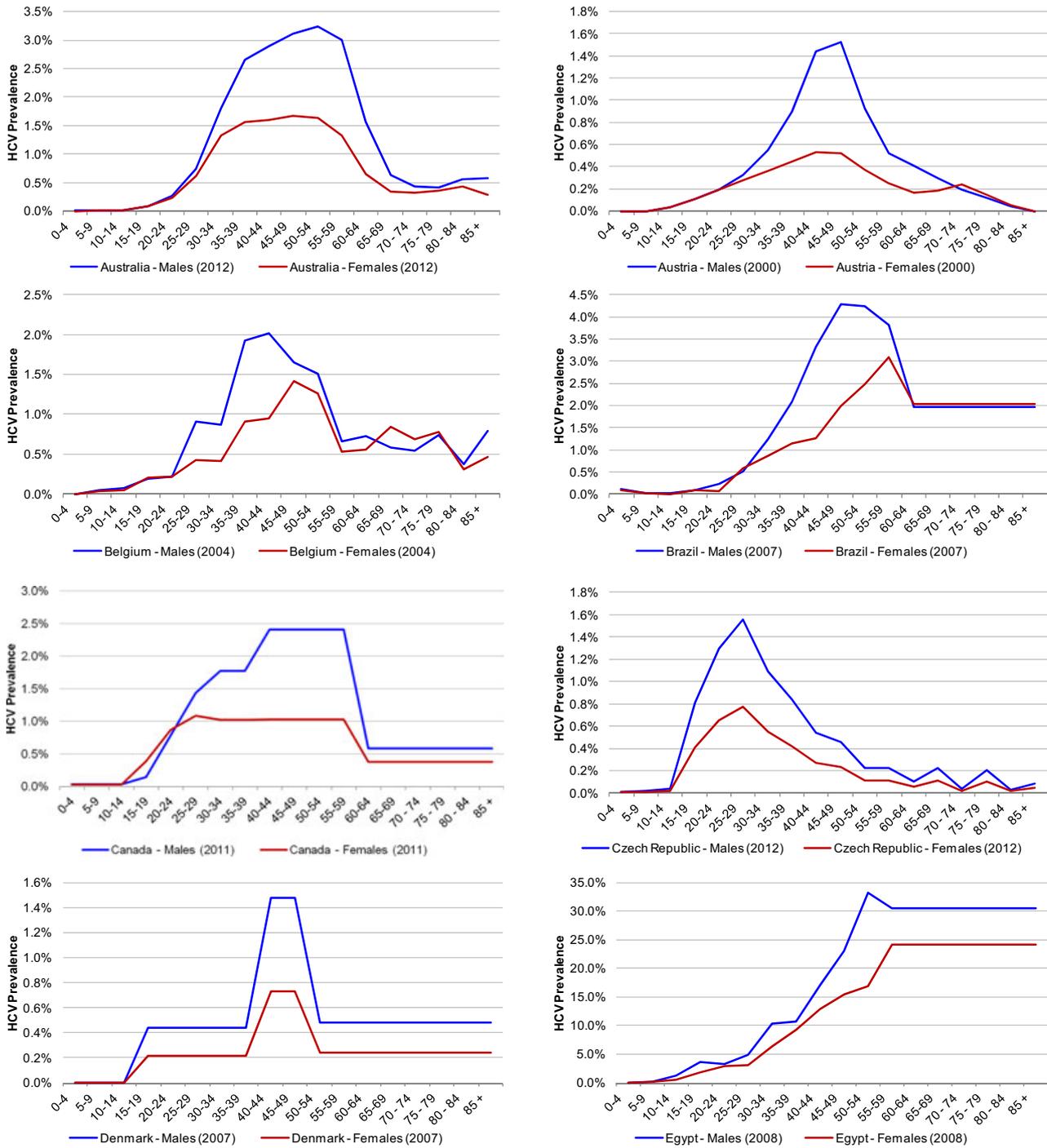


Fig. 1 Viremic HCV prevalence by age and gender.

Treated

In 2011, 1100 patients were treated after analyzing the PEG-IFN unit sale data and taking into account that 10% of units were for non-HCV uses.

Liver transplants

Eurotransplant reported 128 liver transplantations performed in 2011 [31]. Of these, it was estimated that up to

20–25%, or 38 transplants, were due to HCV-related liver disease, according to the expert panel (Table 1).

Belgium

HCV-infected population

Recent population-based studies of the anti-HCV prevalence were scarce and subjected to selection bias. An expert

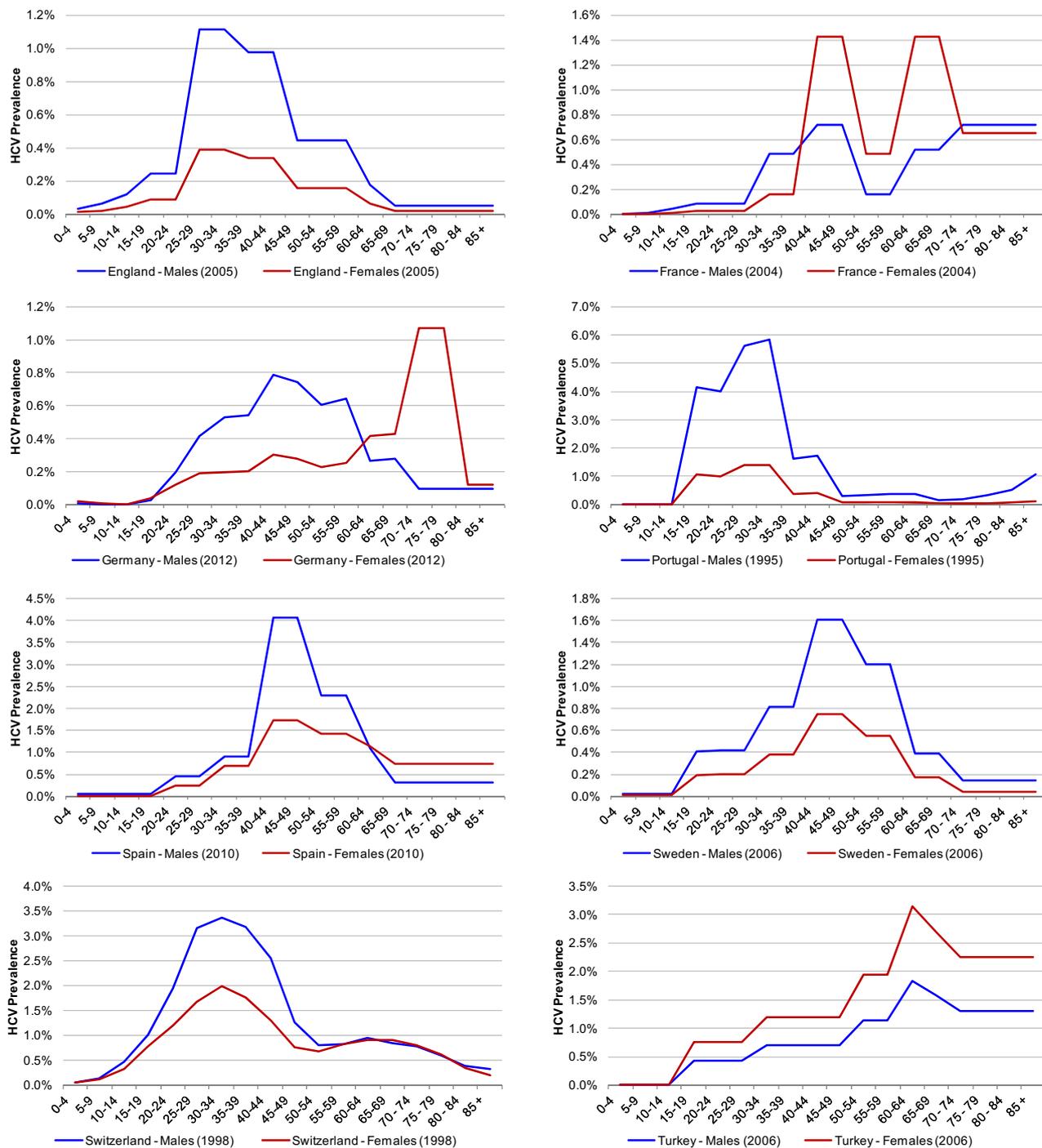


Fig. 1 Continued.

panel agreed that the most representative anti-HCV prevalence estimate for the general population was 0.87% in 1994, with a range of 0.12–1.1% [88 000 (12 000–114 000) viremic individuals] [32–34]. The most commonly cited anti-HCV prevalence, 0.87%, comes from Beutels *et al.*, published in 1997 [32]. These data were based on residual samples from 10 laboratory hospitals in Flanders; however, they were collected in 1994 [32]. A low

value was obtained through a 2003 mail-based study in the Flanders region that measured HCV antibodies in oral fluid, and suggested a prevalence estimate of 0.12% (0.09–0.39%) [33]. A high value was chosen by expert opinion, based on the results of a 2012 report by the Belgian Health Care Knowledge Center (KCE) that estimated an anti-HCV positivity rate of 1.23% among patients with a test funded by one of the seven national sickness funds

[34]. This estimate was generated through a review of the total number of anti-HCV and confirmatory HCV tests reimbursed from 2002 to 2007, and may have excluded tests ordered for high-risk groups, or prior to blood donation [34].

The age and gender distribution of anti-HCV cases (Fig. 1) came from an observational survey conducted with the support of the Belgium Association for the Study of Liver (BASL) [27,35].

To correspond with the prevalence estimate from 1994, a viremic rate of 80% was used assuming a low number of cured patients at that time [36]. The total number of viremic cases in 1994 was estimated to be 70 000 (10 000–91 200), with a viremic prevalence rate of 0.7% (0.1–0.9%) [32–34,36]. The genotype distribution (Table 1) is predominantly G1 (59%) followed by G3 (19%), G4 (14%), G2 (6%) and G5 (2%) [27,37]. The most recent estimate for a G1 split was from 1994, with approximately 85% G1b and 15% G1 other [38].

Diagnosed

As of 2010, approximately 22 900 viremic individuals were diagnosed, with approximately 2900 new viremic HCV diagnoses annually [34,36].

Treated

In 2010, it was estimated that 710 patients were treated. This value was calculated using the standard units of PEG-IFN sold. Five per cent of all PEG-IFN were estimated to be for non-HCV uses.

Liver transplants

From 2008 to 2012, 1159 liver transplants were performed, of which 146 (12.6%) were attributable to HCV infection [39]. In 2011, 299 transplants were performed, 38 of which were attributable to HCV [39]. A panel of experts from centres in Ghent and Leuven reported 10–15% transplant rates due to HCV, whereas those from Liège and Erasme report rates closer to 25%, but also note a lower rate of transplantation in these centres.

Brazil

HCV-infected population

Total seroprevalence was estimated at 1.38% (1.12–1.64%) in 2007, the mid-point of the data collection period (2005–2009) from a national study, equivalent to 2 616 000 (2 332 000–3 000 000) [40]. The low prevalence estimate was based on a study of blood donors [41], while the high estimate was based on expert consensus of a seroprevalent population of approximately 3 million individuals. A viremic rate of 80.5% was applied [42], resulting in 2 106 000 (1 877 000–2 415 000) viremic cases in 2007, and a viremic prevalence rate of 1.1% (1.0–1.3%). The age- and gender-specific prevalence rates were

reported by Brazilian Ministry of Health [43] (Fig. 1). The genotype distribution of the prevalent population was based upon a study of blood samples collected between 1995 and 2000 from all Brazilian states [44]. The distribution of G1 subtypes was based upon data from a separate study [45] (Table 1).

Diagnosed

Based on expert consensus, there were estimated to be 300 000 viremic individuals in Brazil who have been diagnosed with HCV in 2013. Each year an estimated 10 000 viremic individuals were newly diagnosed, based on expert consensus and published data [43].

Treated

In 2011, it was estimated that 11 700 patients were treated in Brazil, after accounting for under-reporting of PEG-IFN units sold [46].

Liver transplants

In 2011, there were 1494 liver transplants performed in Brazil. Liver transplantation has been regulated since 1997, with time on the waiting list used before 2007 as the main criterion for organ allocation. Since 2007, organ allocation has been based upon Model for End-Stage Liver Disease (MELD) scoring [47,48]. Based on expert consensus, it is estimated that 50% of transplants were related to HCV in 1997, declining to 30% by 2011. This was validated using a regional estimate for the proportion of transplants related to HCV [49].

Canada

HCV-infected population

The Public Health Agency of Canada (PHAC) reported anti-HCV prevalence of 0.96% (0.61–1.34%) in 2011, equivalent to 329 760 (209 530–460 280) cases [50] (Table 1). The age and gender distribution of the prevalent population was based upon notification data from PHAC [51] (Fig. 1). An estimated 77% of anti-HCV+ cases in Canada were viremic, resulting in 253 910 (161 340–354 420) cases with a viremic prevalence rate of 0.74% (0.47–1.0%) [52]. Genotype distribution of the prevalent population was based upon data collected from Canadian patients between 1998 and 2004 [53].

Diagnosed

There is considerable variation in data reported for diagnosis levels in Canada. PHAC estimated that 79% of individuals were diagnosed in 2007 [54], while national household surveys conducted from 2007 to 2011 found that 30% of individuals were aware of their infection [55]. Based on expert consensus, it was estimated that 70% of the infected population were diagnosed in 2013. The newly diagnosed population was estimated based on

the number of notifications from the most recent year of data (2011) reported by PHAC; there were 9923 notifications [51], and 23% were assumed to be nonviremic [52]. It was estimated that 176 400 viremic individuals were diagnosed in Canada in 2010, and 7641 viremic individuals were newly diagnosed.

Treated

Between 2001–2003, it was assumed that 5000 patients were treated annually. Between 2004 and 2012, the annual number of Peg-IFN units sold were used to estimate the treated population. Beginning in 2013, it is estimated that 3600 patients were treated in Canada after taking into consideration under-reporting of PEG-IFN units [18]. Historically, more patients were treated (6200 in 2009 and 5400 in 2010), but the practice of deferring therapy until new agents are available (warehousing) has recently increased.

Liver transplants

In 2011, there were 482 liver transplants performed in Canada. Of these, 33% were estimated to be HCV-related. The historical number of transplants completed annually was available through the Canadian transplant registry [56], along with the percentage of transplants attributable to chronic HCV (CHC) infection [57].

Czech Republic

HCV-infected population

There are no national population-based estimates for HCV prevalence. Current estimates were restricted to select regions and select populations such as injection drug users (IDU) and blood donors [58–62]. Without a national community-based study, and because of known regional variation, viremic HCV prevalence for the general population was estimated by an expert panel. The viremic prevalence in the general population was estimated to be 0.4% (0.1–0.5%) in 2012, corresponding to 42 300 (14 800–51 800) individuals. Using a viremic rate of 70%, the anti-HCV prevalence was back-calculated estimating 60 400 (21 100–74 000) individuals. The anti-HCV prevalence was estimated to be 0.6% (0.2–0.7%). The age and gender distribution was developed using 2012 diagnosed data from The National Institute of Public Health (Fig. 1) [63]. Published genotype studies were also limited to select populations such as blood donors [60] and IDU [64,65]. The genotype distribution in Table 1 was developed using 2012 unpublished data collected from treatment centres in five regions in the Czech Republic [66].

Diagnosed

In 2012, there were estimated to be 13 000 viremic individuals living with a diagnosis. Each year, an esti-

mated 800 viremic individuals were newly diagnosed [63].

Treated

In 2010, it was estimated that 880 patients were treated, after taking into consideration the genotype distribution and adherence. The average patient consumed 27 units of PEG-IFN.

Liver transplants

Liver transplant data from 2001 to 2011 were available through the International Registry on Organ Donation and Transplantation (IRODaT) [67]. Transplant data were trended for the years 1993–2000 using available data. In 2011, there were 89 liver transplants performed. In the same year, it was estimated that 15.6% of transplants were attributable to HCV [68].

Denmark

HCV-infected population

The true prevalence of HCV is unknown, as a national survey has never been performed. There were an estimated 34 000 (27 000–35 000) anti-HCV individuals in 2007. This value was back-calculated from a 2007 study of national registries, which estimated 21 400 (16 470–21 470) people living with viremic HCV [69]. The viremic estimate included an estimate of the undiagnosed, hidden population (45.7%) and corresponded to a viremic prevalence of 0.39% (0.3–0.39%) [69]. Back-calculating with a viremic rate of 62.2% resulted in an anti-HCV prevalence of 0.63% (0.48–0.63%) [69]. All registries use a unique 10-digit civil registration number (CPR) assigned to every resident, allowing them to be accurately combined to estimate the true prevalence and undiagnosed population [69].

The prevalence by age among the persons found in the aforementioned registries was 0.12%, 0.40% and 0.13%, respectively, for <40, 40–49 and >50-year-olds. In 2009, the median age was 44 years (Fig. 1) [70].

The distribution of genotypes was most accurately derived from the registries at the Department of Clinical Biochemistry Laboratory at Aalborg University Hospital, where the vast majority of isolated HCV has been genotyped. The distribution derived from more than 6000 patients over the course of 1996–September 2013 is shown in Table 1 (personal communication, Dr. Henrik Krarup, Aalborg University Hospital, Department of Clinical Biochemistry, Denmark, November 2013). G1 (46%: G1a (34%), G1b (12%)) and G3 (43%) are predominant, with significantly fewer G2 (8%) and G4 (3%) (personal communication, Dr. Henrik Krarup, Aalborg University Hospital, Department of Clinical Biochemistry, Denmark, Clinical Chemistry and Gastroenterology, November 2013).

Diagnosed

In 2007, an estimated 11 556 viremic individuals were living with a diagnosis, and annually 400–700 new viremic cases were diagnosed [70].

Treated

Under the current standard of care, approximately 100 patients were treated annually in 2011 [70]. The low number reflects a current ‘warehousing’ of patients waiting for better treatment possibilities.

Liver transplants

In 2011, 51 liver transplants were performed, with approximately five (10%) attributable to HCV (personal communication, Dr. Mette Rye Clausen, Department of Hepatology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, 2013) [71]. The annual number of liver transplants was available from 1990 to 2012 through Scandiatransplant [71].

*Egypt**HCV-infected population*

Estimates for prevalence were based upon data reported from the 2008 Egypt Demographic and Health Survey (EDHS), a large nationally representative sample that included participants in all major Egyptian regions [72]. Seroprevalence and viremia estimates were reported by 5-year age group and gender for individuals aged 15–59 years. For the prevalent population aged <15 years, an exponential decline in viremic prevalence was used. Prevalence in those aged >59 years was set equal to prevalence in those aged 55–59 years (Fig. 1). High and low estimates for overall prevalence were assumed to be equal to 90% and 110% of the overall prevalence. In 2008, it was estimated that 9 387 000 (8 449 000–10 326 000) individuals were anti-HCV positive with a prevalence rate of 12.5% (11.2–13.7%). Viremic prevalence in 2008 was estimated at 8.5% (7.6–9.3%), equivalent to a viremic population of 6 358 000 (5 722 000–6 994 000). The genotype distribution of the prevalent population was based upon expert consensus using published studies [73–75] (Table 1).

Diagnosed

According to the EDHS survey, 1.4% of Egyptians had received a positive HCV diagnosis in 2008 [72]. Based on expert consensus, 15% of the HCV-infected population in Egypt was previously diagnosed in 2013. Accordingly, in 2013, there were an estimated 871 700 viremic individuals living with a diagnosis, with 125 000 viremic individuals being newly diagnosed.

Treated

IMS Health does not capture the number of PEG-IFN units sold annually. The expert panel estimated that approximately 65 000 patients were treated annually—50 000

individuals treated in government hospitals, 5000 through private hospitals and 10 000 individuals who paid cash for their treatment.

Liver transplants

Unpublished data from the National Liver Institute were used to estimate the annual number of liver transplants and the proportion attributable to chronic HCV infection. In 2011, there were 230 liver transplants performed in Egypt, and 92.5% (90–95%) were attributable to HCV (personal communication, Dr. Imam Waked, National Liver Institute, Menoufiya, Egypt, August 2013).

*England**HCV-infected population*

Public Health England (PHE), formerly the Health Protection Agency (HPA), maintains a Bayesian model to estimate the general HCV prevalence in England and Wales and produces annual reports with these findings [3]. Additionally, a 2012 evidence synthesis addressing the excess HCV risk among ethnic minorities was conducted to generate a more robust HCV estimate [76]. This study estimated an anti-HCV prevalence of 0.54% (0.4–0.75%) among the adult population (>15 years) in 2005 [76]. This rate corresponded to an anti-HCV prevalence of 0.4% (0.3–0.6%) in the total population, or approximately 221 000 (153 000–286 000) anti-HCV infections. The age and gender distribution of HCV cases (Fig. 1) came from the 2012 evidence synthesis [76].

A rate of 69% was used to adjust for viremia [77], corresponding to 151 600 (105 100–196 500) viremic cases in 2005, or a viremic prevalence of 0.3% (0.2–0.4%).

The predominant HCV genotypes, as evaluated through 18 sentinel centres from 2007 to 2010, were G1 and 3, accounting for 44% and 47% of infections, respectively, [77], as shown in Table 1. G1a accounted for 23% of all cases [77,78].

Diagnosed

In 2010, there were an estimated 46 200 viremic individuals living with a diagnosis. Each year, an estimated 5600 viremic individuals are newly diagnosed [79]. The estimate of total diagnosed was calculated using notification reports from 1992 to 2010 adjusted for viremia, as well as mortality and cure rates [79].

Treated

In 2010, 5400 HCV patients were estimated to be treated, after taking into consideration the genotype distribution and patient adherence.

Liver transplants

From 1996 to 2012, more than 8630 liver transplants were performed, approximately 1280 of which were attributable to HCV (15%) [79]. In 2011, 572 liver transplants

were performed, and 103 (18%) transplants were attributable to HCV [79].

France

HCV-infected population

Based on national surveillance data, there were 367 100 (269 400–464 800) antibody-positive individuals between ages 18 and 80 years [80]. The age and gender distribution of the prevalent population was based upon published estimates [80] (Fig. 1). Prevalence rates for those aged >80 years were assumed to be equal to that reported for the 70 to 80-year age group. An exponential decrease in younger age groups was modelled based on prevalence rates reported for the 18 to 29-year age group. A viremic rate of 65% was applied, based on national surveillance data [80]. Anti-HCV prevalence was estimated at 0.7% (0.5–0.8%) in 2004, with 394 000 (277 000–490 000) anti-HCV-positive cases among individuals of all ages. Viremic cases were estimated at 256 200 (180 300–318 500) in 2004, for a viremic prevalence rate of 0.4% (0.3–0.5%). The genotype distribution of the prevalent population was based upon data collected through the Institut de Veille Sanitaire (InVS) between 2001 and 2007 [81].

Diagnosed

A national study in 2004 reported that 57% of the seroprevalent population was already aware of their HCV status [80]. Historical InVS notification data and expert consensus were used to estimate that 133 600 viremic HCV individuals were previously diagnosed in 2010, and 9000 cases were newly diagnosed [81].

Treated

In 2011, 10 090 HCV patients were estimated to be treated in France, after taking into consideration the genotype distribution and patient adherence.

Liver transplants

In 2011, 1164 liver transplants were performed in France [82]. Of these, 24%, or 274 cases, were estimated to be HCV-related. Data for the annual number of transplants were available through the National Transplant Registry, which also reported the proportion of transplants attributable to HCV-related cirrhosis [82]. In addition, it was assumed that 40% of transplants related to HCC were HCV-related [83] and that 19% of transplants related to fulminant liver failure were attributable to HCV [84]. It was assumed that the proportion of re-transplantations attributable to HCV was equivalent to the proportion of first-time transplantations.

Germany

HCV-infected population

Through a detailed review of published literature and the analysis of subpopulations, an anti-HCV prevalence

estimate of 0.5% (0.3–0.9%), corresponding to 410 000 (246 000–738 000) anti-HCV infections, was estimated for 2012 (Table 1) [85–92]. A national study conducted in 2011, the German Health Interview and Examination Survey for Adults (DEGS1), estimated the anti-HCV prevalence to be 0.3% (0.1–0.5%) [85]. This study suggested a null prevalence among individuals under the age of 40 [85], which is refuted by data from the Robert Koch Institute (RKI) reporting more than 26 000 notifications of HCV among individuals under 40 years of age from 1973 to 2013 [93]. As DEGS1 likely underestimates the true prevalence, it was chosen as the low bound.

Since DEGS1 and the RKI notifications represented the most up-to-date data available, it was determined that combined they would also provide the most representative age and gender distribution for the population. Each distribution was considered representative of 50% of the total infected population (Fig. 1).

The viremic rate was estimated at 67% of the total population [85,90,94], corresponding to 275 000 (165 000–494 000) viremic infections and a 0.3% (0.2–0.6%) viremic prevalence rate in 2012. G1 was the most predominant (63%), followed by G3, 2 and 4 (27%, 6% and 3%, respectively) [95].

Diagnosed

A laboratory-confirmed diagnosis of HCV requires mandatory notification to the RKI. An estimated 160 000 individuals with viremic HCV were living with a diagnosis in 2012, and approximately 4000 viremic individuals are newly diagnosed annually [96].

Treated

After taking into consideration under-reporting, genotype distribution and adherence, there were 12 700 individuals treated in 2011 [97].

Liver transplants

In 2011, there were 1199 liver transplants performed [31]. Of these, it was estimated that 23%, or 272, were due to HCV. US analogues were used to generate weights for the per cent of viral hepatitis cirrhosis attributable to HCV [98] and the per cent of HCC attributable to HCV [83]. These weights were applied to a list of indications for liver transplants [99] and were summed to generate a final per cent of transplants attributable to HCV.

Portugal

HCV-infected population

Anti-HCV prevalence in Portugal in 1995 was estimated at 1.5% (1.2–1.9%), equivalent to 152 000 (117 000–195 000) [100–102] (Table 1). The allocation of the infected individuals by age group and gender (Fig. 1) was based on a previous national report [7]. A viremic rate of

76% was used utilizing the average rate from three studies, weighted by sample size [103–105]. Viremic prevalence in 1995 was estimated at 1.1% (0.9–1.5%), equivalent to 115 000 (89 000–148 000) cases. The genotype distribution of the prevalent population was based upon the average from two studies reporting data from Portugal, weighted by sample size [106,107]. The distribution of G1 subtypes was based upon data from a separate study [108].

Diagnosed

It was estimated that only one-third of viremic individuals, or 40 600, were diagnosed [109] in 2013.

Data reported by SICAD (the national governmental structure for the coordination policy in the field of illicit drugs and alcohol) were used to estimate the number of newly diagnosed cases, given that IDU is the main source of transmission [110,111]. There were 1500 new HCV-positive serologies reported in 2010 among IDU patients, resulting in an estimated 1300 new viremic individuals diagnosed annually [111].

Treated

It was estimated that 1200 patients were treated in 2011, although this number dropped to 830 by 2013 after the introduction of triple therapy with first-generation protease inhibitors (PI).

Liver transplants

In 2011, there were 219 liver transplants performed, according to the National Organ Transplant Registry [112,113]. It was estimated that 23% of transplants were related to HCV, based on estimates for the proportion of HCV-related cirrhosis (16%) [114], acute liver failure (8%) [114] and hepatocellular carcinoma (HCC, 40%) [83].

Spain

HCV-infected population

There were a number of studies reporting anti-HCV prevalence in Spain; however, there was no national population-based estimate [105,115–117]. The most recent prevalence estimate was from a 2002 study reporting an anti-HCV prevalence of 2.6% among adults 25 years of age or older, using data collected from 1994 to 1996 in the Autonomous Community of Catalonia [105]. In the light of limited national estimates, and because of known regional variation, an anti-HCV prevalence for the general population was estimated by a panel of Spanish experts. The anti-HCV prevalence in the general population in Spain was estimated to be 1.5% (1.1–1.9%) in 2012, corresponding to 702 000 (526 000–877 000) individuals. Using a viremic rate of 69%, 481 000 (361 000–602 000) chronically infected individuals were estimated in 2012 [105]. The 2012 viremic prevalence was estimated to be 1.0%

(0.8–1.3%). The age and gender distribution was developed using 2010 diagnosed data from the Autonomous Community of Catalonia (Fig. 1) [118]. It was assumed the age and gender distribution of the HCV-infected population in Catalonia was reflective of the distribution in Spain. The genotype distribution (Table 1) was developed using data from Echevarria *et al.* [119] with modification-based expert opinion (personal communication, Dr. Maria Buti Ferret, Dr. Jose Luis Calleja, Dr. Javier García-Samaniego, Hospital Vall d'Hebron, CIBERehd, Barcelona, Spain, Hospital Puerta de Hierro, Madrid, Spain, Hospital Carlos III, CIBERehd, Madrid, Spain, October 2013).

It was estimated that in 1994–1996, transfusion accounted for 25.5% of the transmission of HCV infection, whereas past or present IDU accounted for an estimated 10% [105]. Transmission of HCV infection through transfusion and IDU has been declining since 1996. The most common route of HCV infection was through nosocomial infection, accounting for approximately 73% of infections in 2005 [120].

Diagnosed

It was estimated that in 2004, 140 000 individuals in Spain were living with a diagnosis of HCV [121]. Total diagnosis was adjusted annually for mortality and cure, and extrapolation for years not included in the analysis resulted in 167 300 cases in 2010. It was estimated that annually 15 300 viremic individuals were newly diagnosed.

Treated

In 2010, it was estimated that 9800 patients were treated. The annual number of treated patients was calculated using treatment data from the Autonomous Community of Catalonia from 2003 to 2010 [118,122–128]. Figures for Spain were derived by extrapolating treatment data in Catalonia to the national level using INE population data. It was assumed that treatment rates in Catalonia were higher than treatment rates in Spain; thus, a ratio of treated patients in Spain with respect to Catalonia of 0.80 was applied to the analysis.

Liver transplants

Liver transplant data were available through the Organización Nacional de Trasplantes [129]. In 2011, 1137 liver transplants were performed, with an estimated 32% of transplants attributed to HCV [130].

Sweden

HCV population

The anti-HCV prevalence in the general population in 2012 was estimated to be 0.56% (0.5–0.7%), or 53 300 (45 000–65 600) cases, based on previous studies and notifications to the Swedish Institute for Infectious Disease Control (SMI), now the Public Health Agency of Sweden.

From 1990 to 2012, 54 000 individuals with positive anti-HCV or HCV RNA were reported to SMI. Among those notified between 1990 and 2010, 20.5% had died before the end of 2010, resulting in a prevalence of 0.43% with a diagnosed, ongoing or resolved, HCV infection. An undiagnosed fraction of about 20% was assumed, increasing the prevalence to approximately 0.56% (53 300 individuals) in 2012 (Table 1). The age and gender distribution of anti-HCV prevalence in 2006 was derived from reported data (Fig. 1).

A viremic rate of 77% was used to estimate the prevalence of chronic HCV infection. This was an average rate from previous studies of anti-HCV positive populations where the viremic rate ranged from 74% to 91% [131–133]. This resulted in an estimated 41 100 (34 600–50 500) viremic individuals, or a viremic prevalence of 0.4% (0.4–0.5%).

The genotype distribution in a previous study was 45% G1, 19% G2, 34% G3 and 2% G4 [134], and according to data from the quality register InfCare Hepatitis database estimated to be 50% G1 (G1a 40%, G1b 10%), 20% G2, 30% G3 and 0% G4 (personal communication, Dr. Ola Weiland, Karolinska Institutet, Department of Medicine, Huddinge, Sweden, December 2013).

The anti-HCV prevalence was over 80% among IDU [132,135], and the reported route of transmission in the Swedish HCV cohort was IDU in 65% of cases. Previous studies demonstrated that hospitalization for drug-related conditions was common also among the 25% without any reported transmission route [136]. Another 6% were infected through blood transfusions before blood donor screening (introduced in 1991), and 2% reported sexual transmission [137]. The prevalence of co-infection with HIV was low, and according to data from the national InfCare HIV register, about 450 patients (7%) in the Swedish HIV cohort were HCV-infected in 2013.

Diagnosed

The size of the total diagnosed population was described above. It was estimated that 33 000 individuals with viremic HCV infection were diagnosed and alive in 2012. During the last decade, approximately 2000 new HCV notifications occurred annually, of which 35% were under 30 years of age [137]. With an estimated viremic rate of 77%, this corresponds to 1540 new viremic cases diagnosed annually. With an increasing and aging HCV-infected population, the annual number of deaths increases, and during the last years, about 1000 persons in the HCV cohort died each year [138].

Treated

In the last 10–15 years, about 1000 individuals were treated annually [136], 10 000–15 000 total, with an estimated 40–50% cure rate.

Liver transplants

Scandiatransplant reports that in 2011, 156 liver transplants were performed, of which 22% ($n = 35$) were due to HCV [139].

Switzerland

HCV-infected population

A number of prevalence studies among subpopulations, including IDU [140–144], hospital patients [145–148], pregnant women [149] and blood donors [150], were reported; however, there has not been a survey to date in the general population [3]. An anti-HCV prevalence of 1.6% (0.8–1.8%) in the general population was chosen by an expert panel using a 1998 modelling study [151]. A low value of 0.8% was chosen from the mid-point of a range estimated through blood donor and pregnant women studies (0.5–1%) that was commonly cited by the Swiss Federal Office of Public Health [3,152]. These estimates corresponded to 110 000 (57 000–128 000) anti-HCV-infected individuals living in 1998 [3,151,152]. The age and gender distribution of the anti-HCV population was developed through the analysis of 25 years of notification data, provided by birth year [152]. This distribution was applied to the 1998 prevalence, after adjusting for the age of the diagnosed population using the birth year (Fig. 1). A viremic rate of 80% was used, resulting in an estimated 88 000 (45 000–109 000) viremic cases in 1998, with a viremic prevalence rate of 1.2% (0.6–1.4%) [153]. The genotype distribution of the infected population, shown in Table 1, is over 50% G1, with 29% G3 and 10% G4 [154]. The G1 split was estimated by a 2013 subtyping analysis of 1000 G1 patients in the Swiss Hepatitis C Cohort database, with approximately 50% G1a and 50% G1b.

Injection drug use was the predominant transmission route of HCV, accounting for approximately 65% of all HCV infections [155]. Active IDU makes up 21% (15 000) of the anti-HCV positive population. This figure was derived from an estimated total of 25 000 people [156] with problematic heroin use and an anti-HCV prevalence of approximately 60% [157,158].

Diagnosed

In 2012, it was estimated that 32 900 viremic individuals were aware of their HCV infection [152]. Thus, approximately 30% of infected individuals have been diagnosed. The total number of diagnosed cases was calculated from HCV notification reports from 1988 to 2012 and adjusted for age- and gender-specific mortality rates and projected liver-related deaths, resulting in an estimated 41 320 individuals living with a diagnosis of HCV [159]. This value was then adjusted for the portion of the diagnosed population that is viremic. Each year, an estimated 1050 viremic individuals were newly diagnosed [152]. Newly

diagnosed cases from 2011 were used as an analogue for 2012, due to reporting changes and potential duplicate records.

Treated

In 2011, it was estimated that 1100 patients were treated, after taking into account genotype distribution and adherence.

Liver transplants

In 2011, 109 liver transplants were performed [160]. Annually, an estimated 21–30% of liver transplants were due to HCV. The low was estimated from an analysis of liver transplants among the transplant cohort (personal communication, Prof. Beat Müllhaupt, Swiss HPB, Hepato-Pancreato-Biliary Center and Department of Gastroenterology and Hepatology, University Hospital Zürich, Switzerland, September 2013), while the high was estimated through a review of transplants carried out from 2000 to 2012 at Geneva University Hospital (personal communication, Prof. Francesco Negro, Divisions of Gastroenterology and Hepatology and of Clinical Pathology, University Hospital, Genève, Switzerland, September 2013).

Turkey

HCV-infected population

Several prevalence studies were conducted in different regions and reported varying estimates from 0.6% to 2.1% [161–163]. The most representative population-based estimate for HCV prevalence came from a national study published in 2010 reporting an anti-HCV prevalence of 0.95% (0.7–1.1%) in an adult population 18 years of age and older in 2009, corresponding to 667 000 (500 000–833 000) individuals [164]. The viremic prevalence rate was estimated to be 82% [161], resulting in 547 000 (410 000–683 000) viremic infections in 2009 (Table 1). The 2012 viremic prevalence was estimated to be 0.8% (0.6–0.9%). The age and gender distribution was developed using the Turkish Association for the Study of the Liver 2010 study with modifications on the estimated prevalence in individuals 65+ years old by a panel of Turkish experts (Fig. 1) [164]. A number of studies reported the genotypes distribution [165–172]. The genotype distribution used here was derived from unpublished clinical data of 185 patients from Izmir, Turkey (personal communication, Dr. Ulus Akarca, Gastroenterology, Ege University, Izmir, Turkey, November 2013). More than 90% of chronic HCV-infected individuals present with G1, with G1b as the most common subtype [165,166,169,173].

It was estimated that transfusion accounted for 35.3% of the transmission of HCV infection, whereas past or present IDU accounted for an estimated 1.4% [169].

Diagnosed

In 2012, there were estimated to be 81 900 diagnosed viremic individuals. Each year, an estimated 5500 viremic individuals were newly diagnosed. Annual diagnosis was back-calculated from treatment data using a treatment rate of 50%. Total diagnosed was calculated by accounting for cured patients and summing the results for the past 20 years.

Treated

In 2010, it was estimated that 4200 patients were treated annually, using RBV standard units, as PEG-IFN was used in multiple indications.

Liver transplants

Liver transplant data from 2000 to 2011 were available through IRODaT [174]. In 2011, there were 904 liver transplants performed, and it was estimated that 17% of transplants were attributable to HCV in 2012 [175].

DISCUSSION

The results shown here represent the largest undertaking of its kind, in which detailed literature search was combined with data analysis and expert panel input. The combined efforts of many individuals across 16 countries are summarized here to help the healthcare providers, public health officials, policy makers and funders better understand the size of key HCV populations. Special care was taken to present the year of each dataset, as the size of these populations was not static over time. A summary of data sources used for antibody positive and diagnosed cases are shown in Table 2.

This study focused on identifying the number of HCV infections, diagnosed and treated in each country. The number of antibody-positive cases represents all individuals who were exposed to the virus and developed an antibody response, and it includes those whose infection resolved spontaneously or who were treated and cured. The viremic infections represent those who are RNA positive and reflect the level of active HCV infection in a country. In the few countries with a high treatment rate, still an estimated two-third continued to carry the virus (Table 1). In a future with highly effective antiviral therapies, the number of persons with current HCV infections should decline. Thus, this study aimed to establish a baseline for total infected and the percent who have been diagnosed using viremic cases only.

It was difficult to compare the age distribution of the infected population due to wide variances (1995–2012) in the year of the reports (Fig. 1). A comparison of the estimated 2013 age distribution of the viremic HCV-infected population will be provided in the next paper in this same supplement. However, in nearly all countries, HCV prevalence was higher among males than females (reflecting the universal finding of more male IDU), although there were

Table 2 Data sources

	HCV antibody positive cases	Diagnosed	Liver transplants due to HCV
Australia	ME	NDb	NDb
Austria	PS	NDb	EO
Belgium	PS	PS	PS
Brazil	PS	EO	EO
Canada	ME	NDb	NDb
Czech Republic	EO	NDb	PS
Denmark	PS	NDb	EO
Egypt	NS	NS	EO
England	ME	NDb	PS
France	NS	PS	NDb
Germany	NS	NDb	ME
Portugal	PS	PS	ME
Spain	PS	PS	NDb
Sweden	ME	NDb	NDb
Switzerland	PS	NDb	EO
Turkey	NS	EO	EO

EO, expert panel opinion; ME, modeled estimate; NDb, national database; NS, national surveillance study; PS, published studies.

a few exceptions. In France, more females were infected. The same phenomenon was observed in Germany in females over 69. In both cases, the main risk factor was thought to be blood transfusion after childbirth. However, it should be noted that prevalence was low in both countries. Turkey also reported more infected females than males due to nosocomial infections, with hospitalization among females being more common.

The number of liver transplants was readily available in every country, but different data sources were used to estimate the percentage of total liver transplants attributed to HCV (see Table 2). The number of liver transplants was readily available in every country, but different data sources were used to estimate the percentage of total liver transplants attributed to HCV (see Table 2). The number of treated patients could be estimated from the units of current therapies sold in each country and were validated with the expert panels in each country (Table 1). It was generally agreed that a decline in the number of treated patients occurred in 2013 when patients with less advanced liver disease were held back for the availability of the new treatments. However, this reduction in treatment rate was thought to be temporary and the 2011 estimated treatment rates shown here are an accurate reflection of how many patients could be treated by the medical system using the current treatment options.

Data sources varied across countries, and the section below provides an overview of available data and current understanding of HCV epidemiology in countries studied.

Australia

The Kirby Institute is the definitive source for HCV epidemiology data in Australia. It publishes an annual surveillance report that reviews the reported newly diagnosed cases as well as the estimated number of HCV cases by the stage of the disease [19]. The Institute has also developed models that forecast the total number of HCV infections based on key risk groups in Australia. There has not been a national survey to study HCV prevalence in the general population. However, Australia has a robust surveillance program that records all newly diagnosed cases. Since the key risk factor in Australia is IDU, it has been estimated that over 80% of the total infected population has already been diagnosed.

The large pool of chronic HCV in Australia [19] and the 'ageing cohort' effect of this population is related to the high incidence of injecting drug use (IDU)-acquired infection in the 1980s and 1990s [177]. While modeling suggests the incidence of HCV infection is in decline from a peak of new infections in 1999 [177], the rate of incidence of HCV remains greater than the rate of treatment, and the number of people in Australia living with HCV is expected to continue to increase for the foreseeable future.

Austria

Austria is considered a low-endemic country; however, there are limited HCV epidemiological data available on the current infected population, as well as the effects of chronic infection on disease burden [26,27]. While legislation states that all cases of acute viral hepatitis should be registered centrally, a recent analysis of hospital discharge data raised concerns of under-reporting [26]. There is not currently a national screening strategy in place, so individuals are only tested if they are symptomatic or considered to be at risk of acquiring HCV. As only 20% of infected individuals are symptomatic, there may also be considerable under-testing, contributing to the low diagnosis rates.

Belgium

A recent national level prevalence estimate is not available for Belgium. The most commonly cited anti-HCV prevalence, 0.87%, comes from Beutels et al, published in 1997 [32]. These data were based on residual samples from 10 laboratory hospitals in Flanders; however, they were collected in 1994 [32]. A low value was obtained through a 2003 mail-based study in the Flanders region that measured HCV antibodies in oral fluid, and suggested a prevalence estimate of 0.12% (0.09–0.39%) [33]. A high value was chosen by expert opinion, based on the results of a 2012 report by the Belgian Health Care Knowledge Center (KCE) that estimated an anti-HCV positivity rate of 1.23% among patients with a test funded by one of the seven national sickness funds [34]. This estimate was generated through a review of the total

number of anti-HCV and confirmatory HCV tests reimbursed from 2002–2007, and may have excluded tests ordered for high risk groups, or prior to blood donation [34]. Currently, no formal screening strategy exists; however, BASL recommends targeted HCV screening for high-risk populations (including individuals with a blood transfusion or major medical event prior to 1 July 1990, intranasal or IDU and dialysis patients) in addition to nontargeted screening that occurs among pre-operative patients and pregnant women [34]. On average, an estimated 345 000 anti-HCV tests are performed annually [34].

Brazil

HCV infection is a major public health problem in Brazil. There is considerable geographic variation within Brazil, with the North region having an anti-HCV prevalence of 2.1% [40], and other studies have reported relatively high prevalence in the Amazon region [176,177,178]. Prevalence of HCV increases with age in Brazil [40,180,181]. Published data describe the prevalence and genotype distribution at the national level, including variations by region [40,43,44], with G1 found in nearly 65% of cases [44]. In a national study, the use of injected or inhaled drugs was the strongest predictor of HCV seropositivity, but accounted for a small proportion of total cases [40]. Nosocomial transmission, as well as transmission through needle sharing for therapeutic injections in nonmedical settings, contributed to the burden of HCV infection [40,182]. Blood and blood product transfusion was identified as the predominant route of transmission before blood screening began in 1992 [183,184].

HCV is a leading cause of cirrhosis, HCC and liver transplants in Brazil [49,185]. In 2002, the Brazilian Ministry of Health created the National Viral Hepatitis Program with goals for reducing the incidence of viral hepatitis and improving the quality of life for infected individuals [179,186]. Harm reduction measures aimed at reducing transmission among IDU, along with universal precautions for preventing nosocomial transmission, are important in reducing new cases.

Canada

PHAC collects data for reported HCV cases through the Canadian Notifiable Surveillance System. The majority of acute HCV infections in Canada occur through IDU, and peak incidence of new infections occurs among those aged 25–29 years [54]. HCV infection is associated with high mortality from liver disease in Canada [187], which is increasing and is a leading indicator for liver transplantation [188]. There is considerable regional variation in HCV prevalence, with some areas of Canada experiencing HCV prevalence of nearly 4% [54]. A national survey has not been conducted to determine the total

number of HCV infections. However, a modeling approach was used to estimate the total prevalence in the country [54].

Czech Republic

In the Czech Republic, compared to other European countries, the HCV epidemic began later owing to geographical barriers, limited immigration from neighbouring endemic countries and a delayed surge in IDU. However, in recent years, HCV infection has become one of the leading causes of liver transplantation [68]. As the infected cohort ages, the burden of HCV-related disease is expected to increase exponentially.

The Czech Republic is a low-endemic country for HCV infection, with reported estimates between 0.2% and 1% [62,64]; however, little is known on the national level regarding current and future disease burden. There is no general screening programme in the country, and only specific subgroups are screened on a regular basis. These groups include blood donors, pregnant women, healthcare workers, patients on maintenance hemodialysis, prisoners and IDU starting weaning programmes. HCV prevalence varies widely among these groups, with the lowest prevalence reported among blood donors in Prague (0.13%) and the highest prevalence reported among IDU entering weaning programmes (32.4%) [189].

Denmark

Hepatitis C virus was introduced into the Danish population in the late 1960s. Since that time, the majority of the population has reportedly been infected through IDU, with minimal infection through nosocomial or sexual transmission. Nosocomial transmissions are uncommon—fewer than half were acquired before the initiation of HCV screening of blood donors in 1991, and the remainder originated from hospitals outside of Denmark [189–191]. In the 1990s, interventions aimed at drug treatment centres and prisons (including needle exchange programmes, opium substitution therapy and immunization against hepatitis B) were implemented. Harm reduction efforts have had an impact on keeping co-infection with hepatitis B and HIV low [70]. Sexually transmitted cases are believed to be on the rise, with an incidence of HCV infection of 0.4% in the MSM population [193].

Denmark has a very thorough civil registration system, with a unique 10-digit civil registration number (CPR) assigned to every resident. Additionally, several national registers exist from which data on the epidemiology of CHC can be extracted. HCV-specific registers (such as the Danish National Database on Hepatitis and the Danish HCV Database) capture clinical, epidemiological and laboratory data including RNA testing and genotyping [69,70]. Additionally, non-HCV-specific registers (such as

the Danish National Patient Registry, the National Register of Notifiable Diseases and the Drug Treatment Register) capture information regarding hospital discharge data, communicable disease notification and drug treatment [190–192,194]. Most systems, however, require reporting by the treating physician, with the limitations that imply.

Egypt

Egypt has the highest prevalence rate of HCV in the world [195], and HCV-related liver disease is the leading indicator for liver transplantation [196–197]. Nosocomial transmission has been the most common route for new infections. In particular, widespread treatment of schistosomiasis in earlier decades resulted in high levels of HCV transmission [198]. A national survey assessed HCV prevalence in 2008. There is evidence of high levels of ongoing HCV transmission [198] related to unsafe injection in healthcare settings, with high HCV prevalence observed among young individuals [200].

England

The epidemiology of HCV is maintained by Public Health England (PHE), formerly the Health Protection Agency (HPA) [4]. Although the majority of acute infections occurred in the 1990s as a result of a contaminated blood supply, today the primary route of transmission of HCV is IDU [200]. PHE has placed significant emphasis on reducing the transmission of HCV through campaigns to increase awareness and minimize risk behaviours such as needle sharing [200]. Testing is indicated for individuals at high risk of contracting HCV, and it is estimated that 83% of IDU have ever received a voluntary confidential test for HCV [200]. HCV is a notifiable disease, and all new diagnoses are reported to PHE. A national survey has not been conducted to determine HCV prevalence, however, a modeling approach has been used to estimate the total number of infections [3].

France

Of the countries included in this analysis, France has active programmes to manage HCV infection through screening, improving access to treatment and reducing transmission. The epidemiology of HCV is marked by a relatively low prevalence as determined by a national survey. The National Institute for Surveillance created the national surveillance network, which has conducted two national population-based prevalence surveys in 1994 [103] and 2004 [80,202,203] in urban areas. The 2004 study surveyed 14 416 residents ages 18–80, but similar to surveillance studies in other countries, the sampling did not take

into consideration high-risk populations like IDU. The decrease was attributed to a decrease in incidence over time due to positive impacts of a syringe programme and the application of standard precautions in healthcare settings [202–204].

Germany

HCV infection is the primary risk factor for a quarter of HCC cases—the second leading cause next to alcoholic liver disease [205]. The current state of the HCV epidemic is complex and not clearly defined. Typically, a wide prevalence range is cited, as the true number of HCV infections is not known. What is well known, however, are the past and current risk factors of the HCV-infected population. Patients typically fall into one of four risk groups: (i) those with a blood transfusion prior to 1990; (ii) current and former drug users; (iii) immigrants from the former Soviet Union; and (iv) immigrants from other countries (Mediterranean countries in particular).

Portugal

The burden of chronic HCV infection has not been quantified in detail. Prevalence data for HCV infection are scarce and suggest a high variability between risk groups. The epidemiology of the various stages of HCV infection (e.g. compensated and decompensated cirrhosis) also remains largely unknown. Hospital admission data show an increase between 1993 and 2005 in admissions for HCC from all causes [206]. Previously published studies were the basis for much of the data reported here.

Spain

Previously published estimates report the prevalence of HCV in Spain to be among the highest in Europe at 2.6% [3,105]; however, little is known regarding the burden of disease in the country. Chronic HCV infection was the leading cause of mortality among infectious diseases in 2000 [207]. Further, liver transplantation represents a major cost burden nationwide, accounting for more than 25% of organ transplants in 2012 [208].

Currently, there is no national HCV strategy in Spain that considers HCV infection a public health concern. Prevention of advanced disease is possible through early detection of HCV infection and more effective therapies. The development of first-generation DAAs, approved for reimbursement in Spain in 2012, demonstrates greater cure in G1 patients [209–210]. With the advent of new all oral antivirals, HCV may be curable in a greater proportion of treated patients [211]. Thus, the implementation of public health strategies could reduce the burden of HCV and improve population health.

Sweden

In Sweden, the spread of HCV infection started comparatively late, near the end of the 1960s with culmination in the 1970s, most likely as a result of increased IDU, and the burden of HCV-related disease is expected to increase in the coming decade [136,212]. HCV infection has become one of the leading causes of liver transplantation [139], and the number of HCV-infected patients with diagnosed HCC has gradually increased with the aging HCV cohort [136].

The Swedish cohort of individuals with a diagnosed HCV infection (anti-HCV or HCV RNA positive) was identified and characterized using data from the HCV Surveillance Register at the SMI [137] and through linkage to other national registers (Population, Death, Patient and Cancer registers) at Statistics Sweden and the National Board of Health and Welfare [14]. The same approach was used in previous HCV cohort studies on disease burden, cancer incidence and mortality [136,138,213]. Every person in Sweden has a specific personal identification number, used in all healthcare contacts and all national registers. These registers have high coverage and validity, enabling nationwide register studies with high completeness [214–215].

Switzerland

Chronic HCV infection is a major cause of cirrhosis and HCC, and is a primary indication for liver transplantation [194]. HCV transmission peaked in the 1990s because of contaminated blood products, but decreased sharply once blood screening came into effect. Today, transmission of HCV occurs primarily among IDU [154]. In addition, the number of HCV cases is significantly influenced through immigration of individuals from HCV endemic countries (personal communication, Prof. Francesco Negro, Divisions of Gastroenterology and Hepatology and of Clinical Pathology, University Hospital, Switzerland, May 2013) [3,215].

Mandatory notification of positive tests for HCV has been in effect since 1988 [3,215]. HCV screening is currently limited to blood products only; however, a national hepatitis strategy is in the planning stages. In addition, the country has recently implemented a strategy of provider initiated risk-stratified testing [215].

Turkey

A recent national survey was conducted in Turkey, but the results of that analysis have not been published. In addition, a registry was put in place to track newly HCV diagnosed cases in 2011. Reporting adherence is still low and insufficient data is available. However, it has been shown that the majority of HCV positive individuals are

above the age of 50, implying that the risk of infection was higher 20 years ago [216].

The data presented here represent what is available based on the best of our knowledge today. However, the country level discussions above highlight a number of limitations. One limitation was the assumption that data reported here are representative of the countries' HCV infected population. For example, many countries have a centralized registry that keeps track of the number of diagnosed cases over time. These registries could have a bias as testing and reporting may be incomplete and not uniform across subpopulations. This was observed and corrected in Germany, where the RKI data showed a much younger population as compared to the national survey. Of the countries reported here, only Egypt, France, Germany and Turkey had conducted a national surveillance study using random samples from multiple regions. In addition, viremic rate and genotype distribution were typically based on studies with relatively small sample size. Data from multiple studies were compared to minimize bias, but it is worth noting that both variables can change over time because of 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), and it was difficult to compare treatment rates in this report, as the total number of infections and number of diagnosed were reported in different years. Several factors contribute to low HCV treatment rates, including toxicity of interferon-based therapy, prolonged course of treatment (24–48 weeks), social marginalization of many people with chronic HCV, lack of treatment infrastructure (particularly in opiate pharmacotherapy, prison, community health and primary care settings), and lack of awareness of the curative potential of treatment. Poorer HCV treatment responses in those with advanced liver disease also limit the impact on disease burden. 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 by using expert panels.

The quality of the assumptions for the size of the diagnosed population varied across countries. A number of countries had centralized registries for diagnosed HCV cases—Australia, Austria, Canada, Czech Republic, Denmark, England, Germany, Sweden and Switzerland. HCV was a notifiable disease in Brazil, although compliance in reporting newly diagnosed cases was limited. In addition, Turkey's HCV registry, which started in 2011, suffered from the same limitation. In other countries, the number of diagnosed cases was based on studies (Belgium, Egypt, France and Spain) or estimates (Brazil, Spain, Portugal and Turkey).

In conclusion, in order to develop strategies to address the impending increase in HCV disease burden, it is important to understand the current number of infections, diagnosed and treated individuals. Many countries represented here have developed a range of options to monitoring HCV infections. These countries could be a valuable resource for designing systems, in other countries, that can measure the impact of active strategies to manage HCV disease burden as new therapies become available.

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