



Hepatitis C elimination: a Public Health Perspective

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Abstract

Purpose of review Hepatitis C virus (HCV) infection is a principal cause of morbidity, mortality, and economic burden, and the global elimination of HCV is now considered a public health objective. Globally, an estimated 71 million have chronic HCV infection with an estimated annual mortality of 3,99,000.

Recent findings The 69th World Health Assembly has endorsed the global HCV elimination strategy by 2030, which is made possible because of all oral, cost-effective, efficacious, generic direct-acting antivirals. The public health strategy targets not only diagnosed chronic hepatitis C patients but also asymptomatic undiagnosed HCV-infected individuals, persons living with human immunodeficiency virus (HIV), post-transplant, thalassemia, persons who inject drugs, and the pediatric population.

Summary Mobilization of state-sponsored HCV elimination programs in a global coalition against HCV has taken root in Egypt, India, Georgia, Mongolia, China, Australia, and Brazil. This review summarizes current HCV elimination initiatives in terms of medical progress, barriers to HCV elimination, and current gaps in knowledge and social outreach from the public health perspective.

Introduction

Chronic hepatitis C virus (HCV) infection affects about 71 million persons worldwide and is a major cause of cirrhosis, end-stage liver disease (ESLD), and hepatocellular carcinoma (HCC) and is associated with increased mortality. [1, 2] The natural history of HCV suggests that about 25–30% of persons affected with the virus clear the virus spontaneously and remain non-viremic, albeit with persistence of the anti-HCV antibodies. However, these persons remain susceptible to reinfection. In patients who eventually develop chronic hepatitis C (CHC), about 40% progress to cirrhosis in 20–30 years, with an annual risk of 1–5% of developing HCC thus mandating careful surveillance for decompensation, ESLD, and cancer. The presence of comorbidities like human immunodeficiency viruses (HIV)/hepatitis B virus (HBV) coinfections, ethanol intake, or obesity accelerates the disease progression to ESLD [3]. Since chronic viral hepatitis is a major cause of public health burden globally, the 69th World Health Assembly proposed a global strategy to eliminate HBV and HCV by the year 2030, which will prevent nearly 7 million deaths. As per the World Health Organization, the elimination of HCV is defined as a 90% reduction in new HCV infection and a 65% reduction in HCV-related deaths. [4•] Elimination of CHC is feasible by reducing the burden of disease and preventing new infections which are aided by inexpensive reliable diagnostic tools, cost-effective direct-acting antivirals (DAAs) improved blood safety, and infection-control programs [3, 5].

To achieve elimination, the public health strategy should involve implementation of safe injection practices, patient education, DAA-based universal treatment for CHC, and targeted interventions for high-risk groups like persons who inject drugs (PWID), coinfection, thalassemia, and other frequent blood component recipients, and patients on dialysis. [5, 6] However, the main barriers to HCV elimination globally are limited financial resources, niche populations, and lack of political will for funding. In general, elimination of HCV is a public health policy to improve the health outcomes of entire populations and a means of averting HCV-related morbidity, mortality, and economic burden. [6] The WHO has defined HCV eradication as “the permanent reduction to nil of worldwide incidence of HCV” via concerted global efforts. [7] On the other hand, HCV elimination is defined with specific levels of control like 90% reduction in new chronic HCV infections, with a target of < 1 million new HCV infections annually and

65% reduction in HCV-related deaths to fewer than 0.5 million deaths annually. [8, 9] The WHO advocates structured HCV elimination goals specific to different regions as per disease burden, existing health infrastructure, and economic reserves. [10] As of 2019, many countries including Egypt, Georgia, India, Brazil, Australia, Italy, Iceland, Japan, UK, Mongolia, Pakistan, France, Netherlands, Spain, and Switzerland have launched HCV elimination programs. [5, 10–22] These goals are dynamic as treatment outcomes improve once experience and resources accumulate in a state health program. [23] Mathematical modeling lends support to the economic logic of mass HCV treatment with a bid to eliminate HCV. A course of generic DAA-based treatment is available for less than \$100 in countries with licensing programs and is shown to be cost effective across various health settings. [10, 24, 25] This review examines the global burden of CHC, existing HCV elimination programs, the challenges highlighted by current elimination strategies, and outline actions that can be taken to overcome each of the issues.

Modes and patterns of HCV transmission

Current HCV transmission shows that there are temporal and geographical variations, attributable to variable modes of transmission in different countries. [26] These include blood and blood component transfusion-related infections and non-sterile injection usage, particularly among PWIDs, tattoos, and in untrained /unsupervised community healthcare. [9, 12, 21, 27] The reuse of needles and syringes, use of multidose vials without adequate sterilization, and unsafe dental and dialysis settings are primary sources of HCV transmission. Unregulated and unsupervised healthcare procedures like unsafe injections and intravenous drug use (IDU) continue to be the leading cause of new HCV infections annually. It is estimated that IDU in PWIDs accounts for nearly 1% and 23% incidence of HBV and HCV infections respectively worldwide. [26, 27] In the state of Punjab, in India, among 21,753 patients who were interviewed for risk-factors, unsafe medical practices (11,877; 54.6%), injection drug use (1640; 7.5%), prior surgery (1420; 6.5%), unsafe dental practice (948; 4.3%), and unprotected sex (112; 0.5%) were the main suspected modes of HCV transmission. [12] The HCV epidemic in Egypt is attributed to the reuse of unsterilized glass syringes

during the schistosomiasis treatment campaign. [1]. It is feasible to prevent HCV by screening and treating the reservoir, preventing new transmission by contaminated blood products, injection safety practices in healthcare settings, and lastly improving access to deaddiction treatment and needle exchange/opioid substitution programs for PWIDs. [26].

Global HCV-related disease burden

Accurate estimations of CHC-related disease burden are required globally, regionally, and nationally to plan national health policies and resource allocation. The WHO has estimated that in the year 2015, about 257 million and 71 million persons were living with HBV and HCV infections worldwide. [28] In the same year, a large survey conducted by the Centre for Disease Analysis that four countries contributed to nearly 40% of the global reservoir of HCV. China has about 10 million

persons living with HCV, followed by Pakistan (7.2 million), India (6.2 million), and Egypt (5.6 million) [29] As per the global health sector strategy on viral hepatitis, HCV elimination can be achieved by diagnosing 90% of infected persons and treating 80% of the persons diagnosed (Fig. 1 and Table 1).

The goals of the Global Strategy Against Viral Hepatitis are (a) to reduce transmission of HCV and improve patient care, (b) to reduce morbidity and mortality, and (c) to ameliorate the socio-economic impact of HCV treatment. [29] Treatment expansion has accelerated in Australia, Brazil, Egypt, Georgia, India, and Mongolia (Table 2). The support from the government and civil society enables them to develop public health HCV eliminations programs, allocate resources, and negotiate agreements with industry that improve screening and treatment access, regulatory and licensing

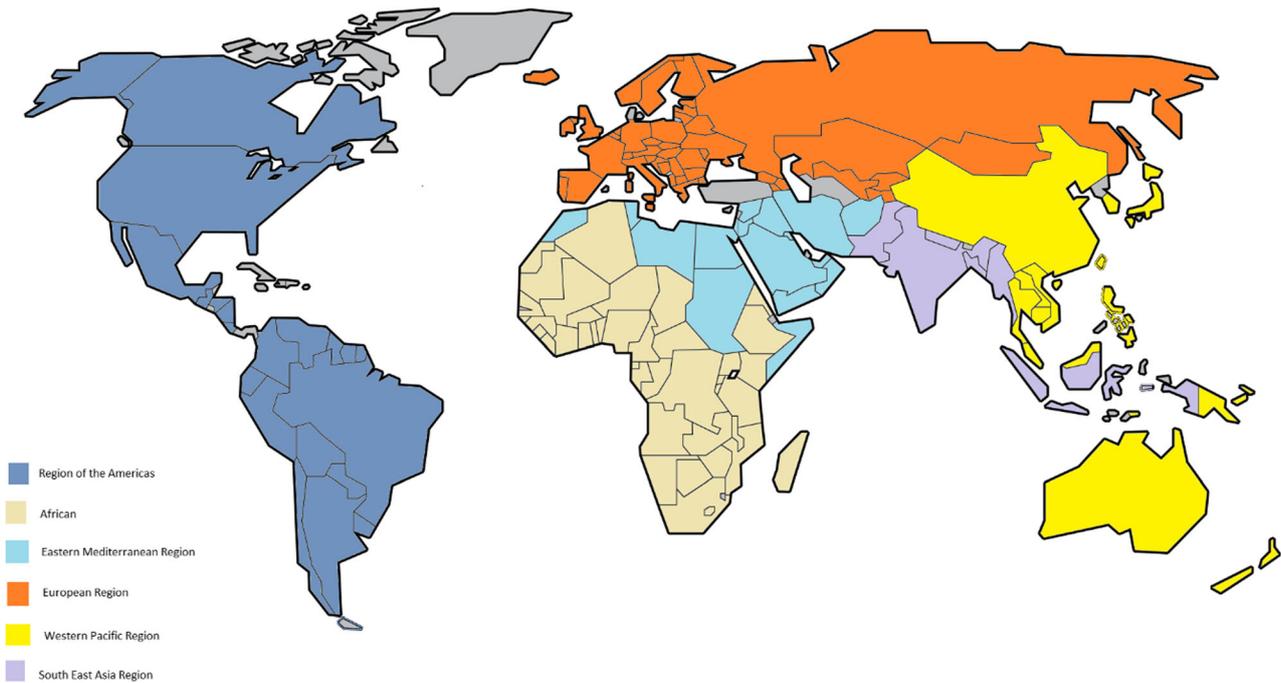


Fig. 1. Development and implementation of public health elimination programs. The goals of the Global Strategy Against Viral Hepatitis are (a) to reduce transmission of HCV and improve patient care, (b) to reduce morbidity and mortality, and (c) to ameliorate the socio-economic impact of HCV treatment. [29] Treatment expansion has accelerated in in Australia, Brazil, Egypt, Georgia, India, and Mongolia.(Table 2). The support from the government and civil society enables them to develop public health HCV eliminations programs, allocate resources, and negotiate agreements with industry that improve screening and treatment access, regulatory and licensing actions, price agreements with originator companies, licensing of generic DAAs, and integration of laboratory testing and drug procurement into existing health systems [4•, 6, 23, 28, 29].

Table 1. Prevalence and incidence rates of HCV infection (HCV RNA positive) in the general population, by WHO region, with uncertainty intervals, 2015 [4, 6, 10]. see Fig. 1.

WHO region	HCV infection			
	Estimate of the prevalence (%)	Estimate of the prevalence (millions)	Incidence rate (per 100,000)	Incidence rate (000)
African	1 (0.7–1.6)	11 (7–16)	31 (22.5–54.4)	309 (222–544)
Americas	0.7 (0.6–0.8)	7 (6–8)	6.4 (5.9–7.0)	63 (59–69)
Eastern Mediterranean Region	2.3 (1.9–2.4)	15 (13–15)	62.5 (55.6–65.2)	409 (363–426)
European Region	1.5 (1.2–1.5)	14 (11–14)	61.8 (50.3–66)	565 (460–603)
South East Asia Region	0.5 (0.4–0.9)	10 (8–18)	14.8 (12.5–26.9)	287 (243–534)
Western Pacific Region	0.7 (0.6–0.8)	14 (10–15)	6 (5.6–6.6)	111 (104–124)
Total	1 (0.8–1.1)	71 (62–79)	23.7 (21.3–28.7)	1751 (1572–2120)

Source: World Health Organization (WHO), work conducted by the Centre for Disease Analysis, Global Hepatitis Report 2017. (Modified with permission from <https://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/>) [10]

actions, price agreements with originator companies, licensing of generic DAAs, and integration of laboratory testing and drug procurement into existing health systems. [4, 6, 23, 28, 29]

Interventions to interrupt HCV transmission

The most effective intervention to prevent HCV transmission and premature mortality is the availability of all oral DAA regimens [30, 31]. DAAs have proved to be safe and effective in treating key high-risk groups, which acted as reservoirs of infection, and are easier to roll out in community and outreach settings than interferon-based therapies. [32] All oral DAAs options are now available for patients with HBV or HIV coinfection, cirrhosis, ESLD, post-solid organ transplantation, chronic kidney disease, and children [33, 34]. Sustained virological remission has been shown to decrease liver inflammation, fibrosis, and improvement in portal hypertension and progression to ESLD. However, the public health strategy should be to treat all infected individuals, as even those with no significant liver fibrosis have clinical benefits with sustained viral response (SVR), health-related quality of life and work productivity in addition to reducing the prevalence of potentially transmissible and hitherto undiagnosed HCV infection which make the program cost effective. [35]

In the absence of a vaccine for HCV, unsafe injection practices, and IDU, the main modes of current transmission need to be addressed in a public health program.

HCV transmission has reduced from 7 to 14% in the 1980s to 1 in 1,900,000 donations in 2002. As per the mandate of the WHO Blood Transfusion Safety program, about 97% of blood donations are being screened for HBV and HCV infections (available from <http://www.who.int/bloodsafety/en/>). [31] The second approach is the use of safe non reusable injection equipment with better biomedical waste disposal. An example is the adoption of safety engineered or reuse prevention (RUP) syringes that prevent needle-stick injuries and reuse episodes. [36, 37] In PWID, another group at high risk of transmission, Csete et al. estimate that a minimum of 300 sets/PWID/year would be needed for harm reduction and effective termination of transmission of HCV [38].

Adoption of these protocols has resulted in an 88% reduction in proportion of unsafe injections and an 83% reduction in incidence of new HCV infection. [36, 37] The injection safety program includes education of PCPs to follow sterile procedures and stringent biomedical waste management and to inform the public to choose oral drugs rather than injected medications when equivalent options are available. Mathers et al. [39] have indicated that the successful termination of HCV transmission is subject to infection control among PWIDs. Adequate access to needle exchange programs and opioid substitution therapy (OST) reduces the risk of HCV transmission by nearly 74%. [40, 41] The sustained virological response or cure rates for HCV in PWID are comparable with those of the general population.

Table 2. Health programs in different countries to eliminate HCV

Public health program	Estimate prevalence	Year of starting	Numbers screened	Treatment initiated	Drugs used	SVR-12	Cost
Georgia	5% (150,000)	2015	52,856	45,334	SOF/LDV	98.2%	Agreement with Gilead; treatment Given free of charge
Egypt	10–14.7%	2006	800,000		SOF/peg-IFN- α 1a-2a/RBV or SOF/ ribavirin (RBV)	78.7–98%	US \$ 7.50 for a 28 day
India (state of Punjab)	3.6%	2016	55,000	48,088	Current: DCV, D/O/P/r, SMV, SOF, SOF/DCV and SOF/LDV SOF/DCV or SOF/LDV \pm Ribavirin	91.60%	US \$ 25–40 for a 28 day
India (National Viral Hepatitis C Program)	0.9% and 1.9%	2018	–	Enrolment started	Noncirrhotic- SOF/DCV compensated cirrhotic-SOF/VEL decompensated cirrhotics-SOF/VEL \pm Ribavirin	–	–
Iceland	0.30%	2015			SOF, DCV, SMV and LDV		
Australia	0.9%(range 0.7%–1.0%) or 227,000 people (range 167,620–249,710)	2016	69,000		SOF, DCV, LDV, SMV D/O/P/r: dasabuvir +ombitasvir / paritaprevir /ritonavir		Pharmaceutical benefits scheme; AUS \$ 1 billion
Mongolia	6.80%	2015	72,000	7000			US \$ 35–300
Argentina	1.5–2% (estimated 342,000)	2012	1200		SOF based		
Brazil	2.5% and 4.9%	2015	48,500		SOF based		US\$ 686–1399
China	1–3.2% or 14–40 million	2015	200,000		SOF, DCV, LDV		US\$ 1300 for 28 days
Romania	3.2–4.5%	2015	27,600		SOF, DCV, LDV		
Ukraine	2.50%	2015	4500		SOF, DCV, LDV		US\$ 680 for 28 days
Rwanda	3.1–4.1%	2015	1300		SOF, DCV, LDV		US\$ 280 for 28 days
Morocco	0.8%(0.5–1.2)	2016	10,000		SOF, DCV, LDV		
Pakistan*	2.5–5.4%	2016	226,000		SOF, DCV, LDV		
France*	1.1% and 500,000 to 600,000 infected, an estimated 80% are viraemic	2015		onwards		Between 80,000 and 90,000	SOF, DCV, LDV, SMV D/O/P/r: dasabuvir +
Spain*	1.10%				ombitasvir/paritaprevir/ritonavir		
UK*	0.08 to 0.72%; estimated 214,000				SOF, SOF/DCV and SOF/LDV		US \$ 8000 and US \$14,000
Switzerland*	(1–1.3%) estimated between 50,000 and 80,000				SOF, DCV, LDV, SMV D/O/P/r: dasabuvir + ombitasvir/paritaprevir/ritonavir SOF/DCV, SOF/LDV or SOF/VEL		US\$ 10,500 to US\$ 17,000 for a 28 day

Table 2. (Continued)

Public health program	Estimate prevalence	Year of starting	Numbers screened	Treatment initiated	Drugs used	SVR-12	Cost
USA	(1%) 2.4–3.5 million				SOF, DCV, LDV, SMV D/O/P/r: dasabuvir + ombitasvir/paritaprevir/ritonavir		

The data and other information presented in these tables are based on responses to the 23-country WHO survey and interviews, all conducted in mid-2017
DAA, direct-acting antiviral; *DCV*, daclatasvir; *D/O/P/r*, dasabuvir + ombitasvir/paritaprevir; *HCV*, hepatitis C virus; *LDV*
 *Private health care and insurance data

Importantly, active drug use should not preclude treatment in the public health setting as the risk of reinfection is minimal (0.0–6.4/100 person-years) as compared with the benefits of interrupting transmission of HCV. [38, 40] Models indicate that combining DAA treatment, OST, and syringe exchange programs combat HCV transmission better than either strategy alone. [42]

Expand testing and access to DAAs to eliminate HCV

Global estimates indicate that of the 71 million persons infected with HCV, 14 million (20%) have been diagnosed, and only 7% of whom have received treatment. To improve this cascade of care in HCV, active screening of high-risk groups like PWID, HIV infection, incarcerated individuals, and populations with more than 5% seroprevalence of HBV and HCV. [43]

Expanding access to public health programs involves assessment of the disease burden and existing infrastructure, logistics of procurement, funding, licensing agreements, formulation of decentralized targeted interventions, civil society, and political support, identifying social and industry partners and a sustainable model. Appropriate data monitoring, audit, and operational research are key to a program’s success. Innovative models that incorporate HCV prevention and treatment services within existing health systems ensure cost-saving delivery of services. In addition, public–private partnerships facilitate pooling of resources and culturally appropriate locally available health services in an existing healthcare system. [44]

Experience from global HCV elimination programs

Several countries have already initiated national programs, even before the WHO Global Hepatitis C strategy was elaborated and demonstrated how global HCV elimination is feasible and successful.

Georgia

Georgia has initiated a national HCV elimination plan in 2015 through a public–private partnership with Gilead Sciences Inc. and the Center for Disease Control and Prevention. Free of charge DAA therapy (sofosbuvir and ledipasvir) was provided through a partnership with Gilead Sciences Inc. By 31st March 2018, a total of 52,856 HCV-infected persons were diagnosed, 45,334 started treatment, 29,620 had SVR-12 done with 29,090 (98.2%) having achieved SVR-12 per protocol. Other program activities include adoption of improved blood banking and safe injection usage across all healthcare settings in the country. [17, 20]

Egypt

In Egypt, the prevalence of CHC is 10–14% with healthcare costs consuming 4% of the state's total health budget. [13] The aim of the Egyptian HCV elimination program, started in 2006, was a reduction in HCV prevalence to <2 % within 10 years and later to <1% by 2030, in accordance with the WHO strategy. [21] In pursuance of these goals, the Egyptian HCV elimination program has treated a cumulative total of 1.5 million people. The initial all oral regimen, with sofosbuvir (SOF) and ribavirin (RBV) (group 1), for 6 months had the lowest SVR-12 of 87.7%. Other drug combinations were associated with SVR-12 rates between 94 and 98%. Under this program, triple therapy (group 2) with SOF/peg-IFN- α -2a/RBV for 3 months was prescribed in genotype 4 CHC patients. SVR-12 was 94% and in group 2 the SVR-12 was 78.7% [22] In order to meet the 2030 elimination goal, the Egyptian program needs to diagnose and treat 350,000 persons annually [23].

India

While anti-HCV prevalence in India ranges between 0.9 and 1.9%, it has been reported to be as high as 3.6% in north Indian state of Punjab. [11, 24] In the state of Punjab, 48,088 patients (63.8% male; mean age 42.1 years; 80.5% rural; 14.8% cirrhotic; 69.9% genotype 3) were enrolled between 18 June 2016, and 31 July 2018. While 38,748 (80.6%) patients completed treatment, 5497 (11.4%) had treatment interruptions and 3843 (8.0%) patients are currently ongoing treatment. SVR-12 was achieved in 91.6% of patients who completed treatment and returned for SVR testing as per protocol and in 84.4% of patients who had treatment interruptions [12]. Now, the Punjab Model is being replicated countrywide with the establishment of the National Viral Hepatitis Control Program (NVHCP) with the establishment of model treatment centers countrywide and training of primary care providers to deliver no cost specialized care at a local center. [45]

Brazil

An estimated 700,000 people in Brazil are living with hepatitis C. In 2017, the Brazilian Ministry of Health has ensured that 50,000 patients were treated by 2017. [46] Though a licensing agreement is not available, Brazil was able to secure a 90% price discount from the US list price for sofosbuvir– daclatasvir by mass public health procurement. Another strategy was to create consortia

involving private pharmaceutical companies and public laboratories, called productive development partnerships which ensured delivery of services. [47]

Iceland

The Icelandic HCV elimination program must tackle the estimated 880–1300 persons (0.3% prevalence) who are living with HCV. The predominant mode of transmission is IDU. The Iceland HCV elimination plan was initiated in 2015, with a goal for 80% reduction in HCV incidence in 2025. In the allied syringe exchange program, PWID receives 430 sets of sterile injection equipment annually to interrupt disease transmission. [18]

Australia

The Australian government started their HCV elimination program with a corpus of AUS\$1 billion (US \$766 million) using a unique “subscription” model of service delivery. In 2015, the government negotiated an agreement to spend the corpus sum over a period of 5 years for an unlimited volume of DAAs for HCV from suppliers. This unique scheme of reimbursement enables testing for HCV, referral, and DAAs-based treatment between 2016 and 2022. [12, 13] As per WHO estimates, about 69,000 persons (26% prevalence) were treated in 2016–2017 alone, and the Australian HCV Elimination program is the most likely to meet targets to eliminate HCV by 2030. [23, 48]

Mongolia

In Mongolia, CHC prevalence is estimated to be 6.8% with a high rate of HCC-related morbidity and mortality. The project approach in Mongolia involved priority care of cirrhotics and ESLD, in addition to universal treatment of all HCV-infected patients. This staged targeted strategy, envisages mortality reduction due to HCV and an elimination goal in the country.. Under the Mongolian program, 72,000 persons were screened for hepatitis B, C infections and over 7000 people with chronic HCV underwent treatment using a combination of SOF/ledipasvir by November 2016. [49]

Extension for community healthcare outcomes programs

Several other projects have utilized a model called project ECHO that enables primary care providers (PCPs) to deliver specialized care for complex conditions like chronic HCV. Arora et al. first implemented the University of New Mexico's ECHO operation for CHC using Peginterferon + RBV, which

showed SVR rates and improved survival, and healthcare cost. [32] Project ECHO Ireland HCV pilot [50] and Show Me ECHO in Missouri [51] emulated this approach and mirror the success of these decentralized programs. The ECHO approach connects disease specialists (hub) with PCPs at peripheral centers (spokes) across the state ensuring decentralized HCV screening and treatment. [52] The process is known as “telementoring” and ensures better adherence, low cost, and effective use of existing health delivery infrastructure. The use of pan-genotypic regimens with cost-effective and quality-assured generic drugs is the backbone of the elimination programs for HCV [53].

Approach for HCV testing, care, and treatment linkage

Operational research and data collection are integral to the success of HCV elimination programs. Developing new vaccines and rapid diagnostics for screening and confirmation of HCV in a low-cost setting is of interest. Timely correction of shortcomings of current day screening and treatment strategies in the program audit leads to better health outcomes. [54, 55] The ability to target niche groups like injection drug users is essential. [56] Surveillance data provides operational information on treatment, prevention, vaccination, and to reach elimination goals and to guide financial resource allocation for HCV treatment in a primary care setting. [57, 58] Use of HCV Core antigen testing as a cheaper alternative to RNA sequencing is of use. Next-generation sequencing can identify HCV case clusters with similar viral quasi-species with a common source of transmission and identify resistance-associated substitutions. [59]

Mathematical models suggest cost-effectiveness of HCV screening seems most sensitive to disease

prevalence, treatment efficacy, and linkage to DAA treatment, in a defined population and less affected by costs of screening and treatment in the public health setting. [52–54] Another barrier to HCV elimination is the cost involved in HCV genotype testing and makes the use of pan-genotypic regimens an attractive cost-effective option in a public health program. Simplifying testing algorithms and lowering the cost of monitoring can dramatically cut costs of treatment for HCV in the future. [53, 60] Future research can guide innovative strategies for averting perinatal HCV transmission in pregnant women. [61] Utilization of shorter treatment regimens to reduce costs is of interest. [6, 62, 63] Lastly, a global alliance by creation of a Task Force in the World Health Assembly will meet the goals for elimination of HCV infection by 2030 [6, 63].

Future directions and conclusions

Elimination of CHC by 2030 will be cost effective and cost saving and will prevent more than 7 million HCV-related deaths making it vital for public health outcomes. Blood safety programs, screening of HCV, and mass free-of-cost treatment with generic drugs and injection safety protocols are the keystone of HCV elimination strategies resulting in reduced HCV incidence, morbidity, and mortality. Programs that target interrupting new HCV transmission in PWID by providing safe injection equipment and early treatment, improve blood safety, and prevent unsafe medical procedures medical practices, in combination with education, screening, and linkages to DAA treatment are likely to be successful. Initiatives which require involvement of concerned stakeholders including civil society, industry, and state institutions will result in better outcomes.

Compliance with ethical standards

Conflict of interest

Radha K. Dhiman declares that he has no conflict of interest. Gagandeep S. Grover declares that he has no conflict of interest. Madhumita Premkumar declares that she has no conflict of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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