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Hepatitis C: Is eradication possible?

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Abstract

Hepatitis C has a relevant global impact in terms of morbidity, mortality and economic costs, with more than 70 million people infected worldwide. In the resolution, "Transforming our world: the 2030 Agenda for Sustainable Development" was included as a focus area in the health-related goal with world leaders pledging to "combat" it by 2030. In response, WHO drafted the Global Viral Hepatitis Strategy carrying the ambitious targets to reduce the number of deaths by two-thirds and to increase treatment rates up to 80%. Despite the availability of highly effective therapeutic regimens based on direct-acting antivirals many barriers to HCV eradication still remain. They are related to awareness of the infection, linkage to care, availability of the therapeutic drug regimens and reinfection. Overall, if an effective prophylactic vaccine will not be available, HCV eradication appears difficult to achieve in the future.

KEYWORDS
DAA, HCV, HCV-vaccine, linkage to care, viral eradication

1 | INTRODUCTION

Only 30 years have elapsed since the discovery of hepatitis C virus (HCV), and many are convinced that we are entering in the dusk era of this infection. Since 2014, the widespread availability of all-oral, short-course, well-tolerated and extremely effective drug regimens based on direct-acting antiviral agents (DAAs) have dramatically changed the landscape of HCV therapy. What once was a chronic disease, that could be eradicated in only a fraction of patients with a long and side-effect prone therapy has evolved into a disease that can be eradicated in 8-12 weeks, in almost all patients with no significant comorbidities, taking one to three pills daily.[1] Despite this epochal event, and the fact that the number of HCV viremic patients was already decreasing since 2007, HCV infection still is a global concern.[2] Based upon the latest reports, there are around 71 million people infected with HCV, for a global prevalence of 1.0%.[2] The number of HCV-related deaths has increased from 200 000 per year in 2000 to 400 000 per year in 2015, in contrast to the decrease in deaths related to HIV/AIDS, TB and malaria.[3] The prevalence of advanced liver disease and the corresponding cost for health system will increase further in the future if specific actions against HCV are not adopted.[4] Despite some recent controversial results from a Cochrane meta-analysis, which was unable to determine the effect of DAAs on hepatitis C-related morbidity and all-cause mortality, data from observational studies and trials using surrogate outcomes show that modern pan-genotypic DAA regimens are efficacious against HCV-related morbidity and mortality, also in patients with early fibrosis/non-advanced liver disease.[5,6] Notwithstanding, HCV prevalence is declining in the general population, HCV incidence is increasing between special populations such as persons who injects drugs (PWID), men who have sex with men (MSM) and prisoners. In this article, we will review the perspective of HCV eradication, especially in view of the United Nation resolution on 2030 Goals for a Sustainable Development and the World Health Organization (WHO)'s Global health sector strategy on viral hepatitis, 2016-2021 (GHSS).

Abbreviations: Ad6, human adenovirus 6; ChAd3, chimpanzees adenovirus 3; CHC, chronic hepatitis C; DAAs, direct-acting antiviral agents; DBS, dried blood spot; EASL, European Association for the Study of the Liver; ELISA, enzyme-linked immunosorbent assay; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HCV-Ags EIA, HCV antigens enzyme immunoassay; HIV, human immunodeficiency virus; LMICs, low- and middle-income countries; MMPHCRF, Mukh Mantri Punjab Hepatitis C Relief Fund; MVA, modified vaccinia Ankara; nAbs, neutralizing antibodies; NHANES, National Health and Nutrition Examination Survey; NS, non-structural; NSP, needle syringe programmes; OST, opioid substitution therapy; PegIFN, pegylated interferon; PWID, person who injects drugs; RBV, ribavirin; RDT, rapid diagnostic test; WHO, World Health Organization.

2 | THE UN 2030 GOAL

In October 2015, to replace the Millennium Development Goals, the General Assembly of the United Nations approved the resolution 70/1, called "Transforming our world: the 2030 Agenda for Sustainable Development." The agenda contains 17 Sustainable Development Goals and 169 targets in different areas of critical importance for humanity and the planet to be achieved within 2030. The ambitious goal 3 in the target 3.3 stated: "…end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases…".[8] According to this, the GHSS of the World Health Organization (WHO) aims to a world where viral hepatitis transmission is halted, and infected people have access to safe, affordable and effective care and treatment. The goals for HCV are 80% reduction in HCV incidence and 65% reduction in HCV-related mortality.[9] To obtain that, different service coverage targets are defined regarding blood safety, safe injections, harm reduction, diagnosis and treatment. Informed by global goals and targets, countries should develop their own programme to achieve the above-mentioned targets, tailored upon country viral hepatitis epidemiology, healthcare system and financial resources.

Key Points

- DAA availability increased hopes of HCV elimination and WHO defined that as a goal to be achieved by 2030.
- DAAs proved to efficiently eliminate HCV in specific settings/populations, but economical and logistic reasons make extremely difficult to apply this approach globally.
- A therapeutic vaccine is considered essential to reliably target HCV eradication.

3 | THE CURRENT EPIDEMIOLOGY

The latest global HCV disease burden estimates, based on 2015 data, showed that about 71.1 million people worldwide are viremic, corresponding to a prevalence of 1%.[2] The number of infections is substantially lower than in previous estimates, probably owing to the lower prevalence estimates in China and Africa, the ageing of the population and the mortality from liver-related causes. Ten countries showed a 10% or greater increase in prevalence since 2007 as a consequence of manpower immigration from endemic countries, iatrogenic infections and infections among PWID. Prevalence is not homogenous: the WHO Eastern-Mediterranean Region (EMR) is the area with the highest number of infected subjects (about 15 millions), followed by the European Region (ER; 14 million), the Western-Pacific Region (WPR; 14 millions) and the African Region (AR; 10 millions).[10] Interestingly, according to the 2017 World Bank list of economies, half of the 30 countries accounting for 80% of HCV infections worldwide are in the low- and lower-to-middle-income group (Figure 1). This raises

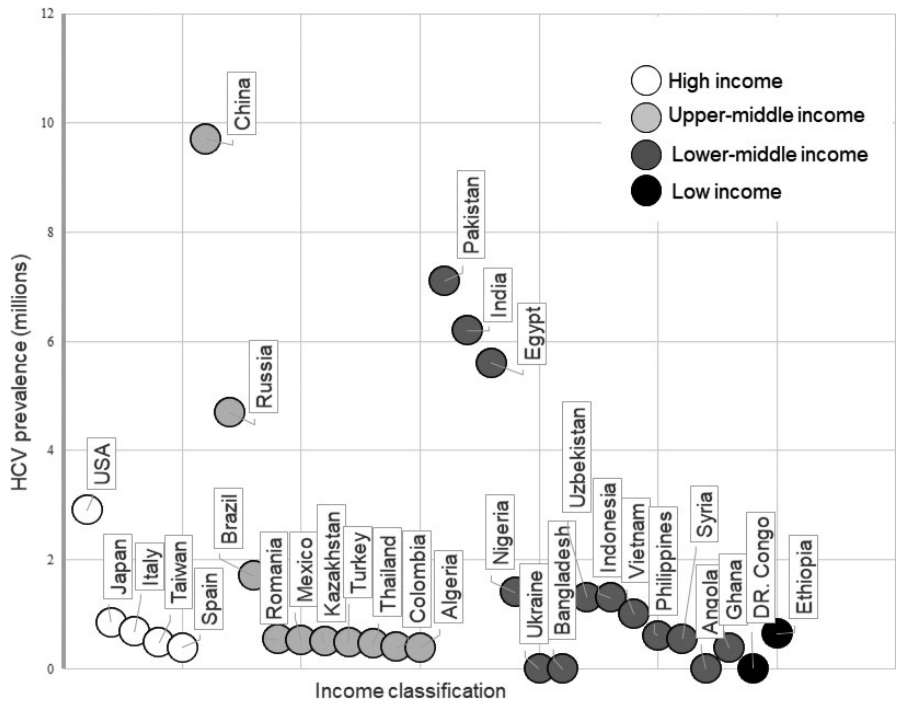

FIGURE 1 HCV prevalence and income classification. Relationship between HCV prevalence and income classification. The 30 countries with the highest HCV prevalence are represented relative to their income classification. Income classification is based on the June 2018 World Bank list of economies. Prevalence is highest in countries with lower-middle-to-low income

some concerns about the possibility of these countries' health system, with few exceptions, to enforce and sustain HCV elimination programmes.

The global incidence of HCV in 2015 was estimated in about 1.75 million (23.7 cases per 100 000). The highest incidence was recorded in the EMR (62.5/100 000), followed by the ER (61.9/100 000).[10] Incidence is largely driven by unsafe healthcare practise in EMR, whereas in ER incidence of HCV is largely caused by injecting drugs. In high-income countries, the incidence is concentrated in some specific populations, such as PWID and MSM, who are also at risk for reinfection after being cured with DAAs. Overall, the 5-year recurrence risk between HCV monoinfected "low-risk" patients is about 0.95%, compared to a 10.67% 5-year recurrence risk in HCV monoinfected "high-risk" patients, defined as PWID or prisoners.[11] In the USA, the HCV incidence has increased by 13% annually in non-urban counties between 2006 and 2012, because of intravenous drug use in young people who had previously been prescribed opioids.[12] These groups cannot be marginalized, both for the role that they have in virus transmission and the portion of the infected population they represent. Indeed, it is estimated that 5.6 million (8%) of the HCV-infected people currently inject drugs.

In terms of treatment, 950 000 patients were treated in 2015, and SVR was reached in about 700 000; for the same year, the WHO estimated 1.7 million new infections. In a given area and time frame, the sum of the dead and the cured minus the new infections gives the net cure rate, a parameter used to evaluate the profile of the HCV epidemics in relation to linkage to care. It has been estimated that an annual net cure rate of 7% is needed to achieve the 2030 UN goals.[13] Despite the availability of DAAs in 2016, most WHO regions showed a negative net cure rate: Sub-Saharan African Region and Central and Eastern European Region had a net cure rate of −2.15% and −4.3% respectively. At the national level, in 2016, only 10 countries had five times more people reaching SVR than there were new infections; they were all high-income countries apart from Egypt, a low-middle-income country (LMIC) that has not allowed any patent on DAAs. By contrast, in 23 countries there were five times fewer people reaching SVR than there were new infections in 2016, none of them was from a high-income country.[13] Overall, only a marginal net cure rate of 0.43% was estimated worldwide in 2016. In 2018, the scenario has improved: based upon the Polaris Observatory data, 12 countries are now on track to achieve WHO elimination targets: Australia, Egypt, France, Georgia, Iceland, Italy, Japan, Mongolia, the Netherlands, Spain, Switzerland and the UK. However, the 2030 goal still appears improbable to achieve.

4 | THE CASCADE OF CARE

Direct-acting antiviral agents are an extraordinary tool to curb the burden of HCV infection, but the simple availability of these drugs is not sufficient to obtain a real impact on morbidity and mortality, even less to target virus eradication. Clear knowledge of epidemiology, with the identification of infected people, linkage to treatment administration structure and surveillance programmes after viral

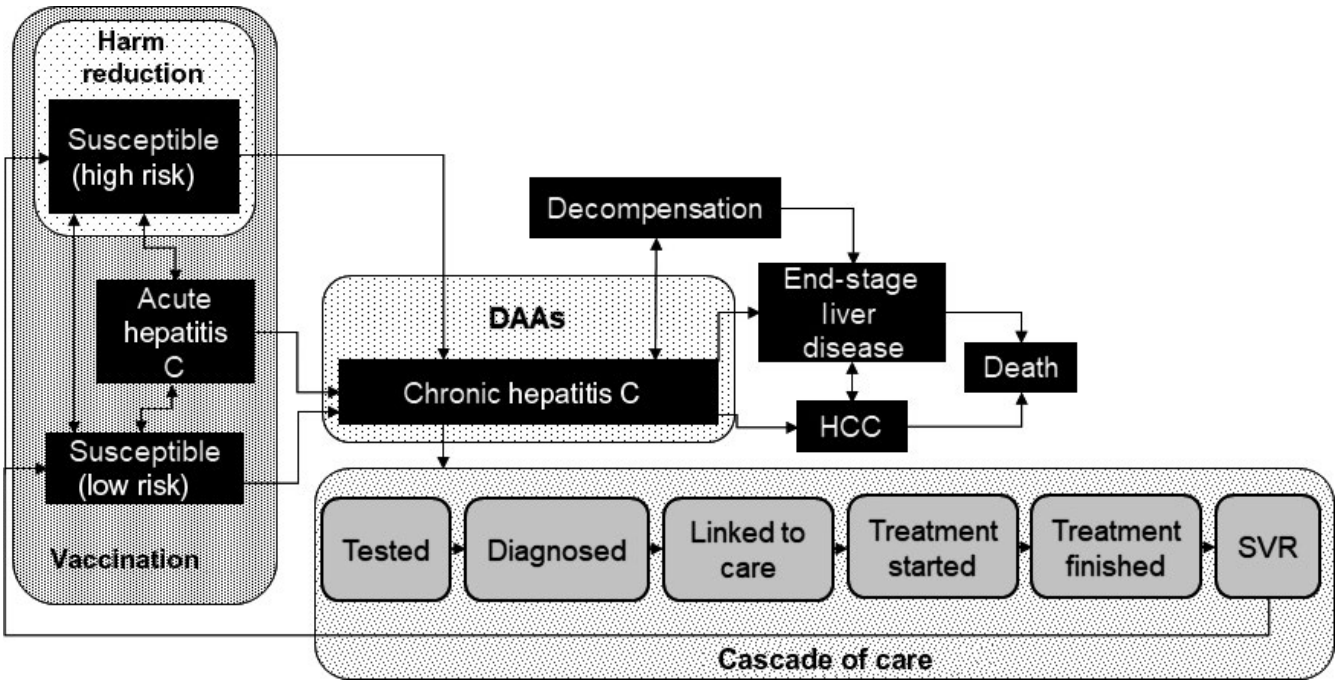

FIGURE 2 HCV natural history and possible interventions. Vaccination acts before CHC develops, preventing the infection. Harm reduction strategies, that is, opioid substitution therapy, needle syringe programmes, can help reducing the infection in high-risk populations. DAAs allows to resolve CHC but do not prevent reinfection. Cascade of care is composed of different steps as shown in the figure

eradication for people with advanced liver disease are the key elements in the so-called "HCV cascade of care" (Figure 2).

The first step in the cascade of care is the identification of infected people, so that the sequence of care can be initiated. Based upon 2017 WHO Global Hepatitis Report, of the 71 million people with HCV worldwide, only 20% of them (14 million) are aware of the infection. A large study conducted in the USA from 2001 to 2008 in the general population showed that fewer than half (49.7%) of those infected with HCV were aware of their status.[14] In another study based on the National Health and Nutrition Examination Survey (NHANES), patients who were unaware of their infection were just as likely to have cirrhosis as those who knew about their infection, meaning that even advanced liver disease can pass unnoticed.[15] The situation is slightly better in PWID, where screening and education programmes probably increased awareness: 56% (784/1386) of the HCV-positive PWID in a Swedish study reported correctly their status who was verified through HCV-Ab and HCV RNA determination.[16] Overall, a large part of the infected subjects are unaware of their condition and these individuals must be identified, possibly before the development of end-stage liver disease and related conditions, through screening programmes that involve easy, accurate and rapid point-of-care tests (POCT).

HCV epidemics can roughly be classified into three main epidemic patterns: infections related to high-risk behaviours and populations, ongoing infections in generalized population epidemics and historic infections related to past generalized HCV exposures, now removed. Accordingly, in high-income countries testing guidelines suggest one-time hepatitis C testing for persons with behaviours, exposures, and conditions or circumstances associated with an increased risk of HCV infection, persons born from 1945 through 1965 without prior ascertainment of risk (baby boomers) and persons with unexplained alteration of liver enzymes.[17] For LMICs no guidelines exist, although Egypt is doing more than any country to reach the WHO 2030 goals, as well as Georgia and Mongolia. Screening programmes are commonly supported by non-governmental or international organizations and they usually test specific populations and only marginally perform routine testing in the general population. Moreover, testing is principally hospital-based.[18]

To identify infected people who are unaware of their status, efforts must be made in two main directions: access to test must be expanded and easier and faster instruments to determine HCV status must be provided. In high-income countries, testing of specific high-risk populations must be maintained and increased. Identification and treatment of high-risk individuals allow to hit the epidemic in those who are maintaining it, realizing the concept of treatment-as-prevention. A recent work by Deuffic-Burba et al[19] showed how, in a high-income country such as France, universal screening is the most effective strategy and it is cost-effective, regardless of patients' fibrosis stage, with an estimated €31 100/QALY (Quality-Adjusted Life Year). In developing countries, the presence of rudimental or even the absence of health systems leads to the absence of screening programmes, with the vast majority of patients being unaware of their diagnosis. In Africa, only a marginal 19% of blood transfusions are screened for HCV, because of cost constraints,[20] although significant heterogeneity may exist in health system quality. Moreover, CHC does not represent a core issue in the activity of contributors to global health development and screening programmes are not implemented.[21] This leads to the absence of clear data about prevalence, mortality and morbidity and it hampers any elimination programme.

A possible contribution to the problem, applicable both to developed and developing countries, could be represented by the introduction of new diagnostic tests. The ideal test must be inexpensive, easy to use and store and with a one-step design. Nowadays, HCV diagnosis is a time-consuming two-step process, which many patients never complete.

Antibody-based rapid diagnostic tests (RDTs), point-of-care tests (POCTs) and dried blood spot tests could facilitate preliminary screening. RDTs are rapid but require special equipment and sometimes trained personnel. POCTs are also rapid, and no special equipment or electricity is required: they are easier to perform, and cold chain is not required. Many researches focused on the development of RDTs able to identify specific HCV proteins present in the serum only during active viral replication.

Actually, only one POCT has been approved by the WHO, the SD BIOLINE HCV, produced by Standard Diagnostics, Inc (South Korea). This is an immunochromatographic test that use recombinant core, NS3, NS4 and NS5 antigens to detect HCV antibodies in human serum, plasma or whole blood. The test showed a sensitivity and a specificity of 78.8% and 100%, respectively, and allows to get a result within 20 minutes.[22] Unfortunately, this test can reduce costs and time but still needs a confirmatory HCV RNA-positive test.

Finally, the efficacy and reliability of dried blood spot (DBS) tests for detection and genotyping of hepatitis C virus RNA have been shown, also in the setting of coinfection with HIV.[23,24] Already in use worldwide for neonatal screening of congenital disorders, the DBS technique consists in the collection of a small amount of blood on filter paper, that can be conserved at room temperature and subsequently shipped to a reference laboratory, where HCV-Ab testing, HCV RNA and genotyping if necessary, are performed.[25] Nevertheless, also DBS requires a follow-up visit to provide the results and eventually start a treatment.

A step forward in the "HCV cascade of care" is linkage to care, defined as the effective "take charge" of a patient with CHC by a healthcare specialist. A large study conducted in the US general population in 2014 showed that only 43% of those aware of having been diagnosed with CHC had access to outpatient care, whereas the remainder did not receive any treatment.[26,27] Absence of linkage to care recognizes different causes: social stigmatization, inadequate treatment infrastructure, lack of awareness of disease and therapy benefits, dual-step nature and costs of HCV tests (especially in LMICs), being a PWID, an MSM or an immigrant in Western countries and unemployment.[28,29] Recent work by Bottero et al[30] showed how, in a high-risk population composed mainly of African immigrants, the adoption of a POCT-based strategy can improve linkage to care (90% vs 60% with standard serology-based testing) highlighting the importance of providing rapid results. Another way to increase linkage to care is expanding

the providers' pool, to guarantee an easier access to care. However, it must be emphasized that certain patient categories still need highly specialized care, including compensated and decompensated cirrhotics, patients with HCC, patients with renal failure, patients with extrahepatic manifestations such as lymphoproliferative disorders, patients who experienced DAA failure and drug resistance, patients requiring post-SVR HCC monitoring owing to comorbidities.

5 | ERADICATION AND ELIMINATION

On 8 May 1980, the delegates of the 33rd World Health Assembly, unanimously accepted the conclusion of the Global Commission for the Certification of Smallpox Eradication, namely, that smallpox eradication had been achieved worldwide and that there was no evidence that smallpox would return as an endemic disease.[31] To date, this remains the only successful case of infectious disease eradication from the planet.

The term eradication has been used inappropriately even by international health agencies, the correct definition being the global absence of a disease because of a deliberate effort with control measures that are not anymore necessary. Elimination has a more restricted significance, meaning the absence of a disease in a circumscribed geographical area because of a deliberate effort with control measures still necessary to prevent resurgence of the disease. Communicable diseases cannot necessarily be considered eradicable, unless there are specific features. Firstly, the eradication must be feasible from a scientific point of view: the disease must be easy to diagnose, without an animal reservoir, it must be curable with drugs or preventable with a specific vaccine, and it must already be eliminated in a defined area in the past. Secondly, eradication must be feasible also from a political and economic point of view. Indeed, the cost of eradication should be sustainable by healthcare systems and non-profit organizations; eradication of the disease should be relevant and accepted by the society, with the political situation allowing health interventions.[32] After smallpox, many diseases have been considered suitable for eradication, but only two were targeted by WHO: dracunculiasis (Guinea worm disease) in 1986 and poliomyelitis in 1988.[33,34] Despite being for years close to eradication, in 2017 the WHO reported a global burden of 24 cases of dracunculiasis and 21 cases of wild-type virus poliomyelitis. The case of poliomyelitis is emblematic of the importance assumed by geopolitical and social factors: outbreaks in Afghanistan and Syria are related to war in those countries, and resurgence of the disease in Nigeria, Pakistan and Afghanistan was caused by religious opposition by Muslim fundamentalists.[35-37]

HCV meets all the criteria necessary to define it as an eradicable disease.[38] To achieve overall global eradication, the most suitable way is to progressively eliminate the disease in different areas, with methodology and timing specific for the considered area: a community, a city, an island or an entire state. The work of Scott et al,[39] who investigated with a mathematical model feasibility and timing of HCV elimination in accordance with the WHO elimination target in a restricted area such as Iceland, provides an example of that. The authors proposed to consider Iceland as a model comparable to a large city in other countries and they envisaged four possible scenarios. Overall, they showed how the achievement of elimination target hinges on PWID testing and treatment, with the astonishing result of HCV elimination by 2020 if more than 188/1000 PWID are treated per year. As a warning, the authors say that once elimination has been achieved, HCV infections must not be allowed to recur between PWID; moreover, it would be crucial to accurately know the current testing rate in this population to predict elimination.

HCV eradication strategies have been promoted also in developing countries, which have essential health systems and larger population to treat with less circumscribed risk factors. One example is the Mukh Mantri Punjab Hepatitis C Relief Fund (MMPHCRF), a public health programme launched by the Indian state of Punjab that offers free HCV treatment to all residents of the state through a highly decentralized network. The goal of the initiative is HCV elimination in Punjab.[40] The programme provides that an anti-HCV test should be offered to all people at risk for infection. After infection is proven, treatment with generic drugs should be assigned based upon a specific algorithm: SOF + DCV for 12 weeks for people without cirrhosis, without genotype test needed, SOF + LDV + RBV for 12 weeks for genotype 1 and 4 cirrhotic and SOF + DCV + RBV for 24 weeks for genotype 3 cirrhotic. Drugs are provided by the Punjab Health Systems Corporation and patients will be tested again for HCV RNA 12 weeks after the end of treatment. Overall, 1 year after the beginning of the project, about 30 000 people have been screened and SVR has been achieved in 11 100 patients (92.5%), with similar results in cirrhotic vs non-cirrhotic (93.1% vs 92.4%) and genotype 3 vs non-genotype 3 (92.6% vs 93.1%) patients.[41] These results highlight the importance of implementing HCV elimination programmes also in low-resource settings. Success depends of course on the availability of low-cost generics and a capillary network of healthcare providers, with basic knowledge in HCV diagnosis and treatment.

A possible solution to overcome the complexity of HCV eradication programmes, especially in LMICs and countries with a large number of infected subjects, can be represented by micro-elimination strategies. This approach suggests to "break down national elimination goals into smaller goals for individual population segments, for which treatment and prevention interventions can be delivered more quickly and efficiently using targeted methods".[42] Conceivable target populations, to be defined based upon country's epidemiology, could be aboriginal and indigenous communities, birth cohorts with high HCV prevalence, children of HCV-infected mothers, haemodialysis patients, HIV/HCV-coinfected people, migrants from high-prevalence countries, PWID, people with haemophilia and other inherited blood disorders, MSM, prisoners and transplant recipients.[43] Micro-elimination strategies must be tailored on population's characteristics, applying the most relevant and suitable intervention. Moreover, they should not be considered the target of HCV elimination strategies themselves, but rather a brick in the

TABLE 1 Treatment scale-up model in PWID and predicted results

Study	Geographical site	Population size	Anti-HCV prevalence in PWID (%)	HCV RNA prevalence in PWID (%)	Treatment scale up	CHC reduction
Fraser *et al* (2018)[52]	Amsterdam, The Netherlands	1874	59.4	33.0	50/1000 PWID/y	99.7% in 2026
	Belgium	9080	43.3	31.6	50/1000 PWID/y	69.3% in 2026
	Czech Republic	41 816-46 563	35.0	20.9	50/1000 PWID/y	99.9% in 2026
	Denmark	16 500	—	39.9	50/1000 PWID/y	84.1% in 2026
	Finland	15 611	76.0	56.1	50/1000 PWID/y	55.9% in 2016
	France	80 000	66.4	47.3	50/1000 PWID/y	47.6% in 2026
	Hamburg, Germany	8492	67.7	49.6	50/1000 PWID/y	71.9% in 2026
	Norway	15 500	—	42.9	50/1000 PWID/y	81.1% in 2026
	Scotland	16 000	58.0	42.3	50/1000 PWID/y	80.8% in 2026
	Slovenia	6000	27.3	16.2	50/1000 PWID/y	99.9% in 2026
	Sweden	8021-26 550	81.7	60.0	50/1000 PWID/y	47.9% in 2026
Cousien *et al* (2017)[71]	Montréal, Canada	4000	70.0	53.1	From 10% to 20% of PWID/y	36.6% in 10 y
Gountas *et al* (2017)[72a]	Athens, Greece	8300	80.0	64.0	4%-8% PWID/y	46%-90% in 2030
Fraser *et al* (2017)[73]	Scott County, Indiana (USA)	436-600	70.0	45-65	159/1000 PWID/y	90% in 2030
Scott *et al*(2017)[39]	Iceland	880-1300	—	38.0	55/1000 PWID/y	80% in 2030
Scott *et al* (2016)[74]	Australia	184 000	—	50.0	59/1000 PWID/y	94% in 2030
Van Santen *et al* (2016)[75]	Amsterdam, The Netherlands	1500	—	60.0	100/1000 PWID/y	37% in 15 y for genotype 1-4; 54% in 15 y for genotype 2-3
Echevarria *et al* (2015)[76]	Chicago, USA	32 000	54-59	47.0	35/1000 PWID/y	50% in 10 y
Martin *et al* (2015)[77]	Bristol, UK	3200-4400	—	43.0	26/1000 PWID/y	14%-20% in 10 y
	East London, UK	2400-6000	—	43.0	26/1000 PWID/y	13%-20% in 10 y
	Manchester, UK	2300-4000	—	52.0	26/1000 PWID/y	7%-16% in 10 y
	Nottingham, UK	1300-2500	—	41.0	26/1000 PWID/y	12%-19% in 10 y
	Plymouth, UK	1100-2000	—	33.0	26/1000 PWID/y	16%-21% in 10 y
	Dundee, UK	2000-3000	—	23.0	26/1000 PWID/y	18%-22% in 10 y
	North Wales, UK	1700-3400	—	30.0	26/1000 PWID/y	18-22 in 10 y
Martin *et al* (2013)[78]	Edinburgh, UK	4240	34.0	25.0	22/1000 PWID/y	75% in 15 y
	Melbourne, Australia	25 000	66.0	50.0	54/1000 PWID/y	75% in 15 y
	Vancouver, Canada	13 500	88.0	65.0	98/1000 PWID/y	75% in 15 y
Hellard *et al* (2012)[79b]	Victoria, Australia	25 000	—	50.0	25/1000 PWID/y	50% in 30 y

CHC, chronic hepatitis C; IFN, interferon; PWID, people who inject drugs.
[a]Associated with 2%/year increase in harm reduction strategies.
[b]IFN-based regimens.

achievement of HCV eradication in the entire population. Evidence supporting feasibility and effectiveness of micro-elimination strategies is mounting, both in developed countries and LMICs and in different target populations.[44-48]

6 | SPECIAL POPULATIONS

Targeting HCV eradication in specific high-risk populations appears to be a highly effective strategy to reduce disease burden. Injecting risk behaviours among PWID and high-risk sexual practices among MSM are important routes of HCV transmission. PWID are considered, at least in Western countries, the key drivers of HCV transmission. In average, one in four people who acquired HCV through injecting drug use have recently injected drugs, continues to be exposed to the virus and represents an active reservoir.[49] In the USA, based upon the Centers for Disease Control and Prevention statistics, HCV incidence showed a rapid rise over the past several years, probably in connection with the ongoing opioid use epidemic.

Numerous theoretical modelling studies have explored the potential impact of HCV treatment in PWID. Even before the availability of DAAs, hepatitis C treatment among active injecting drug users has been associated with a reduction in viral transmission and infection prevalence.[50] Past guidelines did not recommend treatment of this population, because of concerns of poor adherence, high reinfection rates, interferon toxicity and ribavirin teratogenicity. With the advent of DAAs, the landscape has changed radically and HCV treatment as prevention has become a doable strategy. PWID quickly moved from the bottom of the list to a target group that must be treated to reduce the viral reservoir. A mathematical model developed by Martin et al[51] showed how treatment of a relatively small proportion of PWID can reduce HCV prevalence in the global population in a significant manner. The results were influenced by the prevalence of chronic HCV infection, treatment availability and concomitant accessibility to harm reduction strategies, such as opioid substitution therapy (OST) and needle syringe programmes (NSPs). This study caused the blossoming of papers forecasting the number of PWID that must be treated every year in different populations to reach WHO 2030 goals. Table 1 shows different treatment scale-up models based on real populations worldwide. Overall, HCV prevalence can be significantly reduced, even in a short period of time, in different locations across the globe. In some settings, such as Amsterdam, the Czech Republic and Slovenia, elimination of CHC in PWID can be predicted to be achieved in 10 years, with a treatment target of 50/1000 PWID per year.[52]

7 | ELIMINATION IN LOW-RESOURCE SETTINGS

To achieve global eradication, HCV must be tackled down not only in the well-defined setting of developed countries but also in the more intricate situation of developing countries, where the disease is generally not confined within restricted populations and economical resources are limited. The first step is again the correct identification of those who are infected. In LMICs, <5% of the patients are aware of their status, an even lower proportion than in developed countries.[53] The WHO recommends any LMICs to develop a specific screening strategy based upon the characteristics of the HCV-infected population.[54] In the absence of precise epidemiological data, evidence supports focused testing of high-risk groups such as PWID and MSM to be cost-effective, as birth cohort testing. The evidence for routine population testing is less strong and the cost-effectiveness largely depends on HCV prevalence.[55]

Reducing iatrogenic spread of HCV is another key step. Indeed, blood transfusions from unscreened donors and unsafe therapeutic procedures are considered the leading causes of HCV transmission in LMICs.[53] Hauri et al[56] estimated that in 2000 two millions infections were related to unsafe healthcare practice and that would lead to 24 000 future early deaths between 2000 and 2030 for an overall burden of 324 198 disability-adjusted life years (DALYs). Currently, the WHO considers unsafe 5% of healthcare-related injections but they have decreased significantly from the 39% documented in 2000.[53] Reaching 0% of unsafe injections in 2020 is a primary goal of the Global Health Sector Strategy on viral hepatitis. The ways to achieve this goal are mainly two: to decrease the number of healthcare injections given with equipment reused without sterilization and guarantee adequate screening procedures of blood donations. To this day, among LMICs, 34% of blood donations are not screened using basic quality procedures.[53]

In low-resources settings, DAAs cannot be provided at the same fees of developed countries, for obvious economic reasons. The minimum cost of hepatitis C treatment and associated diagnostic tests, assuming that large-scale treatment programmes can be established, has been estimated to be around US$171-360 per person without genotyping or US$261-450 per person with genotyping; these low prices could make widespread access to HCV treatment in LMICs a realistic goal.[57] In India, generic sofosbuvir, ledipasvir and daclatasvir are available produced by several generic manufacturers, at a price as low as $110 for a 12-week therapy. Regimens based upon these drugs have been shown not only to be safe and efficacious, but even cost-effective within 2 years, and cost-saving within 10 years of their initiation overall and within 5 years in persons with cirrhosis.[58] Pan-genotypic drugs will contribute to further reduce costs for HCV cure.

8 | WILL A VACCINE EVER EXIST?

Despite the availability of extremely efficient DAAs, HCV eradication remains a difficult task to accomplish in the absence of a vaccine. Smallpox is the only successful example of disease eradication, a result achieved through the global use of prophylactic vaccine, which required more than 20 years of dedicated efforts worldwide,

TABLE 2 HCV prophylactic vaccines in development or previously tested

Sponsor	Clinical ID	Compound	Stage of development	Results	References
—	—	DNA vaccine encoding gpE2	Animal model (Chimpanzees)	Vaccine did not elicit sterilizing immunity, it might modify infection and prevent chronicity	Forns X *et al* Hepatology (2000)[80]
—	—	Recombinant HCV-like particles containing HCV structural proteins (core, E1, and E2)	Animal model (Chimpanzees)	Immunization induces HCV-specific cellular immune responses that can control HCV challenge in the chimpanzee model	Elmowalid GA *et al* Proc Nat Acad Sci USA (2007)[81]
—	—	Core protein and ISCOMATRIX™ adjuvant	Phase I (30 participants)	Antibody responses were detected in all but one of the participants. CD8+ T-cell responses were only detected in two of eight participants receiving the highest dose	Drane D *et al* Hum. Vaccines (2009)[82]
National Liver Institute, Egypt	NCT01718834	Cenv3 peptide (3 envelop peptides: p315 from E1, p412 and p517 from E2)	Clinical Trials Phases I and II (28 participants)	The article showing the results of the trial has been withdrawn at the request of the author(s) and/or editor	El-Awady MK *et al* Vaccine (2010)[83]
NIAID	NCT00500747	Recombinant gpE1/gpE2 plus adjuvant MF959	Phase I (60 participants)	Completed, vaccine is safe and generally well-tolerated. Possible generation of interfering antibodies blocking the neutralizing activity	Frey SE *et al* Vaccine (2010)[84] Kachko A *et al* Hepatology (2015)[85]
NIAID	NCT01436357	Viral vectors AdCh3NSmut1 + MVA-Nsmut	Phase I/II (548 participants)	Ongoing, estimated primary completion date July 2018. Preclinical studies showed durable, broad, sustained and balanced T-cell responses	Folgori A *et al* Nat Med (2006)[66] Barnes E *et al* Sci Transl Med (2012)[67] Swadling L *et al* Sci Transl Med (2014)[68]

ChAd3, chimpanzees adenovirus 3; gp, glycoprotein; MVA, modified vaccinia Ankara; NIAID, National Institute of Allergy and Infectious Diseases; NS, non-structural protein.

beside over two centuries of vaccine availability. Poliomyelitis, which is still endemic in some countries, can benefit of two prophylactic vaccines: the inactivated polio vaccine (Salk's vaccine) and the oral polio vaccine (Sabin's vaccine). In general, to control an epidemic the number of new infections must be lower than the sum of the cured and the dead. In a recent work published by Hill et al,[13] the number of new infections exceeded the number of subjects who reached SVR in 47 of the 91 countries analysed. Overall, very few countries are on target to achieve HCV elimination by 2030, let alone eradication. A prophylactic vaccine can impact HCV eradication in different ways. Firstly, especially in low-resources settings, it can guarantee a larger population coverage given the lower cost compared to DAAs. Secondly, it can prevent reinfection, an event common in high-risk populations. Finally, it can be administered widely without the need of population screening and subsequent linkage to care, efficiently preventing the development of end-stage liver disease, in which DAAs are less effective and the associated healthcare costs, including liver transplantation, are extremely high.

Despite many years of intense efforts in the development of an effective vaccine, the goal remains elusive. Indeed, the extreme diversity of the different virus genotypes and minor variants, that are responsible for the typical quasispecies distribution of HCV makes the development of neutralizing antibodies against conserved epitopes a very difficult task.[59] Moreover, the immune mechanisms responsible for viral eradication are not entirely clear. It is widely accepted that T cells play a pivotal role in clearing acute HCV infection while the role of neutralizing antibodies in disease progression is far from being clarified. Several lines of evidence support the ability of neutralizing antibodies (nAbs) to prevent HCV infection in vitro and in animal models.[60-62] Moreover, studies in PWID showed how clearance of reinfection is associated with the generation of cross-reactive nAb and depends on the magnitude, breadth and quality of the HCV-specific memory T-cell response.[63] The virus has two principal mechanisms to escape from the action of T cells: the high transcription error rates of the viral polymerase leading to emergence of viral variants that are not recognized by the existing T-cell response, and the continuous exposure of T cells to viral antigens leading to exhaustion through the activation of various T-cell inhibitory pathways, including check-point inhibitors such as PD-1/PDL-1.[64] Viral escape from antibody response is more complex and it involves the high viral diversity, the glycosylation of structural surface proteins, the ability of the virus to spread through cell-to-cell transmission,

the association of viral particles with lipoproteins, the presence of interfering antibodies and the existence of mutations altering the normal use of the host cell receptors by the virus.[65]

In the past decades, several prophylactic vaccine candidates have been developed but none have reached use in real life. Based upon the failure of early attempts to achieve sterilizing immunity, the only prophylactic vaccine actually in phase I/II clinical trial has been designed trying to unconventionally elicit a T cell-mediated response against non-structural viral proteins. To this end, Folgori et al[66] designed a vaccine composed by a platform able to elicit a broad and potent T-cell response, using the human adenovirus 6 (Ad6) and the chimpanzees adenovirus 3 (ChAd3) as vectors, and an immunogen that comprises a vast part of the non-structural (NS) region of the HCV polyprotein. The selected adenoviruses rarely infect humans, consequently possible interference of pre-existing nAbs is unlikely. Moreover, the non-structural region has an amino acid conservation range of 72%-79% across the six major genotypes, potentially allowing universal coverage. Strong CD8+ and CD4+ T-cell responses were induced in chimpanzees which received the vaccine that were linked to viral control in four of five immunized animals. In a subsequent phase I study of healthy human volunteers, the adenovirus-based vaccine was able to prime T-cell responses against HCV proteins. These T-cell responses targeted multiple proteins and were capable of recognizing heterologous strains; moreover, after being boosted by the heterologous adenoviral vectors, they lasted at least 1 year.[67] Another work of the same group showed that HCV-specific T cells induced by ChAd3 are optimally boosted by the administration of the modified vaccinia Ankara (MVA) and generate very high levels of both CD8+ and CD4+ HCV-specific T cells targeting multiple HCV antigens.[68] Clinical trial NCT01436357, of which preliminary completion date was due in May 2018, is a two-stage, phase I/II, double-blind, randomized, placebo-controlled study which enrolled 548 active PWID negative for HCV infection. The individuals in the study have received ChAd3NS vaccine at day 0 followed by MVA-NS as a booster 56 days later, or placebo, and they have been followed for 18 months plus 9 additional months in case they became viraemic. In addition to safety profile, the study evaluates the efficacy of the vaccine in humans; however, the results have not been released to date. Table 2 shows the HCV prophylactic vaccines in development or tested in the past, from which t is clear that sterilizing immunity will be extremely difficult to achieve. Two studies, one based on the Canadian population the other on the population of the Sao Paulo state (Brazil), assessed the cost-effectiveness of a hypothetic HCV vaccine during the peg-IFN + RBV era.[69,70] The Canadian study showed that a vaccine of even moderate efficacy would be cost-saving in high-risk groups and economically quite attractive ($18 000/QALY, 93% probability of being <$50 000/QALY) in a low-risk general population cohort. In both studies, an indiscriminate vaccination strategy was found to be more cost-effective than anti-HCV therapy. Unfortunately, these simulations were realized comparing a hypothetic HCV vaccine against the old peg-IFN + RBV dual therapy. Nevertheless, the studies assumed a treatment cost of about $8000, not far from the price of most DAA regimens in Europe at the time of writing. A more recent simulation considering DAA treatments is greatly needed to assess the comparative effectiveness of a vaccine vs DAA treatment as prevention of HCV infection and reinfection.

9 | CONCLUSIONS AND OUTLOOK

Current DAA treatments offer the unprecedented opportunity to significantly reduce HCV infection and related complications, fulfilling WHO Global Health Sector Strategy on viral hepatitis (2016-2021). This rather ambitious result could hopefully be obtained by combining universal treatment with specific policies for high-risk, HCV-infected populations, such as PWID, MSM and prisoners. Treatment must be preceded by the identification of those who are infected, particularly in highly endemic countries, considering that a large proportion of viremic subjects is still unaware of being infected. Although elimination could be close to reality in selected virtuous countries, global HCV eradication appears to be a pipe dream without the development of an effective prophylactic vaccine, able to control the HCV epidemic in all populations worldwide. Only a prophylactic vaccine can offer long-lasting protection at a reasonable cost and without side-effects. The results of the first field clinical trial NCT01436357 are eagerly awaited.

CONFLICT OF INTEREST

The authors do not have any disclosures to report.

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