INTRODUCTION

Disease elimination and eradication, the ultimate goals of disease control, can achieve large health benefits and ensure global health equity. HCV meets the benchmarks of a major public health problem whose elimination is feasible [1–3]. In 2016, the World Health Organization released the Global Health Sector Strategy on Viral Hepatitis 2016–2021: Towards Ending Viral Hepatitis, which set goals to be achieved by 2030 that would indicate progress toward the elimination of hepatitis C virus (HCV) as a public health threat. The goals are 90% reduction in global incidence and 65% reduction in global mortality by 2030 [4]. If those goals were met, then estimated global HCV incidence would decrease from 1.75 million per year in 2015 to 175 000 per year in 2030; and global mortality would decrease from approximately 400 000 deaths with HCV as the underlying cause in 2015 to 140 000 per 100 000 population in 2030 [5]. In 2015, the World Health Organization (WHO) estimated that 71 million people were infected with HCV globally. In 2016, the World Health Assembly (WHA) passed a resolution of endorsement supporting the WHO goals and adding HCV to the select group of diseases targeted for global elimination [6].

Biologically, HCV is a virus that is easily transmitted via parenteral exposures to contaminated blood with low infectivity through other routes. Global initiatives have greatly reduced transmission in healthcare settings, increasing the proportion of cases attributable to injection drug use. The latency from HCV infection to onset of severe disease is several decades, providing ample time for early diagnosis and treatment to prevent premature mortality. Tests for anti-HCV and HCV RNA reliably detect HCV infection. New all-oral therapies for HCV, a major advance in medicine, cure over 90% of people who complete treatment [7]. The HCV elimination goals provide the impetus for countries to put in place their own comprehensive HCV prevention programs. The development of such programs is just beginning, and the knowledge and experience gained from past elimination efforts (e.g. smallpox and polio) can be employed to successfully eliminate HCV. In this chapter, we will review the health burden of HCV infection, the process for development of HCV elimination goals, the successes and challenges in the implementation of interventions to reach these goals, field studies illustrating the essential components of effective elimination programs, and the key research that will accelerate progress toward elimination of HCV infection.

THE PUBLIC HEALTH PROBLEM OF HCV INFECTION

Diseases must be of sufficient magnitude to warrant the prioritization of resources for a dedicated elimination program. HCV is a substantial public health problem globally: in 2015, an estimated 71 million people (1% of the global population) were infected with HCV [5]. HCV is present in almost all countries. However, HCV varies greatly at the national level, reflecting differences in risk exposures and the importance of reliable data to reveal local patterns of transmission and burden of disease.

First, based on genetic differences, HCV is classified into seven genotypes which differ in frequency by country [7]. Certain countries have high prevalence of HCV infection, including Mongolia (6.7%), Egypt (6.4%), Pakistan (3.8%),
Russia (2.9%), and Romania (2.5%) [8]. Prevalence can also vary at the sub-national level. For example, in Egypt, a country of high prevalence, the prevalence is higher in Lower Egypt (8.2%) compared with Upper Egypt (2.2%) [9–11]. In the United States, the estimated 1.67% anti-HCV prevalence in 2010 varied by state, ranging from a high of 3.34% (Oklahoma) to a low of 0.71% (Illinois) [12].

Globally, the population with highest prevalence of HCV infection is persons who inject drugs (PWIDs). In 2017, of an estimated 15.6 million people with a history of drug injection, 8.1 million (52%) have been infected with HCV [13, 14]; 58% of PWIDs with HCV have a history of incarceration. As a result, in 2012, an estimated 2.2 million incarcerated persons (26%) have been infected with HCV [15]. In the United States, an estimated 1.5 million people who are currently injecting drugs or did so in the past are infected with HCV [14].

In 2010, an estimated 3.5 million people were infected with HCV in the United States [16]. HCV is a leading cause of mortality from infectious disease in the United States [17]. Deaths from HCV surpassed the number of deaths from HIV in 2007 and in 2014, deaths from HCV exceeded the number of deaths from the 60 other reportable infectious diseases in the United States [17, 18]. In 2016, a total of 18, 153 deaths (4.5 deaths/100 000 population) were associated with HCV infection [19].

In 2015, a total of 1.7 million new HCV infections occurred globally, with 40% attributed to unsafe injection in healthcare settings and about one-third attributable to current injection-drug use [5]. Exposures in healthcare settings include receipt of unscreened blood and blood products from HCV-infected donors and procedures with nonsterile injection equipment [5, 7]. The proportion of HCV attributable to healthcare and injection drug use varies globally. Receipt of unscreened blood and poor infection control are the major modes of transmission in low and middle income countries. PWIDs account for most new infections in high and some middle income countries.

Other routes of HCV transmission are less common. Children born to HCV-infected mothers have a 6–14% risk of HCV infection [20, 21]. Other incidental perinatal contacts with blood, intranasal inhalation of drugs, unregulated tattooing, and ritual scarification are associated with the spread of HCV [7]. Sexual transmission of HCV is rare except among certain populations of HIV-infected men who have sex with men (MSM) [22]. Prevention is important in these populations. However, achieving HCV elimination goals hinges on preventing the most common routes of transmission from unscreened blood and blood products and nonsterile injections in healthcare and community settings.

THE PROCESS FOR SETTING HCV ELIMINATION GOALS

The development of the WHO strategy for HCV elimination followed a series of policies and actions globally. As new data revealed mounting mortality from HCV infection, there were progressively urgent calls for improvements in HCV prevention, care, and treatment. The licensure and demonstrated effectiveness of antiviral therapy in curing HCV infection added to the international call for action to apply this new prevention tool to more effectively prevent HCV transmission and disease. From 2000 through 2010, HCV-related mortality increased 10% globally, whereas mortality from other infectious diseases, including HIV, malaria, and TB, declined during this time period [23]. In 2010, 2014, and 2016, the WHA passed three resolutions recognizing HCV and other forms of viral hepatitis as global public health problems [2, 24, 25]. In 2010, the WHA called on WHO and member states to take greater action to improve viral hepatitis prevention diagnosis and treatment. In 2011, the first-generation oral antiviral therapies that required continued use of interferon-based therapies for HCV infection were licensed in the United States by the US Food and Drug Administration (FDA). In 2012, WHO released the first action plan to prevent viral hepatitis and began to assist countries with local prevention planning [26]. At the time, only 37% of 126 member countries had national plans for viral hepatitis prevention [27].

In 2014, the WHA called for continued improvements in HCV prevention and emphasized the importance of prevention measures to protect PWIDs [24]. Importantly, the WHA requested WHO examine the feasibility of setting goals for elimination of HBV and HCV infection. In 2014, the first all-oral therapies for HCV infection were licensed in the United States by the FDA.

To respond to the WHA request, WHO convened numerous stakeholder consultations with member states, organizations in the United Nations system, and other multilateral agencies, donor and development agencies, civil society, nongovernmental organizations, scientific and technical institutions and networks, and the private sector. WHO also commissioned models to estimate the impact of various prevention strategies on transmission and burden of disease. While this process was underway in 2015, the United Nations, in the Sustainable Development Goals, called for a global response to combat viral hepatitis [28].

In 2016, WHO released the WHO Global Health Sector Strategy on Viral Hepatitis 2016–2021: Towards Ending Viral Hepatitis [4]. In the global strategy, WHO set global targets for the elimination of HCV as a public health threat, defined as a 90% reduction in the incidence of HCV infection and a 65% reduction in HCV-related mortality by 2030. A discussion regarding setting and communicating elimination goals follows below. Countries are encouraged to set more ambitious national goals based on the local assessment of burden of disease, the populations affected, the capacity of clinical care and public health systems, and the resources available for mobilization. The 2016 WHA resolution endorsed the strategy and elimination goals. WHO has set performance targets for 2020 and 2030 for the key prevention interventions, including HCV diagnosis and treatment (Figure 70.1).

In parallel with global actions, steps were taken in the United States to strengthen the policy foundation for HCV prevention. In 2010, the US Institute of Medicine (IOM) reported findings from an expert panel that the national prevention capacity for HCV and other forms of viral hepatitis was inadequate and recommended improvements in viral hepatitis surveillance and prevention services [29]. The IOM called for the US government to draft a national action plan. In May 2011, the national action plan for viral hepatitis prevention was released by Assistant Secretary of Health Dr. Howard Koh [30]. The national action plan was updated in 2014 and 2017.
In 2017, the National Academy of Sciences, formerly the IOM, released two reports recommending the global HCV elimination goals be adopted as national goals for the United States. The National Academies proposed a set of actions to build the prevention and clinical capacity to achieve these goals [31].

**SETTING A GOAL FOR ELIMINATION OF HCV AS A PUBLIC HEALTH THREAT**

The terms “eradication” and “elimination” are sometimes used interchangeably, as both convey information about the intended scope of disease control. The concept of disease eradication originated with Edward Jenner, who developed the first smallpox vaccine. Jenner wrote in 1801 “It now becomes too manifest to admit of controversy, that the annihilation of the Small Pox, the most dreadful scourge of the human species, must be the final result of this practice” [32]. However, organized efforts to eradicate diseases from humans did not begin until the early and mid-twentieth century. Yellow fever (1915–1977), yaws (1954–1967), malaria (1955–1969), and smallpox (1955–1980) were the first diseases targeted for eradication [32]. Of these, only smallpox has been eradicated as certified by the WHA in 1981 [33–35]. The successful campaign to eradicate smallpox sparked interest in targeting other diseases for eradication, including dracunculiasis (i.e. guinea worm) in 1986 and polio in 1988; both of these efforts are ongoing [1, 36].

The terms eradication and elimination both convey information about the intended scope of disease control. Decades of academic discussion including conferences in Berlin (1997), Atlanta (1998), and Frankfurt (2010) [4, 36] resulted in general acceptance of standard definitions for disease eradication and
elimination. Eradication is the permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts. Elimination of transmission (also referred to as interruption of transmission) is the mean reduction to zero of the incidence of infection caused by a specific pathogen in a defined geographical area, with minimal risk of reintroduction, as a result of deliberate efforts. Continued actions to prevent re-establishment of transmission may be required [37]. De Serres et al. have pointed out that zero incidence is essentially unattainable in the absence of eradication because of the continued risk of importation with limited subsequent spread [38].

In practice, the term elimination has been used to describe different targets – specific levels of control (e.g. reduction of neonatal tetanus deaths to <1/100 000 live births in all districts or reducing incidence of tuberculosis to <1/million population), or interruption of neonatal tetanus transmission as manifested by no chains of transmission lasting >1 year [39–43].

There remain considerable differences in perspectives in the use of the term disease elimination. For example, the international collaboration to eradicate measles prefers to use the term elimination for national and regional achievements and preserve the term eradication for the global goal [2, 43, 44]. Similarly, the global strategic framework to eliminate malaria sets national and regional goals for cessation of transmission to achieve a global goal of a 90% reduction in incidence of malaria by 2030 [45]. For the END-TB campaign, the elimination goal is reducing incidence to less than 1 per million populations by 2035 [40–42].

In 1997, WHO introduced the concept of “elimination as a public health problem” as defined by achievement of measurable global targets set by WHO in relation to a specific disease. When reached, continued actions are required to maintain the targets and/or to advance the interruption of transmission. This concept of disease elimination is controversial and not as well accepted as zero goals [36, 46]. First, there is an absence of a standard definition to designate a disease as a “public health problem.” Second, the targeted improvements in transmission or morbidity/mortality required to designate a disease as no longer a “public health threat” can be perceived as arbitrary. The definition may vary depending on circumstances, resources, etc. For some conditions (e.g. lymphatic filariasis,) there is no specification of the level representing elimination; consequently, it may not be possible to know when elimination has been achieved [44].

Resolution WHA69.22 of the 2016 WHA adopted the “global health strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections, for the period 2016–2021” [4]. These strategies included a call for elimination of hepatitis B and C as a major public health threat by 2030. Specific targets set were 90% reduction (compared to 2015 levels) in new infections and 65% reduction in deaths. Interim targets for 2020 were 30% reduction in infections and 10% reduction in deaths. Despite the imprecision of WHO’s general definition of HCV elimination as a public health threat, the hepatitis targets, as stated, serve several purposes. First, the elimination targets convey a sense of urgency, increasing awareness of the opportunities for improving health through improved HCV prevention and cure and helping to engage partners and build capacity to support delivery of prevention and clinical services. Second, numerical goals can be used to drive program planning, prioritize resources, and monitor program performance. Lastly, in contrast to elimination programs for other infectious disease agents that cause most morbidity at the time of infection, WHO’s definition appropriately encompasses both HCV transmission and later disease as targets for elimination. The interventions to prevent HCV transmission (e.g. clean injections, safe blood supply) differ in large degree from the interventions necessary to eliminate the risk of mortality for those with chronic HCV infection (testing and treatment).

In summary, WHO has set feasible targets for reductions in HCV transmission and disease in the framework of the elimination of HCV as a public health threat. The WHA and the International Task Force for Disease Eradication, two authoritative bodies, have endorsed HCV joining the select group of diseases targeted for global elimination. However, the global elimination goals are not necessarily final. HBV and HCV elimination goals can be revised as program experience is accrued and operational research is conducted. WHO encourages national and local programs to develop numerical goals appropriate for their epidemiologic circumstances and health system capacity. This flexibility fosters the accumulation of a wide body of experience from programs with ambitious goals for HCV elimination providing the evidence needed to revise global goals. As progress is made, more stringent targets may be defined, potentially ultimately leading to an eradication goal.

**DETERMINANTS FOR SETTING FEASIBLE TARGETS FOR HCV ELIMINATION**

Knowledge has been gleaned from other disease eradication and elimination programs, revealing the essential criteria to target a disease for elimination [1, 2, 5, 33–36] (Table 70.1).

HCV infection meets three biologic features for disease elimination. First, humans are essential in the life cycle of the agent: HCV does not propagate in the environment, and intermediate hosts are not involved in the replicative cycle of HCV.

Second, tests of high sensitivity and specificity are widely available to detect and diagnose HCV infection. Practical diagnostic tests are available to reliably detect past or current HCV infection. Laboratory assays can detect antibodies to HCV cellular proteins within two weeks of HCV infection with a sensitivity and specificity of 97% and 99%, respectively [47–49]. HCV antibody testing is also available as a point-of-care assay with equivalent performance as laboratory-based testing. Of HCV-infected persons, 25–30% will clear infection spontaneously; people cured of their infection continue to have HCV antibody detectable on serologic tests [7, 50]. Following a positive test for HCV antibody, a second virologic test, typically for HCV RNA, is necessary to diagnose current infection [51]. HCV RNA tests detect evidence of infection before antibody testing and the use of both tests improves detection of HCV in blood donations and safety of the blood supply [52–54]. HCV RNA testing is required for monitoring response to therapy, and document virologic cure after completion of treatment. Point-of-care assays are...
Third, effective interventions are available that can stop transmission and prevent morbidity and mortality. HCV is a bloodborne virus with constrained modes of transmission. HCV does not penetrate intact skin, and there is no evidence of vectorborne or airborne transmission. As a result, an HCV-infected person is estimated to transmit only two new infections over the course of their infection. This reproduction number (R0) of 1.2–2.9 for HCV is much less than the reproduction number for smallpox (4.5), a disease successfully eradicated, or for polio (6.0) and measles (14.5), diseases successfully eliminated in several regions of the world [60–62].

The final biologic characteristic that makes possible the achievement of HCV elimination goals is the long latency period from HCV infection to development of severe disease, which provides ample time for diagnosis and treatment to prevent premature mortality [7, 63–73]. Acute HCV infection rarely causes clinically significant disease [65]. Most HCV-related morbidity and mortality is caused by chronic HCV infection, which can be clinically silent for decades before causing cirrhosis, hepatocellular carcinoma (HCC), and other extrahepatic manifestations (e.g. non-Hodgkin’s lymphoma, cryoglobulinemia, and renal disease) [7].

### Technical feasibility

In the absence of a hepatitis C vaccine, multiple interventions are effective in interrupting parenteral transmission of HCV in the blood bank setting and related to unsafe injections in the healthcare and community setting. The WHO has set performance indicators to monitor the implementation of key interventions to eliminate HCV (Figure 70.2).

#### Donations screened with high-quality tests

Once a common mode of transmission, the strategies of routinely screening donors for HCV-associated risks factors, HCV testing of donated blood, and removal of HCV-contaminated blood donations from the blood supply, virtually eliminates transfusion-associated HCV. In 1992, the United States and other countries began implementing these interventions [52–54, 74–83]; new generations of tests improve sensitivity and specificity. Over time, the risk of HCV infection among recipients of blood products fell from 7% to 10% (during the 1980s) to 1 per 1 000 000 donations in 2010 [67–71, 74–83]. HCV antibody testing of donated blood is highly cost effective or cost saving [84]. The cost effectiveness of the addition of HCV RNA testing varies according to the prevalence and incidence of HCV in the donor population [84, 85].

Because of financial issues and the lack of laboratory infrastructure, HCV testing in blood banks was not immediately adopted by all countries. Progressively, through the WHO Blood Transfusion Safety Program (http://www.who.int/bloodsafety/en/), PEPFAR support for blood safety (https://www.pepfar.gov/documents/organization/83108.pdf), and regional efforts (e.g. the Strengthening Laboratory Management Toward Accreditation program in Africa) (https://slmta.org/), an increasing number of countries have adopted routine HCV testing of blood donations. By 2016, 174 of 175 countries responding to a WHO survey reported having a policy in place for screening
donated blood for HCV [86]. Overall, 89% of donations are screened following procedures to assure quality of testing. However, the expansion of HCV antibody and RNA testing can reduce transmission to as low as 0.5 transmissions per million transfusions [83]. This testing is currently available in only a quarter of the countries reporting routine HCV testing of the blood supply. Efforts to optimize blood bank screening are particularly important for low-income countries, where 1 in 100 blood donors have evidence of HCV infection [86].

**Reducing the proportion of unsafe injections**

The major risks for HCV transmission include reuse of injection devices and contamination of multidose vials [6, 87–92]. The implementation of universal precautions for infection control result in substantial declines in the prevalence of HCV among patients and healthcare workers [90, 91]. The steps toward universal precautions include setting up infection control programs with staff, monitoring and responding to lapses in infection control, educating clinicians in infection control, assuring reliable supplies of safe injection equipment, and using injection equipment that makes reuse impossible or extremely difficult [90–92]. Universal precautions to prevent HCV is cost saving [91].

In 2000, an estimated 2,000,000 (40%) of new HCV infections globally were attributed to exposures to unsafe injections [93]. Since that time, initiatives like WHO’s Safe Infection Global Network have guided ministries of health and other stakeholders to improve infection control. As a result of these initiatives, exposures to unsafe injections declined 88% from 2000 through 2010, contributing to an 83% decline in the number of HCV infections attributed to unsafe injections [94]. In several regions of the world, 5% or less of injections involve reused syringes and needles [5, 94].

In summary, the proportion of injections administered with nonsterile equipment has dramatically declined. Reducing this number even further requires enhanced community-based efforts to educate patients about the availability of oral medications that are equally as effective as those administered via injection. A substantial number of patients in some parts of the world strongly prefer and receive injectable medications despite availability of oral equivalents, unnecessarily increasing HCV risk exposures [9, 95]. This is particularly problematic in Egypt, where the prevalence of HCV infection among patients is high and health facilities lack adequate infection control procedures [9].

**Improving access to sterile syringes and needles for persons who inject drugs**

HCV transmission among PWIDs is preventable with implementation of a combination of interventions, such as opioid substitution therapy (OST), syringe service programs (SSPs), and HCV testing linked to therapy [96–101]. Based on a review of published studies, adequate access to OST and SSP reduces transmission risk by 50% and 23%, respectively, and together by 71% [97, 98]. Syringe services are highly cost effective or cost saving [98, 102, 103].

Although SSPs and OST reduce HCV incidence among PWIDs, only antiviral therapy can lower HCV prevalence and risk for HCV-related morbidity. Health models suggest that increasing the numbers of PWIDs tested, diagnosed, and cured of their HCV infection can lower prevalence and force of infection, leading to >90% declines in incidence [100, 101]. Because of reductions in both HCV transmission and disease, treatment of PWIDs for HCV is highly cost effective or cost saving [102, 103].

Globally, in 2010, an estimated 27 sets of syringes and needles were exchanged per user, per year, a rate far below the WHO targets of 200 and 300 of such exchanges for the years 2020 and 2030, respectively [13, 104, 105]. A study of PWIDs in North America, Australia, and the Netherlands from 1985 through 2011 found an overall incidence rate of 22.6 per 100 person-years of observation (PYO), with declines in incidence among PWIDs observed over this period from 24.6/100 PYO to 18.8/100 PYO [97, 106]. The greatest declines in HCV incidence were observed in Australia and the Netherlands, two countries that began in the 1980s to expand access to SSPs and OST. In contrast, HCV risk behaviors and incidence among PWID are high in North America, where access to SSPs and OST is limited. From 2010 through 2016, HCV incidence in the United States has increased threefold, temporally associated with increases in the injection of prescription opioids and heroin [19]. Increases in HCV incidence are greatest in states with no or few SSPs [107].

The recent rise in HCV transmission in the United States might cause some to question the feasibility of reducing HCV incidence by 90% from 2015 to 2030. This questioning is a desired outcome of the disease elimination process [1, 2, 33–35]. The sense of urgency created by setting limited elimination goal leads to an examination of prevention capacity. Indeed the recent rise in HCV transmission in the United States adds to the challenges of reaching elimination targets. However, the new infections are not the result of changes in the virus or new modes of HCV transmission that increase spread of HCV. The new infections in the United States are among PWIDs [19]. Evidence from other countries demonstrate that strong prevention programs sustained over time result in low HCV incidence among this risk population [106]; the availability of curative HCV therapies is the new intervention that can further decrease transmission. The incidence trends in the United States are the result of a poor HCV prevention infrastructure for this population. With sufficient improvements in prevention capacity, which are totally feasible for a high-income country such as the United States, HCV incidence will decline among PWIDs and elimination goals can be achieved.

**Increasing the proportion of infected persons diagnosed with HCV**

HCV testing is the essential step in a plan to reduce the prevalence of HCV and subsequent mortality. However, few silent HCV carriers have been diagnosed with HCV, and even fewer have received treatment. WHO estimates that in 2015, a total of 71 million people were infected with HCV globally [6, 8, 104], of whom only 14 million (20%) have been diagnosed [104]. Reaching the HCV elimination goals will require diagnosing 90% of HCV-infected persons [1].

The first step on the care continuum, HCV testing, must be scaled up to potentiate increased access to treatment.
plans guided by local epidemiologic data must include policies prioritizing testing for populations at greatest risk (e.g. persons receiving unscreened blood donations and PWID) [5, 6]. The Centers for Disease Control (CDC), the United State Preventive Services Task Force (USPSTF), professional societies, and WHO recommend routine HCV testing of certain populations based on risk exposures, settings, and demographic characteristics indicative of increased prevalence of HCV infection [108–111]. HCV testing and treatment of PWIDs is highly cost effective or cost saving in low, middle, and high-income countries [99, 112–117]. Similar returns on investment are seen for HCV testing and treatment of particular demographic subpopulations, including age and birth cohorts, PWIDs, and the incarcerated.

In most countries, targeting multiple populations for HCV testing is needed to fully capture the universe of persons at risk for HCV infection. Testing of individuals for HCV based on risk behaviors (e.g. recipients of unscreened blood, injection drug use) is a core strategy; HCV testing of incarcerated populations augments risk-based testing. However, many people with exposures in the distant past do not recall drug-use risk behaviors, or are unaware of risks in healthcare settings or of perinatal transmission [115, 118, 119].

High incidence of HCV in earlier decades has resulted in a cohort of chronically infected individuals who are becoming increasingly ill as their infection progresses, manifesting as chronic liver disease. Cohorts of older adults who have been infected for decades are at highest risk for severe liver disease. In the United States, 81% of the 3.5 million people living with HCV in 2010 were born during 1945–1965; of these, one in four has clinical evidence of severe fibrosis or cirrhosis [118–120]. In other countries, different birth cohorts are disproportionately affected by HCV based on different epidemiologic characteristics and different policies for controlling risk (e.g. initiation of HCV screening in blood banks) [116, 121, 122]. In the United States, the CDC and the USPSTF recommend a one-time test for HCV for people born during 1945–1965 [109, 110]. Accordingly, a birth cohort strategy is one population-based approach that is cost effective while making HCV testing broadly available [123]. Other strategies include testing all people in a particular setting, such as correctional facilities, emergency departments, and all people receiving inpatient services. Testing all adults for HCV can also be cost effective and readily implemented [124, 125]. In 2018, WHO recommended routine HCV testing in settings with a ≥2% or ≥5% of HCV antibody seroprevalence in the general population [126].

The release of a policy to guide HCV testing increases the magnitude of HCV testing [123]. Evidence supports the use of certain strategies to implement policies and increase access to HCV testing for target populations. Reflex testing whereby specimens positive for HCV antibody are immediately tested for HCV RNA improves diagnosis of current HCV infection [127]. The ordering of HCV tests by clinicians is improved by professional education, and electronic reminders that prompt testing. The return of evaluation data can also motivate improvements in clinicians’ testing practices [128–131]. State-based mandates for HCV testing by clinicians also can be evaluated as a means to increase testing [132].
0.4% decline [148]. The estimated 2.1 million new HCV infections annually in this analysis was also a factor in the small declines in HCV prevalence.

In the United States, 22–30% of HCV-infected participants in national health surveys conducted in 2007–2014 reported receiving medications for HCV [149]. This number of HCV treatments will undoubtedly contribute to declines in the national prevalence of HCV infection. The 7% decline in HCV-related mortality observed in 2016 reflects deaths averted among people cured of HCV infection [19]. This level of treatment suggests the United States is on track to achieve the elimination goals for HCV infection. For the United States to reach the national goals for HCV elimination, approximately 250,000 people need to be treated each year [32]. However, to successfully number this number of infected people, large-scale HCV testing and treatment programs must be implemented and sustained over time.

As the price of HCV medications fall, the price of HCV testing represents an increasing portion of the total resources needed for HCV elimination. In some countries (e.g., Pakistan and Egypt), the cost of testing is now equal to or slightly greater than the cost of treatment [10, 126, 150]. To improve access to this foundational and essential prevention tool and make progress toward elimination goals, both HCV testing and treatments must be affordable for individual patients and local programs.

ESSENTIAL COMPONENTS OF HCV ELIMINATION PROGRAMS

HCV elimination programs are in various stages of planning and implementation at the national, sub-national, facility, and risk population level. The experience gained from previous disease eradication and elimination initiatives provide lessons learned regarding the essential components of an HCV elimination program (Table 70.2). First, surveillance data are needed to compile an epidemiologic profile of HCV transmission, burden of disease, and mortality. Information regarding existing HCV community-based activities, and clinical and public health services programs informs program planning and engagement of partners. The lack of a public health infrastructure as a foundation for HCV elimination programs is of concern. Countries often lack public health surveillance and other strategic information of sufficient quality to guide selection of health outcome targets, inform program planning, and monitor program implementation. In 2016, only half of countries with national prevention plans had the data needed to estimate HCV prevalence [5].

Second, a plan of action establishes time-limited numerical targets and guides program implementation. The plan prioritizes activities, helps partners understand their roles, and provides a basis for financial planning [10, 11, 151]. Numerical targets increase the accountability of program staff to reach program goals. However, elimination plans are not yet in place for most countries. In 2017, 82 of 132 countries reported that viral hepatitis plans were in place, compared with only 17 in 2012, yet only 35% of these countries reported dedicated funding for such plans [104]. Few have plans that include HCV elimination targets and plans to reach them.

Civil and political support is as important as technical proficiency in delivering HCV prevention, care and treatment services [2, 32, 36, 46]. Political support increases program acceptance by civil society at the national, state, or community level, increasing the likelihood of the participation of target populations in the program. Political support also can assist with financing of elimination program activities, helping to assure sustainability of activities till elimination goals are reached. At the community level, representatives of target populations can build trust through assistance with education and outreach activities.

The capacity to implement elimination program activities can come from governmental and nongovernmental sources. Some nations have begun to support elimination programs. Disease eradication and elimination programs at the national level also can be supported with resources from external organizations and coalitions. Gilead Sciences, has provided substantial resources for development of HCV programs [152–155]. The Global Fund to Fight AIDS, Tuberculosis and Malaria supports elimination activities for these disease [156]. The Rotary International support for polio eradication is essential to the success of that program [157]. The development of similar global coalitions is needed to place global HCV elimination on a sound financial footing.

Capacity to deliver appropriate interventions also can be built through integration within health systems. HCV testing and treatment can be co-localized in settings where people are accustomed to receiving care, improving the care cascade. An additional benefit to integrating HCV elimination activities within existing care systems includes ownership and empowerment of the community and providers; development of “local champions” facilitates adoption of HCV interventions in new settings and sustains these interventions over time. The WHO strategic framework proposes to achieve HCV elimination by aligning HCV prevention activities with related strategies for HIV/AIDS, sexually transmitted diseases, safe injections, and blood safety [4].

When implemented within existing health systems, interventions associated with HCV elimination can benefit other prevention initiatives. For instance, improved blood donor screening for HCV provides the platform to screen for other transfusion-associated infections, improvements in infection control can reduce other nosocomial infections, and the referral and training relationships cultivated between specialists and primary care professionals can be leveraged to improve the quality of care for other diseases. The secondary benefits of HCV elimination can build support for this effort, including cost sharing with other disease programs.
Strategic information is needed to evaluate program activities. The WHO performance indicators and similar data help maintain the focus on program priorities, and identify successes and gaps in service delivery. Importantly, reliable data regarding HCV incidence, prevalence, and mortality are needed to monitor progress toward the elimination goals. Heath modeling based on reliable data can estimate the benefits of program activities to date (e.g. future deaths averted among the number of people cured of HCV infection to date) and estimate the services needed and related costs to achieve the elimination goals.

Lastly, it is important for elimination programs to participate in operational research. The prevention, care, and treatment needs of target populations change over time. Also new issues arise as trends in HCV transmission and prevalence change. Advances in technology can improve the feasibility of elimination. Programs must remain dynamic, adaptable, and open to change.

As a component of operational research, model programs have a role in field testing program operations, and evaluating interventions for a target population in a defined geographical area or setting. For HCV, a variety of model programs are in early stages of development at the national and sub-national levels; programs have also been developed for specific settings and populations (e.g. micro-elimination). These model programs help demonstrate the feasibility of HCV elimination and provide operational experience in implementing the essential components of HCV elimination programs.

Iceland

Iceland’s demonstration project provides a model program for eliminating HCV in a high-income, low-prevalence country [158, 159]. The focus of Iceland’s project was treating and curing HCV among PWIDs and reducing this population’s risk of HCV transmission and reinfection. Essential features of Iceland’s program include collection of strategic data to guide planning to reach national elimination targets, sound financing, and the engagement of a local coalition of political leaders, healthcare providers, and members of affected populations to implement appropriate interventions for the target population.

In December 2015, the country of Iceland set goals for the elimination of HCV. Of the 340 000 people living in Iceland, an estimated 1100 (0.3%) (almost all of whom are PWIDs) were infected with HCV at that time. Physicians caring for these patients engaged drug manufacturer Gilead Sciences to identify ways to eliminate HCV in the country. These discussions resulted in a pledge from the manufacturer to provide financial support for the form of a donation of HCV medications at no charge to the Icelandic health system. The public-private partnership and plans for the demonstration project to eliminate HCV were approved by the Iceland Ministry of Health and by the directors of participating health facilities.

Iceland’s governmental support of the project included purchase of diagnostic tests and other services related to the nationwide elimination campaign.

HCV is a reportable condition to public health surveillance in Iceland. The number of new (incident) HCV infections was selected as the performance indicator and health outcome goal. Based on data from health models, the program set a goal of an 80% reduction in incidence by 2025. To reach the goal, 75 of 1000 infected PWIDs will need to be treated and cured per year; a similar reduction in incidence would be reached by 2020 if the number of patients treated annually were increased to 188. Iceland’s performance target is to treat most of the HCV-positive people within the first 2 years of the program, with a third year dedicated to locating and treating those infected people who are difficult to find.

Overseen by two committees (one general and the other research-focused), the program is being implemented using a multidisciplinary team approach that includes physicians, nurses, and other healthcare professionals and engages settings that provide psychosocial support services (including shelters for the homeless) and correctional facilities. Key intervention strategies are case registries to identify HCV-infected persons and those at risk for HCV infection, provider training, and outreach to patients including reimbursement for travel. Point-of-care testing was offered in homeless shelters and other settings where PWIDs might be located. The care and treatment protocol was managed by specialists in addiction medicine, hematology, and infectious disease.

During the first 15 months of the program, 557 people with HCV were identified, and 526 started treatment [159]. The program is on track to reach the national HCV elimination goal. The local coalition expressed concerns often voiced by disease elimination programs, namely how to sustain political support after external sources of funding come to an end.

Georgia

The country of Georgia is a low-middle income country with high HCV prevalence. In contrast to Iceland, risk populations include PWIDs, blood transfusion recipients, and patients who have received unsafe injections in medical and dental care settings [152, 156]. In April 2015, the Georgia Ministry of Health in collaboration with the US CDC and Gilead Sciences launched an HCV testing and treatment program to eliminate HCV (defined as a 90% reduction in HCV prevalence by 2020). With technical assistance from the US CDC, a national HCV serologic survey was conducted revealing that 5.4% of the adult population was infected with HCV; men, people 30–59 years of age, PWIDs, and previous recipients of blood transfusions had the highest rates of HCV infection. In 2015, the country began a national HCV testing program in diverse settings; 470 890 individuals were tested for HCV and over 10% were anti-HCV positive. HCV prevalence was greatest for PWIDs (45%). In April 2015, the HCV treatment program was launched following a commitment of financial support by Gilead Sciences, which agreed to donate HCV medications at no cost. A scale-up of sites providing HCV treatment in the country was initiated. From April 2015 through December 2016, a total of 38 113 (65%) of 58 223 people with positive HCV antibody test were evaluated for treatment, 30 046 (79%) were confirmed as having chronic HCV infection, and 27 595 (91.8%) of those completing the evaluation began treatment. Ninety-eight percent of people who received all-oral, interferon-free therapies were cured of HCV infection. The number testing positive for HCV and receiving treatment declined in the last months of this time period, revealing the need for an expansion of testing and
linkage to care services. A national HCV elimination plan was finalized in 2016 to guide expansion of clinical care to additional primary care settings and safe injection services for PWIDs, and to make improvements in infection control within healthcare facilities and in blood donor screening and testing. In 2017, the HCV study team launched a scientific committee to develop an operational research to provide data for expanding HCV testing, care, and treatment to primary care.

The benefits of the Georgia HCV program extend beyond achieving the primary objective of reaching the elimination targets. Long-lasting improvements to the health system have been made that will have the additional benefits of a safer health system, stronger referral networks linking primary and specialty care providers, and improved services for PWIDs, all of which can be used to tackle other public health issues.

Egypt

Egypt has one of the largest HCV-infected populations in the world. More than 6 million people in Egypt are living with HCV infection, mostly resulting from poor infection control associated with a national, community-based campaign against schistosomiasis conducted during 1950–1980 that required the injection of medications [19, 11, 114, 151]. As a result, prevalence of HCV is highest for older adults, and this population is becoming progressively ill with HCV-related disease over time. This large reservoir of infected people and poor infection control contribute to 150 000 new HCV infections annually. Egypt set targets for HCV elimination before the actions of the WHA and WHO led to development of global HCV elimination goals. In 2006, the Egyptian Ministry of Health created the National Committee for Control of Viral Hepatitis (NCCVH), headed by hepatitis experts from Egypt and other countries and charged with leading a national response to the HCV epidemic. The national goal and vision of the HCV management program in Egypt was to reduce HCV prevalence to <2% within 10 years and to approach disease elimination (prevalence <1%) by 2030. In 2011, a comprehensive national plan of action was developed to include all aspects of HCV prevention, including improved infection control, blood bank screening procedures, and policies for HCV testing, care, and treatment. Egypt prioritized infection control, developing collaborations with the WHO Safe Injection Campaign and establishing infection control programs at healthcare facilities.

To encourage people to seek testing, a national media campaign was launched to combat stigma for those with HCV. From 2006 through 2017, a total of 60 HCV treatment centers were opened across the country, a national patient registry was established, and testing and treatment services were made available at low cost to patients [9–11]. Through this HCV treatment network, approximately 1 million patients have received treatment. However, meeting Egypt’s 2030 goal requires that 350 000 people be diagnosed and treated annually.

These data reveal the necessity of scaling up testing policies for broader segments of the population and addressing the financial costs of testing, as the cost of diagnostic testing associated with the national program currently exceeds the cost of treatment. Other barriers to elimination revealed by the Egyptian program are the low rate of follow-up, which is needed to document cure. Despite challenges, Egypt’s program benefits from the continued political and societal commitment to elimination, availability of evaluation data, and conduct of operational research to drive programmatic change. Egypt’s elimination program will likely evolve over time to meet current challenges.

Australia

Australia is another country with a national response to HCV that predates the setting of global HCV elimination goals. HCV elimination in Australia illustrates many of the essential components of a model HCV elimination program [160, 161]. The country first developed a plan for HCV prevention in 2000 and has made updates over time. Second, Australia has garnered involvement from diverse stakeholders representing public health, clinicians, and civil society. Third, political commitment for HCV elimination in Australia is robust: long-standing political support and government funding have increased availability of SSPs and access to HCV testing, and as a result, the country was well positioned to set elimination goals even before availability of curative HCV therapies. Financing of HCV therapy was initially problematic, limiting access to this intervention. However, cost-related barriers were addressed through negotiations involving the national government, civil society, and the pharmaceutical industry. The national government committed a budget of AUSS1 billion to purchase HCV medications in 2016–2020, and restrictions to HCV treatment based on stage of liver disease or history of drug use were removed. A cap was placed on the amount of national funds going to purchase HCV treatments per year so that as more patients are treated the cost per patient treated falls. Out-of-pocket costs per patient were AUSS3–$7.

In 2016–2017, an estimated 69 000 people were treated for HCV in Australia and 26% of the total HCV-infected population has now received treatment. However, even with this solid foundation of national planning, prevention infrastructure, and national commitment to financing a HCV prevention and care program as well as HCV treatment, success in eliminating HCV in Australia is not assured. The number of people treated is declining as the ones diagnosed in previous years are treated and cured, increasing the importance of continued HCV testing and linkage to care. Community education is needed to reach at-risk people who have not yet been diagnosed. Care models for correctional establishments, indigenous populations, and other specific settings are needed to co-localize treatment. HCV prevention services for PWIDs must continue.

Fortunately, Australia is one of the few countries that has both wide access to safe injection equipment (400 needle-syringes distributed per PWID per year) and OST (40 per 100 PWIDs). As the number of people with HCV declines in Australia, continued public attention and sustained political commitment will be needed to achieve elimination goals. The specific targets for elimination help to sustain national commitment by focusing on the end-goals that can be achieved rather than becoming compliant with initial success.

Cherokee Nation

Elimination efforts by the Cherokee Nation of eastern Oklahoma in the United States illustrate a successful sub-national program, exemplifying how elimination activities can be added in an
iterative manner culminating in a comprehensive program [153]. Among racial and ethnic populations in the United States, rates of HCV mortality and incidence are highest for American Indians and Alaskan Natives. The Cherokee Nation is the largest American Indian tribe and operates its own health system; all members of the tribe as well as other American Indians or Alaskan natives can receive clinical care services at no charge to the patient. In recognition of HCV as a health disparity and in response to the CDC recommendation for HCV testing of all people born 1945–1965, the Cherokee Nation health system implemented routine testing for this population. Electronic prompts were added to the health information system, and clinical care providers were trained to provide both HCV testing and care services. A case registry was created to monitor HCV testing, diagnosis of HCV-infected patients, and their receipt of recommended services. Principal Chief Bill John Baker expressed the civic support for the program “our hope is to eliminate this disease entirely within the Cherokee population” [162]. Over a 33-month period in 2012–2015, HCV testing increased sixfold, resulting in over 36% of patients in this 1945–1965 birth cohort being tested for HCV. Among the 1772 patients tested for HCV antibody, 715 (4.3%) were antibody-positive. Among these antibody-positive patients, 488 (68.3%) had a confirmatory HCV RNA test performed, of whom 388 (79.5%) were found to be chronically infected (HCV RNA positive). More than half (57.5%) with chronic HCV infection initiated treatment, of whom 89.6% achieved SVR (the measure of HCV cure).

The training of primary and mid-level providers, including pharmacists, to provide HCV testing care and treatment services greatly facilitated scale-up of services in settings convenient for patients. Based on this initial success, the Cherokee Nation expanded routine HCV testing to include all adults, with the tribal health system managing the costs of HCV testing care and treatment. In October 2015, the tribal leadership launched “The Path toward Elimination of HCV” program with the goal of treating 85% of patients in the health system with HCV infection over a 3-year period. The health system expanded access to HCV testing in dental, emergency care, and other services and co-localized treatment in primary care settings. To reduce new infections and identify people who do not access clinical care services, the elimination program is developing outreach testing and harm-reduction services for the community.

**San Francisco**

Certain communities are responding to the call for elimination of HCV in the United States. One is End Hep C SF, a coalition of San Francisco Department of Public Health, University of California San Francisco (UCSF), and community partners [163]. In the absence of a national or state program, the coalition aims to build the capacity to raise community awareness and develop sites for testing and treatment in clinical and nonclinical settings. To guide local planning, the coalition commissioned a model based on local data, demonstrating that an estimated 21,758 people (2.5% of the adult population) living in San Francisco have been infected with HCV. This exceeds the national HCV prevalence rate of 1.4%. A total of 16,408 people are currently infected with HCV and in need of testing and treatment, including 11,000 PWIDs [164]. These estimates provide benchmark data to guide delivery of prevention services and assess progress toward elimination goals.

**SPECIFIC POPULATIONS AND SETTINGS: MICRO-ELIMINATION**

Field studies of HCV elimination among specific populations and settings, termed “micro-elimination,” provide direct health services and experience to scale up the program to reach the larger community. For HCV micro-elimination projects, populations are targeted based on their high prevalence of HCV and opportunities to integrate HCV testing and treatment into existing health services.

**Incarcerated populations**

Globally, an estimated 26% of incarcerated persons are infected with HCV [15]. To study implementation of an HCV elimination program in this setting, in March 2016, Lotus Glen Correctional Centre (LGCC), a high-security correctional facility in Queensland, Australia housing 800 prisoners, launched an HCV elimination program [165]. HCV testing was provided for all prisoners on intake and for all prisoners with risks for HCV or a clinical presentation suggestive of HCV-related disease. All prisoners with laboratory evidence of HCV infection were referred for treatment. From March 2016 through December 2017, approximately 90% of new prison entrants were tested for HCV. A total of 125 patients were found to have HCV and were assessed for HCV treatment. Of 66 prisoners who completed evaluation and treatment, 64 (97%) achieved virologic cure. With the documented cures among people who completed treatment and the number of cures expected from those still receiving treatment, the prevalence of HCV in the facility will have declined to 1.1%. The prison joined forces with a regional project, “Cairns Hep C Free by 2020,” to promote mutual treatment as prevention among the general community and within LGCC. Lower community prevalence translates to lower prevalence among future prison entrants.

**People with HIV**

People with HIV, particularly those with a history of injection drug use, can have higher HCV prevalence than other populations. People with HIV/HCV coinfection are at increased risk for liver disease compared with other patients infected with HIV alone [7]. Networks of clinical systems caring for people with HIV provide a feasible opportunity to integrate HCV testing and treatment services [166, 167]. Early results from studies of HIV/HCV-infected people treated with all-oral therapies reveal high rates of virologic cure (>95%) equivalent to data from clinical trials. However, a large proportion of people remain to be treated, and programmatic and strategic data are needed to track the successful testing and cure of HCV [168]. Studies have shown that integrating HIV and HCV testing can improve acceptance of both interventions. Also, programs to eliminate HCV can be informed by best practices, including innovative approaches to testing, identified through the HIV operational research agenda.
CLOSING EXISTING KNOWLEDGE GAPS TO PROMOTE SUCCESSFUL ELIMINATION

Operational research

Operational research is an essential component of disease elimination programs. The operational research agenda is built on a good monitoring and evaluation platform that identifies program weaknesses and where changes in practice and technology innovations can improve performance and outcomes. In this regard, field trials, demonstration projects, and program evaluations are forms of operational research. Research can lead to new technologies that improve prevention, diagnosis, and treatment. Examples of the operational research for HCV elimination are listed in Table 70.3.

Collection of strategic data

Collection of strategic information to guide and evaluate program performance and progress toward elimination goals is a challenge. National or community-based serologic surveys are the gold standard for assessing the burden of HCV disease [11, 153, 169]. However, for many jurisdictions, stand-alone surveys for HCV alone are prohibitively expensive. Studies are needed to assess whether surveys with less complex methodology and requirements for testing of a smaller number of subjects will provide comparable representative data. Another approach is to integrate HCV testing into large serologic surveys designed to assess other infectious disease and health conditions. For example, the CDC recently assessed the reliability of HCV testing of dried blood spots often used in large health surveys [170]. The study found high sensitivity in the detection of HCV antibodies in stored dried blood spots but low sensitivity for detection of HCV RNA. This suggests that it is best to use freshly prepared specimens to reliably detect HCV RNA in surveys.

Evaluations can inform development of standard definitions for the performance indicators in the WHO global strategy and development of tools to collect this information from electronic health records. Other indicators can be considered. For example, the proportion of people positive for HCV antibody who have RNA will decline as a growing numbers of people in a populations are successfully treated [171]. This marker can be evaluated as a performance indicator. Evaluations can also inform development of information technology tools to include case registries of people diagnosed with HCV that allow for monitoring of linkages to care and treatment and the outcomes of such treatment [172]. The information obtained through case registries can be used to identify people not responsive to treatment. Such information is critical, as treatment failures can suggest the emergence of antiviral resistance.

Health models based on available surveillance data can help estimate the burden of HCV disease, the impact of various interventions, and progress toward elimination goals [113, 114, 124, 146]. Although more complete and accurate inputs for these models are needed, the Global Burden of Disease provides estimates of HCV burden of mortality for over 190 countries (http://www.healthdata.org/gbd). Models can also guide development of financing strategies for HCV testing and treatment.

Models of HCV testing, care, and treatment in diverse settings

Research is needed to improve the HCV test and cure cascade by increasing the proportion of HCV-infected people tested and aware of their infection status, referred for care and treatment, cured of HCV, and receiving services to prevent reinfection. HCV testing is the necessary first step in the treatment and cure of HCV-infected people. Rates of testing currently are low due to multiple barriers that can be reduced or eliminated through operational research. The effectiveness of HCV testing can be improved by implementing interventions in settings that serve people at high risk. Previous evaluations have identified emergency departments as settings where large numbers of people with previously undiagnosed HCV infection can be found. Yet research is needed to determine how to link people from this setting into care [173]. Correctional facilities have large numbers of HCV-infected people. Models of testing, care and treatment financing and delivery, together with the governmental leadership to prioritize the delivery of these services are needed [174].

Table 70.3 Operational research agenda for HCV elimination

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<tr>
<th>Strategic information</th>
<th>Operational research agenda for HCV elimination</th>
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<td>Serologic surveys to estimate disease burden</td>
<td>• Tools to facilitate HCV testing, linkage to care and treatment</td>
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<tr>
<td>Case registries to monitor HCV testing, care and treatment outcomes</td>
<td>• HCV test, care and treat procedures simplified for integration in primary care settings</td>
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<tr>
<td>Public health data to monitor progress toward elimination targets</td>
<td>• HCV care as prevention strategies for persons who inject drugs (PWID)</td>
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<tr>
<td>Incidence, mortality</td>
<td>• Delivery of comprehensive prevention services for PWID</td>
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<tr>
<td>Laboratory data to detect networks of transmission and emergence of antiviral resistance</td>
<td>New technologies</td>
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<tr>
<td>Health models of cost effectiveness of interventions</td>
<td>• A single test to detect current HCV infection</td>
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<td>Models of care</td>
<td>• Point-of-care tests to diagnose current infection and monitor response to therapy</td>
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<td>Serologic surveys to estimate disease burden</td>
<td>• HCV vaccine</td>
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<td>Case registries to monitor HCV testing, care and treatment outcomes</td>
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<td>Public health data to monitor progress toward elimination targets</td>
<td>• Community involvement in program planning and implementation</td>
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<td>Incidence, mortality</td>
<td>• Social marketing strategies culturally appropriate for the community</td>
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<td>Laboratory data to detect networks of transmission and emergence of antiviral resistance</td>
<td>Education to address stigma and create demand for program services</td>
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<td>Education to address stigma and create demand for program services</td>
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The complexity of interferon-based therapies required management by hepatologists and other specialists. Yet the development of all-oral therapeutic options, which are short in duration, have relatively few serious adverse events, and have high cure rates creates opportunities to co-localize HCV treatment into primary settings. Research is needed to guide this process. Care models that simplify HCV testing and treatment increase the feasibility of primary care clinicians and mid-level providers delivering HCV treatment services [144, 171]. For example, the HCV elimination program in the Cherokee Nation provides evidence that HCV therapies can be managed by pharmacists [153].

Studies are also needed to support integration of HCV treatment into other clinical programs. For example, in some countries, the prevalence of HCV is high among patients in treatment for HIV or active TB; evidence is needed to inform the modification of clinical practices to include provision of HCV testing and treatment. Short courses of therapy can increase the acceptability of treatment for some patients [175]. A better understanding of strategies that can facilitate co-localization of testing and treatment in primary care settings can greatly benefit patients in rural and other areas where specialty care is not routinely available, along with settings serving marginalized populations (e.g. incarcerated and migrant populations).

Studies also can improve testing strategies targeted to PWIDs [176]. Research is needed to identify strategies for quickly detecting new or repeat infections to prevent transmission. Finally, data are needed to inform strategies for improving HCV testing among pregnant women and infants of HCV-infected mothers.

Data can guide the integration of HCV treatment in programs providing drug treatment services. The Patient-Centered Outcomes Research Institute is supporting an eight-site study in the United States of HCV treatment of PWIDs in drug treatment [177]. Available data suggest people currently injecting drugs and HIV-infected MSM are at highest risk for reinfection. New studies can guide case management of these populations and deliver services (e.g. access to drug treatment and social support services) that minimize reinfection risks and sustain cure.

**New technologies for testing and treatment**

Innovations in testing technologies can also reduce barriers to HCV diagnosis. The current two-step process required for HCV testing is complicated and as such may result in substantial numbers completing only part of the testing process and remaining undiagnosed. The development of precise and affordable virologic detection assays available as front-line tests will greatly simplify the testing process and expand the settings where testing can be made available [156]. For example, evaluations of an HCV core antigen assay, a serologic test available at lower cost than HCV RNA testing, found that the assay results were comparable to the results of HCV polymerase chain reaction (PCR) testing [59–61]. Point-of-care testing compounds the advantages of virologic detection assays. At least one point-of-care test for HCV has been licensed for use in Europe [57, 58]. Improvements in test technologies to differentiate acute from chronic HCV infection would help identify patients with recent infection or reinfection.

Next-generation sequencing can detect the relatedness of HCV quasispecies among patient populations, identifying cases with similar genetic sequences indicative of shared patterns of transmission [178]. Studies are needed to determine how to deploy this new technology. Current experience demonstrates HCV genetic sequencing can map social networks of HCV transmission in communities [179]. New interventions trials can evaluate how next-generation sequencing can guide delivery of HCV treatment services to people in social networks, document elimination of HCV transmission, and detect the reintroduction of HCV after elimination is achieved.

Therapies for HCV infection are highly effective. Therapeutic failures are relatively few, and the emergence of antiviral resistance is not a major barrier to the elimination of HCV disease [111]. However, elimination programs need to remain vigilant and collect data to monitor the emergence of antiviral resistance, as this phenomenon has been documented among people who have experienced treatment failure.

**New prevention tools for persons who inject drugs**

With improvements in blood safety and infection control, success in the elimination of HCV transmission will depend on the effectiveness of HCV prevention among PWIDs. A review of data from multiple studies suggests access to programs providing treatment for opioid addiction and those providing safe drug preparation and injection equipment lowers HCV transmission risks, with adequate access to both interventions the optimal strategy. However, studies are needed to determine how best to deliver these services as part of a comprehensive program. Drug-use behaviors, social circumstances of drug users, and access to clinical services vary. Addiction treatments are needed for methamphetamines and other illicit drugs.

Studies are needed to ensure strategies for delivery of prevention interventions are appropriate and effective for PWIDs in an areas targeted for HCV elimination. Theoretical models suggest that combining HCV treatment with these risk-reduction measures will optimize HCV prevention for PWIDs [97, 98, 180, 181]. Treatment as prevention is a well-accepted method for interrupting transmission of HIV. The curative therapies available for HCV potentially increase the impact of this strategy by decreasing the prevalence of HCV in a risk population and lowering the force of infection, resulting in declines in HCV incidence. Several research questions remain to be answered to determine how to most effectively reduce prevalence and impact of HCV infection among PWIDs:

- How many and what percentage of HCV-infected PWIDs must be treated in a given time?
- Is it advantageous to treat PWIDs as they are identified by routine HCV testing?
- What is the effectiveness of strategies that encourage PWIDs in care to refer their injecting partner(s) for treatment?
- Can broad HCV testing including next-generation sequencing be deployed to first map the social network of PWIDs, followed by large-scale implementation of a coordinated HCV test-and-treat program to reduce prevalence as quickly as possible?
• What combination of services is needed to protect individuals cured of their HCV infection from returning to injection behaviors that can lead to HCV reinfection?

Prevention research also can guide the use of HCV therapies as antiviral prophylaxis to interrupt mother-to-child transmission and also sexual transmission, particularly among HIV-infected MSM.

Development of a hepatitis C vaccine

A safe and effective vaccine could help prevent new HCV infections and could be particularly important in preventing transmission among PWIDs [181–184], the population at greatest risk for new infection. An effective vaccine could reduce the risk of HCV transmission if it were routinely provided to people before the onset of high-risk behaviors. Health models suggest even a hepatitis C vaccine of low efficacy could be a cost-effective approach to prevention of HCV among PWIDs [181]. People tend to begin drug injection behaviors as young adults, and the incidence of HCV is highest (26 per 100 person-years of observation) for new injectors [14]. Therefore, to optimize the impact of such an intervention, an HCV vaccine would need to be administered during early adolescence, before the start of injection behaviors. Research to this point has failed to identify a promising candidate. The lone clinical trial in progress is a study of a prime/boost strategy using a chimpanzee adenoviral (prime) and modified vaccinia virus Ankara (boost) vectors to induce HCV-specific T cell responses. The study assessed the safety and effectiveness of the candidate vaccine in reducing HCV incidence among PWIDs [183]. The study found the vaccine candidate not to be effective at preventing chronic HCV infection in adults [184]. Although not successful, a concerted and coordinated research effort by the public and private sectors is needed to assure future studies of other vaccine candidates.

A Coalition for Global Hepatitis Elimination

Many disease elimination efforts are supported by a technical hub of readily available information and access to expert assistance. Examples include HIV (http://www.differentiatedservice delivery.org/home), neglected tropical diseases (http://www.ntdsupport.org/), and malaria (http://allianceformalariprevention.com/). The success of HCV elimination programs hinges on availability of such a resource; as these programs are early in development and individual efforts tend to be relatively isolated. Program leaders have varying levels of experience and training to analyze epidemiologic information and prepare scientific reports. Results of operational research, when available, are often presented or published in multiple locations over time, complicating and delaying access to this information. HBV and HCV elimination programs have limited access to technical experts that can facilitate their work and help overcome barriers to implementation. Guided by experience of elimination programs for other diseases, the Task Force for Global Health launched in July 2019 the Coalition for Global Hepatitis Elimination as a community of practice to determine consensus on elimination goals, bring implementing programs together to share knowledge and experience, provide technical assistance to overcome barriers, generate new knowledge through research, and advocate for viral hepatitis elimination and the resources to achieve it (www.globalhepatitiselimination.org).

CONCLUSION

HCV is a major public health problem. Rising global HCV mortality rates despite availability of curative therapies has prompted a global call for elimination of this life-threatening disease. Clinical studies demonstrate over 90% of HCV infections can be cured, and if initiated early in the course of disease, treatment virtually eliminates HCV-related mortality. New infections can be limited through continued improvements in public health and clinical interventions. The greatest remaining challenges are providing prevention services for PWIDs and implementing large-scale HCV testing programs to identify and link to care persons living with this silent infection. As elimination challenges are met and lessons learned, HCV elimination programs will strengthen existing health systems and help inform other disease control and elimination efforts. The journey toward the elimination of HCV has just begun, and program development and operational research are nascent. Partnerships with global and local organizations are needed to build the capacity to deliver the highly effective interventions available to eliminate HCV. Programs must learn by doing and conduct the operational research needed to capitalize on technologic innovations and existing models of care. By building prevention capacity and working together, HCV transmission and disease can be eliminated.

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70. TIME FOR THE ELIMINATION OF HEPATITIS C VIRUS AS A GLOBAL HEALTH THREAT


THE LIVER: REFERENCES


