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REVIEW

Epidemiology of hepatitis C virus infection

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KEYWORDS
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Abstract Hepatitis C is a global health problem, with an estimated 71·1 million individuals chronically infected worldwide, accounting for 1% (95% uncertainty interval: 0.8—1.1) of the population. HCV transmission is most commonly associated with direct exposure to blood, via blood transfusions, unsafe health-care-related injections and intravenous drug use. The global incidence of HCV was 23·7 cases per 100 000 population (95% uncertainty interval 21·3—28·7) in 2015, with an estimated 1·75 million new HCV infections diagnosed in 2015. An estimated 2.3 millions of people living with HIV have serological markers of past or current HCV infection. Globally, the most common infections are with HCV genotypes 1 (44% of cases), 3 (25% of cases), and 4 (15% of cases). Approximately 10—20% of individuals who are chronically infected with HCV develop complications, such as cirrhosis, end stage liver disease, and hepatocellular carcinoma over a period of 20—30 years. Direct-acting antiviral therapy is curative, dramatically reducing the mortality related to HCV and the need for liver transplantation, but it is estimated that only 20% of individuals with hepatitis C know their diagnosis, and only 15% of those with known hepatitis C have been treated. Increased diagnosis and linkage to care through universal access to affordable point-of-care diagnostics and pangenotypic direct-acting antiviral therapy is essential to achieve the WHO 2030 elimination targets.

Introduction

Hepatitis C virus (HCV) infection is a blood borne disease through direct contact with infectious blood (transfusions) or indirect via contaminated material (unsafe injections and medical procedures). Its spread, based on the rate of development of molecular diversity can be estimated to date back 500—2000 years [1], accounting for the worldwide spread of the virus and leading to a major global health problem in most countries. Hepatitis C acute infection leads to chronic carriage in 70—80% of cases with the risk of development of complications such as cirrhosis and cancer. The development of tools for an easy screening of populations, and of effective treatments have open the way to high-impact interventions aiming at reducing the burden of the disease and finally leading to the elimination of viral hepatitis as a public health threat by 2030. That is the great challenge claimed by the WHO in 2015 [2] at the same time WHO presented its new global strategy to fight hepatitis. In the light of this goal, clinicians and decision makers need reliable data setting

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Table 1 Prevalence of HCV infection (HCV RNA positive) in the general population, by WHO region, with uncertainty intervals, 2015: 71 million persons living with HCV worldwide (WHO global hepatitis Report 2017 (4)).

	Estimates of the prevalence of HCV infection (%)			Estimated number of persons living with HCV (millions)		
	Uncertainty interval			Uncertainty interval		
WHO	Best	Lower	Higher	Best	Lower	Higher African
Region	1.0	0.7	1.6	11	7	16
Region of the Americas	0.7	0.6	0.8	7	6	8
Eastern Mediterranean Region	2.3	1.9	2.4	15	13	15
European Region	1.5	1.2	1.5	14	11	14
South-East Asia Region	0.5	0.4	0.9	10	8	18
Western Pacific Region	0.7	0.6	0.8	14	10	15
Total	1.0	0.8	1.1	1.0	62	79

the baseline for tracking progress in implementing the new global strategy.

Sources of epidemiological data

Very few countries have unbiased population-based data on HCV prevalence at the country level. Notification of chronic HCV infection is rarely mandatory, as well as that of acute hepatitis C which is most often undiagnosed. Usually, at a country level, information is sparse, provided by prevalence studies in some populations like blood donors, persons who inject drugs (PWIDs), prisoners or health care workers, what is obviously insufficient to provide accurate estimates of HCV disease burden.

In 2015, The Polaris Observatory was created to monitor and forecast the disease burden for hepatitis C (and B). Data from 100 countries representing more than 85% of the world's population were gathered, following a comprehensive review of indexed sources and grey literature. They were used to estimate the WHO regional prevalence, and regional prevalence rates were then applied to countries with missing data to estimate the global HCV prevalence. Experts from 59 countries validated the data used as inputs in the models [3]. The huge work provided by the Polaris team led to estimates for HCV viraemic prevalence and genotype distribution. All these results have been endorsed by WHO in its global report 2017 [4].

Hepatitis C prevalence and modes of transmission

In 2015, an estimated 71 million people were living with chronic HCV infection in the world, accounting for 1% (95% uncertainty interval (95% UI): 0.8—1.1) of the population [4]. The infection affects all regions with major differences between and even within countries. The Eastern Mediterranean region has the highest prevalence (2.3%, 95% UI: 1.9—2.4), followed by the WHO European region (1.5%, 95% UI: 1.2—1.5), whereas the South-East Asia region has the lowest prevalence (0.5%, 95% UI: 0.4—0.9) (Table 1). Inside these regions, difference in prevalence can be important. For example, in Central and Eastern Europe, HCV prevalence can be as high as 3.3% (Russia) or 2.5% (Romania) whereas most Western European countries have prevalence below 1% [3].

Transfusion of blood products before the availability of effective HCV testing of blood donations, and unsafe care procedures before the implementation of universal precautions, have been the major routes of transmission in most countries worldwide. Countries that have adopted systematic nucleic acid test (NAT) screening of blood donations have eliminated the risk of transmission through blood products [5]. Countries with high income implemented NAT screening from the late 1990s, but only 32 countries had implemented it by 2010 [6]. Residual risk of HCV transmission through blood components still exists in low income countries where NAT screening cannot be implemented because not cost-effective for such countries. In some African countries, the whole process of blood testing is still unsafe [7]. As well, the adequate sterilization of medical devices or even the use of disposable equipment is not the rule in many developing countries, accounting for a residual nosocomial risk of HCV infection [8].

Intravenous drug use (IVDU) has been the second major route of transmission, initially in the industrialized countries from the 1960s, but now affecting many countries in the world, in urban as well as in rural areas were DU has recently emerged, especially in the USA [9]. HCV prevalence in the population of PWIDs could be 70—95% in high income countries [10], as well as in intermediate or low income countries [11]. Harm reduction policies, needles and syringes exchange programmes, and development of opioid substitution treatments have strongly participated to the reduction of the prevalence in industrialized countries. For example, in France, HCV prevalence in young PWIDs <30 years old, decreased from 44% in 2004 to 9% in 2011 [12]. Unfortunately, harm reduction policies have not been implemented adequately in most low income countries where DU is often badly tolerated or even criminalized, and not considered as a health priority. Indeed, only 11% of countries from African region have needles and syringes programs [13].

The risk of mother-to-infant transmission has been estimated around 6% from HCV mono infected mothers and twice higher from HCV-HIV co-infected mothers [14].

Table 2 Incidence of HCV infection in the general population, by WHO region, 2015: 1.75 million new infections in 2015 (WHO global hepatitis Report 2017 (4)).

Incidence of HCV infection				
	Incidence rate (per 100 000)		Total number (000)	
WHO Region	Best estimate	Uncertainty interval	Best estimate	Uncertainty interval
African Region	31.0	22.5—54.4	309	222—544
Region of the Americas	6.4	5.9—7.0	63	59—69
Eastern Mediterranean Region	62.5	55.6—65.2	409	363—426
European Region	61.8	50.3—66.0	565	460—603
South-East Asia Region	14.8	12.5—26.9	287	243—524
Western Pacific Region	6.0	5.6—6.6	111	104—124
Total	23.7	21.3—28.7	1 751	1 572—2 120

Transmission occurs mainly during delivery and is strongly depending on the viral load of the mother during the third trimester of the pregnancy. The reduction / loss of viral load with anti-viral treatment, when possible during pregnancy, will be the way to eliminating mother-to-child HCV transmission, on the condition of universal HCV screening in pregnant women [15].

Other reported routes of transmission include unsafe tattooing, and traditional scarification which are risk factors in some sub-Saharan African countries.

Incidence of HCV infection

In 2015, the estimated number of persons newly infected with HCV worldwide was 1.75 million corresponding to a global incidence of 23.7 per 100 000 population (95% UI: 21.3—28.7). It exceeded the sum of the estimated number of persons dying from end-stage HCV infection ($N = 399\,000$), and of those being cured ($N = 843\,000$), accounting for the ongoing increase of the global epidemic [4]. However, the distribution of incidence varies widely between regions, strongly depending on the adequate application of universal precautions in care. In industrialized countries, HCV transmission through blood products and health care related injections has almost disappeared since the 1990s. That can partly explain the birth cohort effect observed in these countries [16] where IVDU represents the leading mode of residual HCV transmission, even if harm reduction policies participate in the decrease of the epidemic among young people. However, in developing and transitional countries, unsafe medical injections account for a large part of the incident cases of infection. In 2000, the WHO estimated that unsafe injections accounted for 40% of new infections with HCV [17], what led to the organization of safe infection campaigns worldwide. Ten years later, in 2010, a substantial progress was observed, with a reduction of 83% in the absolute number of HCV infections transmitted through injections. However, between around 160 000 and 315 000 new HCV infections were estimated still related to unsafe injections, occurring for one third in Eastern Mediterranean Region and one other third in West Pacific Region [18,19].

Geographical distribution of HCV incidence is represented on Table 2 [4]. It shows that areas with high rates of new infections are located in Eastern Mediterranean Region and WHO European Region. In this last region, incidence is mainly due to heavy IVDU in Central and Eastern European countries. Beside unsafe health care injections and IVDU, transmission of HCV has also been reported in Europe, Australia and the USA among men who have sex with men (MSM) infected with HIV [20] or even HIV seronegative, but using pre-exposure prophylaxis [21]. However, no estimates are available to quantify the contribution of this mode of transmission to the overall transmission of HCV.

Co-infections with HIV and HBV

HCV, HIV and HBV infections share several leading modes of transmission. An estimated 2.3 million of people living with HIV have serological markers of past or current HCV infection. Of these, 1.36 million currently inject drugs, and it is estimated that young PWIDs are mainly responsible for the rapid spread of HIV and HCV infections. Eastern Europe and Central Asia are the two regions accounting for the largest proportion of HIV-infected persons with evidence of past or current HCV infection related to DU. MSM represent the second more frequent population with HIV-HCV co-infection [22].

No global estimate of HCV-HBV co-infection is available, and it can vary widely, depending on the country and the setting. It has been reported to be 0—3% in Western European countries [23,24], 10—15 % in the USA [25] and 30% in particular populations of China [26]. Usually, HCV replication inhibits HBV replication; HCV-HBV co-infection has been reported to be responsible for more severe liver disease than HBV mono-infection, and for more complications of cirrhosis than HBV or HCV mono-infections [27]. Furthermore, a risk of HBV reactivation after the cure of HCV with direct acting antivirals (DAAs) has been reported [25,28].

Molecular epidemiology

HCV strains are classified in eight different genotypes, named one to eight, and differing from each other at 31—33 % of nucleotide sites [29]. Each genotype has several subtypes that differ at <15% of nucleotide sites for a current total number of 86 subtypes. Globally, genotype 1 is the

Fig. 1 Continuum of HCV services and cascade of care: 4 steps from screening to follow-up of chronic disease are necessary to ensure a good cascade of care. In parallel, prevention should be applied at all steps.

most frequent, accounting for 44 to 46% of all cases of HCV infection worldwide, depending on the studies [3,30]. It is followed by genotype 3 that represents 25 to 30% of all cases, then genotype 4 (8 to 15%).

The distribution of the genotypes varies widely from one region to another [30]. For example, genotype 1 is rare in Central sub-Saharan Africa (<2%) but very prevalent (>80%) in Central Europe and Southern America. Genotype 3 is frequent in South Asia (71%), from where it has spread through drug use. Genotype 4 is the main genotype in Central sub-Saharan Africa (98%) as well as in Middle east, especially in Egypt but of different subtypes. Genotypes 2 and 6 are mainly observed in Eastern Asia. In Western Europe, there is a mix of genotypes, partly due to the successive migratory flows. Furthermore, a strong relationship has been shown between genotypes and mode of transmission. In France, genotype 1b is related to transfusion, genotype 3 and more recently genotype 1a with IVDU [31].

Genotype determination has been useful from an epidemiological point of view and for the decision of the treatment regimen before the era of DAAs. In countries where pangenotypic DAAs are available, genotype and subtype need no longer to be identified [32].

HCV morbi-mortality

HCV infection is a systemic disease associating liver damage and extra-hepatic manifestations. Liver inflammation and fibrosis lead to cirrhosis in 10—20% of cases within 20—30 years, with the risk of end-stage liver disease and hepatocellular carcinoma. Disease progression is accelerated by higher age of acquisition, being male, obesity, high alcohol consumption, HIV co-infection, and immunosuppression. The 5-year risk of developing hepatocellular carcinoma ranges from 1% in people with no liver fibrosis to 13% in those with cirrhosis [33].

In 2015 HCV infection led to 402 000 deaths, one third related to hepatocellular carcinoma and two-thirds to cirrhosis and end-stage liver disease [4]. Mortality has increased since the end of the 20th century and will continue to increase in middle and low income countries if testing and subsequent treatment are not made available at a large scale. In industrialized countries where DAAs have been available since 2014, the use of DAAS has been associated with a reduced risk for mortality and hepatocellular carcinoma [34]. In Europe, the number of liver transplantation (LT) due to HCV infection has rapidly declined in the era of DAAs for both decompensated cirrhosis and carcinoma indications, and post-LT survival has dramatically improved in the same time [35].

Testing and linkage to care

In the absence of testing, persons infected with HCV are usually unaware of their infection. In 2015, only 20% of persons living with HCV had been tested and knew their status. This proportion varies widely from some industrialized countries (46%) where national plans for Hepatitis C and screening policies have been implemented, to middle and low income countries (8%) where funding and access to tests are very limited [4]. Moreover, among people diagnosed with HCV infection, only 7% (1.1 million) started treatment in 2015. Since this date, the number of persons treated has substantially increased in high income countries that can afford DAAs, especially in Europe, Australia and the USA. However, the initial increase in the treated patients after the implementation of DAAs was followed by a decline of treated patients, what emphasises the need for a better screening of undiagnosed patients to maintain a sufficient number of cured people [36,37].

Screening approaches vary by country and can be universal, based on birth cohorts (e.g. baby boomers in the USA and in Canada), or targeted on risk factors, especially PWIDs, prisoners, MSM, migrants from endemic countries. However, PWIDs often represent difficult-to reach populations who need special approaches to give access to testing and retain into care.

For infected people, testing is the first step towards a comprehensive response to hepatitis (Fig. 1). Beside classical serological test on venous blood sample, finger stick whole blood samples for rapid diagnostic tests or dried blood spots have been developed, that allow point-of-care testing and are suitable for large screening campaigns [38]. Efforts could be made to make these tests affordable for low income countries, with consequent unrestricted access to affordable DAA therapy. Few countries have already launched programmes to eliminate HCV infection. Egypt, the country with the highest iatrogenic HCV prevalence has launched a large programme of mass screening followed by DAA therapy, aiming at treating at least 150 000 patients in 3 years [39]. Georgia, a country in the Caucasus region of Eurasia has a high HCV prevalence mainly due to IVDU. It embarked in 2015 in a large programme of screening and linkage to care with DAA treatment provided free of charge by a pharmaceutical company and were able to treat about 20 000 patients in 18 months [40]. In Western Europe, few countries (France, Iceland, Italy, Netherlands, Spain, Switzerland, and UK) are already on track to achieve HCV elimination by 2030 [36]; they had developed comprehensive national plans for hepatitis for many years.

Prevention interventions are necessary all along the cascade of care, to reduce the risk of reinfection in DU. These are harm-reduction interventions including needle and syringe programmes and the provision of opioid substitution therapy. However, primary prevention interventions are the key to reduce HCV incidence: harm-reduction to prevent HCV infection in DU, but also safe blood supply and safe injections to prevent iatrogenic transmission.

Reliability of available epidemiological data

In 2020, the priority for HCV infection at a time of fair safety and almost absolute efficacy of DAAs is to improve the cascade of care and especially screening and access to care.

There was a burn-out diagnosis with 5 times more de novo HCV infections than diagnosis in 2016 (in 10 out of the 91 countries studied); at the same time, the cure rates for hepatitis C infection were 5 times lower than the number of new infections (in 23 out of the 91 countries with available data), and the possibility of elimination of hepatitis C virus seems therefore unlikely when analyzing these figures [41].

We have detailed the incidence and prevalence figures that form the basis of policy decisions for measures to be adopted in the general population and for the populations most at risk. Beyond the wide variations across the different geographical areas mainly related to blood and health care safety and harm reduction policies in PWIDs, it is important to note that the methodologies of assessment of incidence and prevalence remain imperfect. If we take the example of France, two successive population-based seroprevalence surveys, using the same methodology were conducted in 1994 and 2004. In 1994 the prevalence of anti-HCV antibodies in Mainland France was 1.1% and the prevalence of current HCV infection (viraemic patients) was 0.86%. In 2004, the seroprevalence had decreased to 0.84% and the prevalence of current HCV infection to 0.53%. Later, reappraisal of HCV prevalences used other methodologies, modeling studies from prevalences in at-risk groups and remaining general population (2011) and telephone survey with home blood self-sampling on dried blood spots (2016). These last estimations were not comparable to the two first ones, but gave decreasing figures, 0.42% of current HCV infections in 2011 and 0.30% in 2016 [42]. This decline is related to a reduction of incidence following the improvement in blood safety, harm reduction policies in PWIDs with needles and syringes exchange programmes, death of the oldest infected patients, but also to the increasing number of patients treated and the increasing rate of sustained virological response which decrease prevalence and incidence in the community. Thus, it appears that figures have to be evaluated in a dynamic way since they may decrease or increase according to the variable epidemiological situations and they need to be regularly adjusted in a fair way. For example, in France, the number of patients treated with DAAs increased from 11 500 in 2014 to 19 300 in 2017 corresponding to 7% and 19 % respectively of the infected population still to treat, but declined thereafter (data from the French health insurance).

We need to alert readers, advocacy groups, payers and governments that, in the absence of an universal screening, all the figures are open to discussion with risks of both underestimation and overestimation. Underestimation can be due to the ḧidden populationïn the absence of health care system for precarious high-risk population, or underdiagnosed group of patients, e.g. psychiatric patients that are usually not included in incidence and prevalence assessments despite a 4—10 higher HCV prevalence than that of the general population. Overestimation can occur when inputs of models are figures obtained from high-risk populations like drug users or prisoners.

In the absence of universal screening and given the kinetics in the different countries (marked decline in Western countries contrasting with HCV epidemics in parallel to the opioid overdose outbreak in USA), it remains difficult to accurately evaluate the dynamic incidence and prevalenvce of HCV worldwide.

Conclusion

HCV infection is a global health problem, recognized as such by WHO since early 2000s. The availability of effective treatments since 2014 raised the opportunity of the elimination of HCV infection. In 2015 WHO adopted a global hepatitis strategy to eliminate viral hepatitis as a public health threat by 2030. The ambitious targets are a 90% reduction in incident cases, and a 65% reduction in mortality. To reach these targets, 80% of treatment-eligible individuals need access to care. WHO has developed a global health sector strategy 2016—2021 on viral hepatitis that includes increasing public awareness, advances in hepatitis medicines, diagnostics and other technologies, and strengthening commitment to achieve health equity [2]. The way will be long, and the involvement of all stakeholders will be necessary to achieve the optimistic goal of WHO.

Disclosures

Dr Roudot-Thoraval received honoraria as speaker from Gilead and Abbvie.

Conflicts of interest

The authors declare no conflicts of interest.

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