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Hepatitis C disease burden and strategies to manage the burden (Guest Editors Mark Thursz, Gregory Dore and John Ward)

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SUMMARY. Chronic hepatitis C virus (HCV) infection leads to liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC). The recent Global Burden of Disease project estimated that in 2010 among 170 million people living with chronic HCV, an estimated 483 100 people died from HCV-related liver failure or HCC. The last two decades has seen progressive improvements in treatment of HCV infection with the most recent therapies offering simple, tolerable, short-duration therapy with extremely high efficacy. The development of public health strategies addressing emerging epidemics requires sound epidemiological data. This study covers epidemiological data collection, detailed expert opinion input and country-specific mathematical modelling of the HCV epidemic and potential impact of improved HCV treatment strategies in 16 countries. The analysis demonstrates that the HCV epidemics vary considerably in terms of age distribution of the infected population across countries. In addition, the burden of advanced liver disease varies widely. This burden is dependent upon factors including chronic HCV prevalence, age distribution (and duration of infection) of those infected, prevalence of cofactors for disease progression (particularly heavy alcohol intake) and uptake and success of therapeutic intervention. Introduction of new therapies with assumed sustained virological response (SVR) rate of >90% will have a modest impact on projected advanced liver disease burden. A combination of enhanced treatment efficacy and improved treatment uptake will have a greater impact on population-level disease burden. However public health advocacy and both public and private sector investment in the HCV response are required to demonstrate significant reduction in HCV disease burden.

INTRODUCTION

Hepatitis C virus (HCV) infection progresses to chronic HCV in around 75% of cases [1], with the resultant risk of progressive liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC). Development of advanced liver disease generally occurs after at least two decades of HCV infection with higher risk associated with male gender, older age at infection, heavy alcohol intake, co-infection with HIV or hepatitis B virus (HBV) and metabolic syndrome [2]. The recent Global Burden of Disease project estimated that in 2010 among 170 million people living with chronic HCV, an estimated 483 100 people died from HCV-related liver failure (287 400) or HCC (195 700) [3].

The last two decades have seen progressive improvements in interferon-based HCV treatment with the initial addition of ribavirin (RBV), the development of pegylated interferon (PEG-IFN) and the addition of telaprevir or boceprevir as the first direct-acting antiviral (DAA) agents [4]. Despite these improvements, HCV treatment uptake remains low in most settings. Several factors contribute to low interferon-based HCV treatment rates, including toxicity, prolonged duration (24–48 weeks), social marginalization of many people with chronic HCV, lack of treatment infrastructure (particularly in drug and alcohol, prison, community health and primary care settings), limited government-funded therapy in many countries and lack of awareness of the curative potential of treatment. Suboptimal HCV treatment responses, particularly in those with advanced fibrosis, and inability to utilize therapy in those with decompensated liver disease further limit the impact of therapeutic intervention on disease burden.

Fortunately, a revolution in HCV treatment is fast approaching, with the phenomenal extent of DAA therapy development and the move toward interferon-free regimens [5]. Before the end of this decade, simple (single daily dos-

Abbreviations: DAA, direct acting antiviral; HCV, hepatitis C virus; PWID, people who inject drugs.

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ing oral regimens), tolerable, short-duration (6–12 weeks) therapy with extremely high efficacy (cure rates above 90%) should be the norm for the HCV-infected population. The implementation of such therapeutic regimens has the potential to produce one of the major turnarounds in disease burden seen in public health and clinical medicine.

The development of public health strategies, particularly those addressing emerging epidemics with escalating disease burden such as chronic HCV, requires sound epidemiological data. Mathematical modelling also provides specific insights into the potential impact of treatment and prevention strategies, further informing public health policy. The current project, outlined in this introductory overview and subsequent papers, covers epidemiological data collection, detailed expert opinion input and country-specific mathematical modelling of the HCV epidemic and potential impact of improved HCV treatment strategies in 16 countries. Invitations were sent to representative clinical bodies and experts within 36 countries. A total of 16 countries accepted the initial invitation, with countries represented here having completed planned work and being willing for that work to be published in this collated series. Outputs from other countries will be published independently or in later series.

The countries included in this series therefore represent a convenience sample, but cover a wide geographical spread (although no Asian countries are included). They are predominantly high-income countries, but include Egypt, Turkey and Brazil as low- or middle-income countries. A rigorous effort was made to collect data from published and unpublished sources to provide the estimates presented in the following articles. However, countries included in these analyses varied widely in the availability of data representative of HCV prevalence, burden of disease and proportion of HCV-infected population aware of their infection and treated for their disease. To address these deficiencies, the opinions of experts in each country were solicited to identify the best sources of information and refine estimates generated from the model.

Several important epidemiological patterns emerge when examining characteristics across these countries. First, there is considerable variability in HCV genotype distribution, with non-1 genotypes making a major contribution in several countries (Egypt – genotype 4; Australia, England, Denmark – genotype 3; Fig. 1). Such variability may lose clinical relevance if therapeutic regimens with pan-genotypic efficacy are developed, but is likely to remain important for the near future. Second, the population prevalence of chronic HCV varies widely, from 0.3% in Austria, England, Germany and France to 7.3% in Egypt, although the latter is clearly unique, with the second highest prevalence being Portugal at a much lower 1.2% (Fig. 2, Table 1). The estimation of HCV prevalence also varied considerably, with few countries being able to call upon population-based representative serosurveys, thus often leading to wide ranges around estimates.

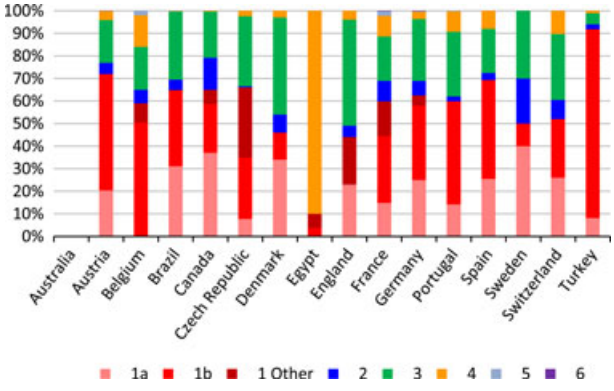

Fig. 1 HCV genotype distribution by country.

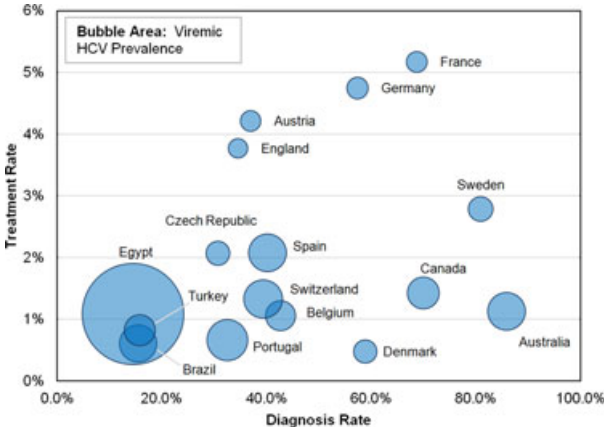

Fig. 2 Estimated chronic HCV prevalence, diagnosis rate and treatment rate in 2013.

Another epidemiological feature with a broad range across countries was the proportion of the HCV-infected population estimated to have been diagnosed. This varied from less than 20% in Egypt, Brazil and Turkey to greater than 80% in Australia and Sweden (Fig. 2). The former countries are low- or middle-income countries, but another feature to distinguish them is that they have more generalized epidemics with lower relative contributions from infections among people who inject drugs (PWID). In contrast, the latter countries, with major PWID contributions, have been able to implement targeted screening of high-risk populations.

Socio-economic factors would not appear to be the major driver of HCV treatment uptake rates, with the lowest proportion of the infected treated per annum in Denmark (0.5%), ten-fold lower than in France (5.2%) (Fig. 2, Table 1). Further, the total number treated is highest in Egypt (65 000 per annum) (Fig. 3), several fold higher than even France or Germany, although given the extremely large chronic HCV prevalence, this only represents 1.1% treated per annum.

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Table 1 Estimated chronic HCV prevalence, treatment rate and diagnosis rate in 2013

	Est. Viremic Prevalence (2013)%	Est. Diagnosis Rate (2013)%	Est. Treatment Rate (2013)%
Australia	1.0	85	1.7
Austria	0.3	37	4.2
Belgium	0.6	43	1.1
Brazil	1.0	15	0.6
Canada	0.7	70	1.4
Czech Republic	0.4	31	2.1
Denmark	0.4	59	0.5
Egypt	7.3	15	1.1
England	0.3	35	3.8
France	0.3	69	5.2
Germany	0.3	57	4.7
Portugal	1.2	33	0.7
Spain	1.0	40	2.1
Sweden	0.4	81	2.8
Switzerland	1.0	42	1.4
Turkey	0.7	16	0.8

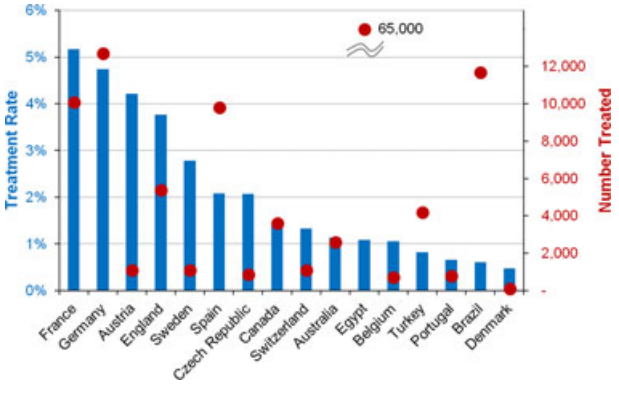

Fig. 3 Estimated HCV treatment rate and total number treated in 2013.

Mathematical modelling across the included countries has also revealed several important aspects of population-level disease burden and the potential impact of improved HCV treatment strategies. First, country HCV epidemics vary considerably in terms of age distribution of the infected population. This country-specific variability is highlighted within Europe, which has both the "oldest" epidemics in France and Germany and the "youngest" epidemic in Czech Republic, with the latter driven by more recent HCV spread among PWID. The relatively younger Czech Republic epidemic explains the high proportion of people with chronic HCV who have early liver disease (>75% F0/1; Fig. 4). In contrast, several countries

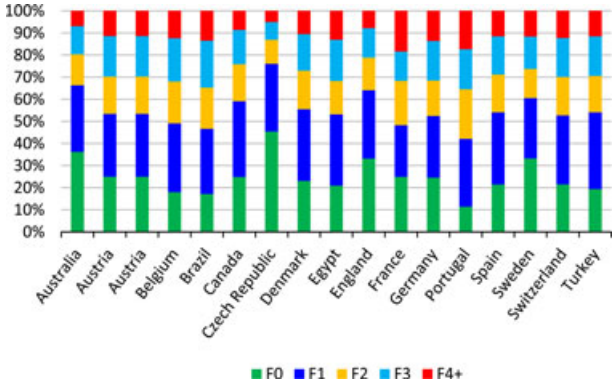

Fig. 4 Estimated liver disease distribution among people with chronic HCV in 2013.

(Belgium, Brazil, France and Portugal) have the majority of people with chronic HCV with significant fibrosis (F2-4).

Second, the burden of advanced liver disease varies widely across countries. This burden is dependent upon several factors including chronic HCV prevalence, age distribution (and duration of infection) of those infected, prevalence of cofactors for disease progression (particularly heavy alcohol intake) and uptake and success of therapeutic intervention. Egypt, with 2013 estimates of people with cirrhosis (770 000), incident HCV-related HCC cases (16 000) and HCV-related liver deaths (33 000), is clearly the country with the greatest burden, driven largely by the extremely high chronic HCV prevalence, but also by the relatively older epidemic age distribution. Brazil (8400) and Turkey (2200) have the next highest burden of HCV-related liver deaths. In contrast, Denmark (80) and Czech Republic (70) have the lowest estimated HCV-related liver deaths due to low chronic HCV prevalence and young age distribution, respectively. Advanced liver disease burden is projected to continue to increase in almost all countries, despite relatively stable chronic HCV prevalence in most countries.

Third, the introduction of interferon-free DAA therapy with an assumed sustained virological response (SVR) rate of 90% or above will generally have a modest impact on projected advanced liver disease burden, if treatment uptake remains at current levels. The exception is France, where the near doubling of SVR through improved HCV treatment would have a sizeable impact on disease burden, as current treatment uptake is relatively high at greater than 5% per annum. Unlike other countries in this series, estimates of advanced liver disease and HCV liver-related deaths in France have peaked; therefore, enhanced HCV treatment efficacy will contribute to a more accelerated decline. In contrast, advanced liver disease and HCV liver-related deaths will continue to increase over the next two decades in Australia and Czech Republic, even with enhanced treatment efficacy, due to relatively lower treatment uptake and "younger" epidemics.

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Fourth, not surprisingly, a combination of enhanced HCV treatment efficacy, improved diagnosis and improved treatment uptake led to greater impacts on population-level disease burden. In most countries with projected increases in advanced liver disease burden, the approaching burden can be prevented, with marked declines over the next two decades, through improved treatment strategies and implementation. The combination of enhanced HCV treatment efficacy and uptake could also produce marked reductions in chronic HCV prevalence, with many countries having the potential to move toward HCV elimination over the next two decades.

Such impacts on advanced liver disease burden and HCV prevalence require many challenges to be overcome. HCV diagnosis rates in most countries represented in this analysis would need to be dramatically lifted, through markedly enhanced HCV screening strategies. Access to HCV diagnosis and treatment will require increases in the capacity of public health systems and clinical care systems to screen, assess and treat HCV infection. To expand access to treatment, HCV drugs must be affordable for countries at every level of development. Although pharmaceutical company and generic production partnerships could benefit low- and middle-income countries, similar to initiatives for antiretroviral therapy access in HIV, these would still need to be supported through a global fund for HCV treatment. Drug pricing will also determine the extent of government-funded programs in many high-income countries; therefore, price reduction will be required to enable broadened access to the HCV treatment levels modelled particularly for marginalized populations including the incarcerated, recent immigrants and persons who inject drugs. Targeted HCV treatment as prevention strategies would also require lower pricing levels. Finally, public health advocacy and both public and private sector investment in the HCV response are required. Quality data collected from public health surveillance, surveys of the general and risk populations and from health systems providing HCV care and treatment are needed to improve the accuracy of the effort presented here, and other health models seeking to help countries make sound decisions regarding the allocation of resources to diagnose, assess and treat HCV infection.

DISCLOSURES

Dore – Advisory Board Membership: Roche, Merck, Janssen, Gilead, Bristol-Myers Squibb, Abbvie Honorarium: Roche, Merck, Janssen, Gilead, Bristol-Myers Squibb, Abbvie Research Grants: Roche, Merck, Janssen, Gilead, Bristol-Myers Squibb, Vertex, Boeringher Ingelheim, Abbvie Travel Sponsorship: Roche, Merck, Janssen, Gilead, Bristol-Myers Squibb.

Thursz has participated in advisory boards for Gilead, BMS and Janssen.

Ward has no conflict of interest.

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