



REVIEW

Eliminate Hepatitis C as a Public Health Threat: A Narrative Review of Strategies, Gaps, and Opportunities for China

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ABSTRACT

Introduction: As a country that is heavily burdened by hepatitis C, China's successful responses to this public health threat have significant implications for the achievement of the global elimination goal.

Methods: This article reviews China's strategies for prevention, screening, diagnosis, access to direct-acting antiviral agents (DAA) therapy, and patient management of hepatitis C. It also analyses the major challenges and summarizes the valuable successful international

experiences that have implications for China to achieve the elimination goal.

Results: To promote the achievement of elimination, China has taken a series of proactive measures to promote the prevention and treatment of hepatitis C. Compared with other middle-income countries, there is still much room for China to achieve universal screening, diagnosis and treatment based on a streamlined disease management procedure. A stronger role of primary care in an integrated healthcare delivery system and integration of hepatitis C with other infectious disease programs should also be the focus of China's efforts.

Conclusions: As a developing country with a large population, a "micro-elimination" strategy with focused screening and proactive diagnosis and treatment for the vulnerable population may be a more practical approach to eliminating hepatitis C in China. Continued efforts are needed to fully overcome the intellectual property barriers of sofosbuvir for forming the more competitive pan-genotype DAA combinations based on the locally developed DAAs. Meanwhile, the safety net for patients in economic hardship needs to be further strengthened. More importantly, it is necessary to promote patients' willingness and compliance with standard treatment through increased awareness of hepatitis C. The development of an integrated healthcare delivery system, a disease management procedure which is suitable for primary care, and full compliance of the

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primary care providers are also important to achieve effective cascade care management.

Keywords: Awareness; Diagnosis; Direct-acting antiviral agents; Elimination; Hepatitis C; Integrated healthcare delivery system; Screening; Disease management procedure; Treatment

Key Summary Points

China has taken a series of proactive measures to promote the prevention and treatment of hepatitis C.

Universal screening, diagnosis, and treatment based on a streamlined disease management procedure within an integrated healthcare delivery system are the focus of China's future efforts.

A "micro-elimination" strategy with focused screening and proactive diagnosis and treatment for the vulnerable population may be a practical approach for China to achieve the goal of complete elimination of hepatitis C.

Continued efforts are needed to fully remove the intellectual property barriers to the production and distribution of sofosbuvir, with the aim to form more competitive pan-genotype direct-acting antiviral (DAA) combinations based on the locally developed DAAs.

Patients' willingness and compliance to standard treatments should be further promoted by increasing public awareness of hepatitis C.

lead to a life-threatening disease, untreated HCV can cause a range of systemic health problems [1]. Once advanced liver scarring has developed, the annual incidence of cirrhosis is about 10%, and people with cirrhosis are at risk for liver failure and liver cancer [2]. Each year, complications from HCV infection claim 700,000 lives worldwide [3]. The treatment of hepatitis C was transformed with the introduction of direct-acting antivirals (DAAs), and at the present time an 8- to 12-week course of oral DAA treatment can cure > 90% of persons with chronic HCV infection. In 2016, the World Health Organization (WHO) set the goal of eliminating viral hepatitis as a major public health threat by 2030 [4]. However, as of 2019, only an estimated 21% of the 58 million people infected with HCV worldwide have been diagnosed, of whom only an estimated 62% were treated with DAA. Approximately 290,000 people die each year from cirrhosis and hepatocellular carcinoma caused by HCV [5].

In China, there are about 10 million people infected with HCV, and the antiviral treatment rate for HCV is < 10%. Worldwide, China has the highest incidence of liver cancer and number of deaths caused by viral hepatitis, including that caused by HCV [6]. In response to the WHO goal of eliminating HCV by 2030, China has taken a series of proactive measures to promote the prevention and treatment of HCV, including adopting the Viral Hepatitis Prevention and Control Plan (2017–2020) [7] and the Work Plan for Actions to Eliminate Hepatitis C as a Public Health Threat (2021–2030) [8].

In this article, we review the strategies adopted by China to eliminate HCV as a public health threat through prevention, screening, diagnosis, access to DAA therapy, and patient management. We also analyze the key issues and challenges faced by China and summarize the valuable, successful international experiences that have implications for China to achieve the WHO goal of HCV elimination.

INTRODUCTION

Hepatitis C virus (HCV) can cause both acute and chronic hepatitis, with the severity of the resulting inflammation ranging from a mild illness, which is usually asymptomatic, to more serious conditions. Although it usually does not

METHODS

Search Strategy and Selection Criteria

Policy documents related to this review were obtained from the official websites of national government agencies and their technical departments, including the National Health Commission (NHC), the Ministry of Human Resources and Social Security, the National Healthcare Security Administration (NHSA), the China Centre for Disease Control and Prevention (CDC), and their local agencies, as well as from the WHO and other relevant international and national organizations. Relevant published articles were identified through searches of various databases, including the China Knowledge Network, Wanfang Data Knowledge Service Platform, PubMed, Emerald insight, and Karger, as well as of the references of the extracted publications. Gray literature was identified through solicitation from the highly regarded reports, working documents, and internal documents of government and international organizations. References cited in retrieved articles and documents were also examined for relevance. Only papers published in English and Chinese were reviewed. The final reference list was generated based on originality and relevance to the scope of this review.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Various “responsive strategies” at local, regional, and national levels, as well as combinations of these, have been implemented to promote the prevention and treatment of HCV infection. These are discussed in the following sections.

Prevention Strategies

Surveillance

The statutory infectious disease case reporting system and the sentinel surveillance system are the two national systems that monitor reported cases of hepatitis C in China [9]. As hepatitis C is a category B statutory infectious disease, cases of hepatitis C are reported online by health facilities and CDCs depending on the route of detection (direct online reporting started in 2004), with the China CDC handling the major outbreaks [10]. Since 2010, China has designated a number of sentinel hospitals in different provinces as centers for HCV management. Such hospitals manage blood donors, health examiners, patients receiving invasive diagnoses and interventions, hemodialysis patients, and those attending family planning sessions. Currently, there are 87 HCV sentinel hospitals nationwide, including 31 for blood donors in 31 provinces, 20 for health examiners in 16 provinces, 13 for patients receiving invasive diagnoses and interventions in 13 provinces, 12 for hemodialysis patients in 12 provinces, and 11 for family planning outpatients in 11 provinces [11].

Prevention Among High-Risk Populations

The HCV antibody positivity rate among drug users in China has been reported to be as high as 40%, and the total HCV antibody positivity rate among people who inject drugs (PWID) range between 55% and 65%, with both rates showing an increasing trend [12]. In recent years, with the help of community methadone maintenance clinics as a platform for human immunodeficiency virus (HIV) prevention and treatment, China has launched a series of programs targeting the sexual partners of drug users, men who have sex with men (MSM) [13], and other persons with high-risk sexual practices [14]. In addition, CDCs and the prison administrations have adopted joint interventions to raise the awareness of prisoners of the risk of HCV infection and avoid risky behaviors [15].

Hospital Infection Prevention and Control

China has introduced a series of norms for infection control, sterilization, laboratory bio-safety, and hemodialysis management in healthcare facilities and has developed guidelines specifically aimed at preventing and controlling nosocomial HCV infection. Hospitals are mandated to provide nosocomial infection training to new physicians and regular training to all medical staff, to strengthen awareness of nosocomial infection prevention and control and to improve compliance with safe practices [16].

Screening, Diagnosis, and Treatment Strategies

Exploration of Proactive Screening

In 2014, China published the “National Standard Screening and Management of Viral Hepatitis C”, which clearly defines the population to be screened, screening time, and confirmation process for HCV screening and management of high-risk groups [17]. In 2015, the “Guideline for the Prevention and Treatment of Hepatitis C” was published [18]. The guideline was updated in 2019 to be consistent with the WHO principles of treatment [19]. Currently, health facilities and health examination institutions have included HCV testing in health check-ups and preoperative examinations. Anti-HCV screening of pregnant women is also required, subject to the informed consent.

Integration of Healthcare Delivery System

China initiated a new round of healthcare reform in 2009, which has continued to strengthen the role and capacity of the primary care. Some regions have formed an integrated HCV prevention and treatment system through close cooperation among the health administrative departments, hospitals, and CDCs (see Boxes 1, 2, 3, 4, for examples). These pilot programs are examples of integrated HCV prevention and treatment, having primary care and CDCs as a joint backup of multi-sectoral cooperation to enhance the public’s awareness and

to bridge the referral between screening, diagnosis, and treatment [20].

Box 1: Primary Care and CDCs as a Joint Backup of Multi-Sectoral Cooperation

Ningbo city in Jiangsu province set up a supervisory management group in primary care to identify referrals based on case information collected by the CDC, who were unable to obtain the correct healthcare. The staff in this group is responsible for mobilizing patients who are not successfully referred, assisting them to access the designated health facilities for diagnosis and treatment, and providing follow-up to patients during the full cascade of care [10].

Box 2: Proactive Screening, Diagnosis, and Treatment Management in Primary Care

Putian City of Fujian Province set the goal of “liver clean”. The township central health centers carry out at least one follow-up visit to all untreated patients with HCV, issue treatment referral cards, and help patients receive standardized antiviral therapy. The local government allocates subsidies to those patients in financial hardship and to towns providing with a high rate of free screening [21].

Box 3: General Practitioner Model in Developed Areas

Shanghai and Chengdu city incorporate HCV into their general practitioner (GP) contract models in the integrated healthcare delivery systems, which were established through the health system reforms. HCV screening is included in the service package at the beginning of GP visits, and HCV management is integrated in the GP contracted services. These systems mobilize community volunteers to carry out health education, and to inform health insurance reimbursement policies, and benefits for HCV treatment. They also raise funds for free screening [10, 22].

Box 4 Medical Consortium Model in Less Developed Areas

Wuwei city of Gansu province has formed the Liver Disease Medical Consortium by linking the central hospital, county hospitals, and township health centers. Physicians from the central hospital provide technical assistance to those at county hospitals, and physicians from the county hospitals provide technical assistance to township health centers [23]. The aim is to enable treatment of local patients by local healthcare providers under the support and assistance of upper-level healthcare providers.

Raising Awareness Strategies

China has incorporated knowledge dissemination and health education on the prevention and treatment of viral hepatitis into its national basic public health service programs, and has established an authoritative information dissemination system on health knowledge and skills to provide the public with scientific information on disease prevention and treatment. The State Health and Welfare Commission has issued the “Essentials of Viral Hepatitis Prevention and Control,” “Essentials of Viral Hepatitis C Prevention and Control,” and other promotional and popular science documents and videos, and also issued timely releases on progress in the area on World Hepatitis Day each year, with the overall aim to mobilize the whole Chinese society to actively participate [24]. According to the characteristics and needs of different target groups, the sexually transmitted disease (STD) and acquired immunodeficiency syndrome (AIDS) units of China CDC have prepared core messages on HCV prevention and education for the general public, drug users, and MSM, respectively [25]. Mainstream media platforms and novel media sources, such as WeChat, Weibo, and Jitterbug, lectures, public service announcements, lecture tours, individualized health education, and other media forms, are widely used for health education on the prevention and treatment of toxic hepatitis.

The Hepatology Section of the Chinese Medical Association organizes the participation of experienced hepatologists in providing regular online and offline training to primary care

providers on the new HCV diagnosis and treatment guidelines through the “Grassroots Western Tour” program. The aim of this training program is to disseminate correct information on HCV prevention and treatment, improve the technical capacity of primary care physicians, and promote early diagnosis and timely standardized treatment of HCV [26, 27].

Improving Access to DAA Treatment

Accelerating Registration of Imported DAAs

To speed up the market entry of novel medicines in China, the Center for Drug Evaluation accepts data generated by international clinical trials, sets up a fast-track channel to speed up the review, and completes the review of first DAA within 6 months, which greatly shortens the time required for novel medicines to be marketed at home and abroad [28].

Supporting Research & Development and Overcoming Intellectual Property Barriers

To fully ensure patient accessibility to medicines for the prevention and treatment of major infectious diseases (including HCV), the government has continued to invest in long-term research and basic research. Through the “Major New Drug” program identified and implemented in the National Medium- and Long-term Scientific and Technological Development Plan, the government gives continued support to the development of DAAs [29]. In 2018, the first locally developed novel DAA was marketed [30], which broke the monopoly on DAAs held by multinational pharmaceutical companies to date. A second locally developed new DAA [31] was also included in the latest version of WHO hepatitis C treatment guidelines in July 2018. Several other new DAAs are currently in the pipelines of a number of domestic pharmaceutical companies. Sofosbuvir (SOF), a generic DAA, was developed by a domestic company in China and could contribute to a number of locally developed potential pan-genotype DAA combinations in China. It is expected that SOF will break the monopoly on imported pan-genotype products [32].

Publicly Funding the Most Competitive DAAs Through Price Negotiation

Before national health insurance coverage, some areas had started to pilot public funding programs for DAA treatment, which significantly reduced patients' financial burden and improved their quality of life. Tianjin took the lead in 2018, including DAAs in the local basic health insurance and implementing the capitation payment of DAA treatment for HCV [33]. Chengdu City also implemented capitation payments to cover the cost of DAAs, the rest of the testing and treatment costs were co-paid by patients and basic health insurance [34]. The capitation approach significantly reduced the patient's financial burden while keeping health insurance fund expenses under control [35]. Since 2019, Zhejiang Province has been exploring a fixed-payment program for DAA treatment of HCV and allowing DAAs to be dispensed by designated community retail pharmacies [36].

Although some regions have not pioneered novel payment methods, they have used various means to reduce the cost of DAAs for the treatment of HCV. Changchun City and Jilin Province negotiated with the designated health facilities and pharmaceutical manufacturers and included DAA treatment of HCV in a low out-of-pocket program. The patient paid DAA cost reduced over 97% [37]. Henan Province included DAAs in the outpatient specialist medicines list, and the reimbursement rate of urban and rural resident health insurance programs reached 80% [10].

Starting in 2020, several DAAs have been included in the national health insurance medicines reimbursement list. As of early 2022, eight DAAs, including locally developed products, have been included in the basic health insurance through national price negotiations, which reduced the cost of DAA treatment to US\$200–\$1500 per 3-month period. Setting the reimbursement rate at 70% for category B medicines, the individual out-of-pocket payment for DAA treatment is US\$150–\$450 per 3 months. This has greatly reduced the financial burden on patients.

DISCUSSION

Major Challenges

Cascade Care Monitoring System to be Established

China's national infectious disease case reporting system and national hepatitis C surveillance sentinel system only monitor reported cases of HCV. Moreover, a large number of people infected with HCV are not reported and not diagnosed with infection because they are unaware of their HCV infection [38]. The underreported rate of HCV infection is the highest among all category B legally reported infectious diseases [39]. A national survey on duplicated reporting of HCV showed that the national infectious disease case reporting system had an average duplicated reporting rate of 3.8% from 2009 to 2011 and a 3-year duplication rate of 6.9% [40]. China's national hepatitis C surveillance sentinel program also limits its analysis to reported cases. Under the universal basic health insurance system, health insurance and individuals share the financing of HCV diagnosis and treatment. The health insurance funds are pooled at the municipal level.

In China, the employee program and the urban and rural resident health insurance program, originally two separate programs, were only unified into one system in 2017–2018, but it has not yet been used for disease treatment monitoring. The NHSA was established in 2018. The information systems of various health facilities that keep the medical records of HCV are also separately managed by different hospitals. The China Disease Prevention and Control Information System recently expanded the functions of case management of the reported cases. China has not yet established monitoring systems for the cascade care of HCV that cover screening, diagnosis, treatment, and subsequent follow-ups at either the provincial or national level. The number of HCV cases treated is extrapolated from small sample size studies.

Hospital-Acquired Infection Prevention and Control to be Further Strengthened

The overall anti-HCV positivity rate among Chinese hospital patients ranges from 3.2% to 10.5%, which is significantly higher than that of the general population (0.4%) and has been increasing in recent years [41]. The increased use of invasive diagnostic tools, increased number of interventions, and the increased use of dialysis in a modern medical setting may be associated with higher risks of hospital-acquired hepatitis C infection [42].

The rate of hepatitis C infection among medical staff is also much higher than that of the general population, mainly related to flaws associated with medical activities and sterilization procedures [43]. Especially in recent years, reform of the national healthcare system has focused on strengthening primary care services, and dialysis in the lower-level hospitals has increased sharply. The rapid establishment of dialysis centers in primary health facilities has led to increased HCV infections due to defects in healthcare-associated infection prevention and control [44].

Awareness of Non-Hepatology Specialists and the Public to be Enhanced

Currently, awareness of HCV infection among medical professionals in China is generally low, especially among healthcare providers in primary care and those in less developed areas. A survey of Chinese non-specialists showed that 44% of the respondents would not advise patients who tested positive for anti-HCV antibodies to consult a specialist, and nearly 50% believed that there was no effective treatment for HCV. Even in major cities, such as Shanghai and Tianjin, the awareness of HCV protective measures among medical professionals was found to be only 60% and 80%, respectively [45, 46]. Public awareness of HCV in China is even lower [47]. According to a WHO global survey in 2015, only 25% of the Chinese public had any knowledge or understanding of HCV before being diagnosed [10]. This was the lowest level in the WHO Western Pacific region [10] and was even lower than the target of “over 50% public awareness of viral hepatitis prevention and treatment” set in the “China Viral Hepatitis

Prevention and Control Plan (2017–2020)”. Lack of awareness of HCV among medical professionals and the public is also one of the major reasons for the underreporting, low diagnosis rate, and low treatment rate of HCV.

Inadequate health education is one of the major factors contributing to the low public awareness of HCV infection [48]. Only 1.6% of the total public health budget of the NHC was allocated to public health promotion in 2019, among which the allocation to public education on HCV was even more limited. Public education on hepatitis C is organized by CDCs, but also partly undertaken by departments in hospitals focusing on disease prevention. Efforts have been made by some civil societies, charitable organizations, and volunteer teams to carry out various types of activities promoting scientific knowledge and preventive health programs on HCV in the community. However, the effect is not satisfactory due to the low levels of publicity efforts and isolated approaches [10].

Proactive Screening and Referral Mechanisms to be Improved

Currently, proactive screening of HCV has been conducted in high-risk and/or vulnerable populations, such as dialysis patients, pregnant women, hepatitis B patients, or HIV-infected patients. Drug users, HIV-infected patients, and MSM are the neglected populations of such proactive screening systems [49]. Most importantly, it has been found that people with detected HCV antibody positivity are not appropriately diagnosed and treated accordingly. Even for those HCV-infected patients receiving methadone maintenance therapy (MMT), access to treatment remains poor [50]. At this stage, the referral mechanism in most areas of China still need to be improved, and there is no appropriate referral system for persons with HCV infection to be directed to physicians or healthcare institutions which can provide standardized diagnosis and treatment. The referral is now usually limited to suggesting patients to visit specialist hospitals and departments, which is not effective in keeping patients under treatment. One major reason of such inefficiency may be associated with the financing mechanism of treatment

that the cost is share by the individuals and the health insurance. Cost sharing may discourage many potential patients with HCV from being diagnosed and ultimately lead to a lost chance for timely treatment and cure.

Integrated Healthcare Delivery System to be Continuously Strengthened

Although China's primary health care system has been strengthened through reforms of the healthcare system since 2009, the capacity to treat HCV infection is still inadequate in primary care. Treatment is still mainly provided by large speciality and general hospitals. Patients in less developed areas still need to go through one or more referral procedures to access effective treatment. These obstructions in the referral system further reduce the treatment rate [16]. The complexity of the current treatment model for HCV and the inadequate capacity of primary care are the major barriers to primary care playing an important role in the management of HCV. This lack of good-quality primary care physicians with a sufficient knowledge of HCV to diagnose the infection and initiate antiviral treatment is linked to a high proportion of HCV treatments still being dominated by herbal treatments for liver protection. A study in nine hospitals across five provinces in 2017 and the 2017–2019 national hepatitis C sentinel hospital study showed that only 5.5% and 8.7% of the 599 and 16,241 reported hepatitis C cases received antiviral therapy. This number was as low as 2.1% in the secondary hospitals reported in the 2017–2019 study [52, 52].

Safety Net for the Vulnerable to be Further Consolidated

At present, the cost of DAA treatment for HCV in China is its lowest level ever, which means that most patients do not have to make catastrophic payments for treatment. However, hundreds of dollars of out-of-pocket payments may still be a large expense for patients in financial hardship. According to the civil affairs statistics published in 2021, 34,892,000 people in China were still living under the poverty line, and the average minimum government subsidy

is only \$75 per person per month. For type 1b HCV patients, even those who are treated with the DAAs at the lowest price level of \$200 per 3-month period, with the additional cost of genotype testing, which is not reimbursed in the basic health insurance program, the amount to be paid out-of-pocket is almost equivalent to nearly 2 months of the minimum living subsidy. Patients with HCV other than type 1b infections will encounter an even heavier financial burden of \$1500 per 3-month period [53].

Competitiveness of Domestic DAA Combinations to be Enhanced

Since 2018, although some locally developed novel DAAs have been marketed and included in health insurance programs, the DAA market in China is still dominated by the imported pan-genotype combinations. The locally developed novel DAAs can only form a potential pan-genotype combination with the core DAA (SOF), which will give it stronger market competitiveness. Although part of SOF's patent in China was challenged in 2020, the generic SOF has already been registered by a local company, the National Intellectual Property Review Committee has again initiated a re-examination of SOF's core pre-drug patent and is likely to grant patent protection accordingly [54]. This means that domestic generic SOF cannot be officially marketed and sold until the expiration of the core patent of SOF in 2028 [55–58]. In practice, the local company must market its own novel DAA by adding the generic SOF as a gift to form a pan-genotype combination. The national health insurance program must limit the indication of this DAA to a specific genotype, and not for pan-genotype therapy.

Successful International Experiences and Implications

Universal Screening, Diagnosis, and Treatment Strategies with a Public Health Approach

Mongolia has the world's highest rate of liver cancer mortality, being approximately 12-fold higher than the global average [59]. In 2016, the Government of Mongolia developed the

Hepatitis Prevention Control and Elimination Program (HPCEP) for 2016–2020 and allocated US\$96 million for implementation [60]. Supported by the public health insurance fund, Mongolia launched national free HCV screening, diagnosis, and DAA treatment [61]. The national primary care plan also included ultrasound screening of liver cancer in the basic primary health care package. Viral hepatitis screening became part of a routine prenatal screening program, including integrated screening for HIV, syphilis, and viral hepatitis, with the aim to eliminate mother-to-child transmission [62]. Mongolia has also established a viral hepatitis surveillance system which shares information with the National Cancer Registry to provide up-to-date information on patients. Mongolia is an upper-middle-income country, as is China, and made a clear political commitment, gave strong budget support, and implemented a public health strategy for disease management, which is integrated with other infectious disease elimination programs. All of these strategies provide the roadmap for China to achieve the goal of eliminating HCV.

Egypt is one of the countries with the highest burden of HCV infection in the world, and it has also integrated HCV prevention and treatment into its public health policy. In 2018, Egypt initiated a widespread screening program which covered the entire adult population (aged > 18 years) within 1 year and provided state-funded treatment to all infected individuals [61, 63]. As there is no patent protection for the core DAA (SOF) in Egypt, the locally produced SOF reduced the cost of a standard 12-week course of DAA treatment from US\$84 in 2015 to US\$54 in 2018. Egypt also purchased affordable HCV screening kits and real-time quantitative PCR assay kits, which reduced the cost of HCV screening to US\$85 and the total cost of monitoring and curing patients to US\$130 [63]. Between 2014 and 2020, over 50 million people were screened in Egypt, and four million patients were treated [64], which made Egypt potentially the first country in the world to eliminate HCV. Egypt is lower-middle-income country, and its strong political commitment and the excellent collaboration between the government and domestic pharmaceutical

companies within the framework of the public health strategy are also worthy of notice by China.

Combining strategies for increased testing, improved linkage, and universal treatment access are keys to reaching targets for the elimination of HCV. Many countries have adopted a “micro-elimination” strategy, which is a focused screening and treatment strategy in key areas and in high-risk populations to achieve local elimination of hepatitis C [65]. Adopting this strategy, the Italian Ministry of Health issued a specific decree (Decreto Milleproroghe 17.12.2020) to enable targeted HCV screening in special populations by December 2022 [66]. The Spanish prison system has developed multiple strategies to address the high burden of HCV among inmates that include high screening rates (approx. 80%) and treatment for all, this led to a drop in HCV-RNA prevalence from 11% in 2016 to 1.9% in 2019 [67]. The UK implemented the Hepatitis C Micro-Elimination Project (Springburn) in Glasgow that targeted the populations in alcohol and drug addiction rehabilitation programs falling under community-based outpatient care, 95.7% of the targeted population were screened, among which 68% were treated within 12 months [10].

Given the large population of China and the low prevalence of HCV in the general population, whole population screening may not be the most cost-effective screening strategy to adopt. A “micro-elimination” strategy that focuses on pregnant women, dialysis patients, and the vulnerable population co-infected with hepatitis B and HIV, as well as high-risk populations, such as drug users, polysexual partners, MSM, and prisoners, may be a more practical approach as an entry point for proactive screening in China [49, 68].

Overcoming the Intellectual Property Barrier with a Public Health Perspective

The Malaysian government also made a clear political commitment and integrated HCV and HIV programs to provide free HCV diagnosis and treatment to its citizens. Malaysia is an upper-middle-income country, similar to China, and has an intellectual property protection system that does not allow it to produce or

import generic SOF. Unlike Mongolia, Malaysia was initially not given a voluntary license by the patent holder of SOF to import generic SOF from its licensed Indian company. However, the treatment cost with the originator SOF was far beyond the government's financial capacity. The Malaysian government therefore used compulsory licensing as a policy tool to import affordable generic SOF from Egypt [69], which ultimately forced the patent holder to give Malaysia the license to import generic SOF from the licensed Indian companies. To achieve its purpose, the Malaysian government adopted a profound far-reaching approach to enable more options for imported generic SOF and implemented the compulsory license to import much cheaper generic SOF from Egypt. As daclatasvir was not patent-protected and its generic product was available in Malaysia, treatment cost fell from US\$11,200 to US\$30–\$35 per month. To further promote competition, Malaysia has also partnered with the Foundation for Innovative Diagnostics (FIND) and Drugs for Neglected Diseases Initiative (DNDi) to develop rapid diagnostic test kits and innovative DAAs to accelerate the expansion of free screening and DAA treatment for people who were tested positive and are subsequently diagnosed with HCV infection [56]. This has accelerated progress toward universal health coverage in the country. Neither China nor Malaysia were granted the license voluntarily. However, unlike China, which developed its own DAAs, Malaysia developed DAAs in partnership with international non-profit organizations. More importantly, Malaysia recognized the importance of the core DAA (SOF) for the development of pan-genotype DAA combinations at a very early stage and laid out the clinical studies of ravidasvir in combination formulations. Implementing compulsory licensing for government use forced the patent holders to give voluntary licenses to Malaysia. The subsequent price competition significantly reduced the treatment cost within a very short period. Furthermore, the collaborations with international non-profit organizations resulted in significant savings in the procurement cost of rapid diagnostic test kits for HCV. The multifaceted achievements of Malaysia are important

safeguards for the rapid expansion of DAA treatment [58]. Except for the same universal free testing, diagnosis, and treatment strategy as implemented in Mongolia and Egypt, Malaysia's efforts to overcome the intellectual property barriers of the core DAA (SOF) for the pan-genotype DAA combinations made its DAA market more competitive.

Simplified Management Model in an Integrated Healthcare Delivery System

Since 2016, Médecins Sans Frontières (MSF) has established a community-based simplified management model for HCV patients in Cambodia [70]. The model adopts rapid bedside diagnosis, which greatly reduces pre-treatment assessment and case follow-up, shifts many clinical tasks from physicians to nurses and pharmacists, and achieves high cure rates [71]. It is estimated that the program has provided testing for approximately 135,000 people and treatment for 18,000 patients by the end of 2020 [62].

Also, strategic planning at the national level has provided training for non-specialist physicians and nurses to strengthen laboratory capacity. In addition to MSF's exploration of an integrated healthcare delivery system based on streamlined diagnosis and management processes in Cambodia, Georgia has implemented another innovative approach to integrated screenings of hepatitis C, HIV, and tuberculosis at the primary care level [72]. Even least developed countries (LDC), such as Rwanda, have implemented a strategy of decentralized screening with free testing and treatment by nurses at the primary care level with a simplified treatment process. In Rwanda, the number of treatments increased from approximately 300 in 2015 to 25,000 by the end of 2020 [73, 74].

Some high-income countries have adopted similar integrated and more comprehensive approaches to care for HCV. Through the Managed Care Networks in Scotland, all stakeholders involved in HCV care (NHS, Health Boards, addiction centers, penitentiary system, third sector, patient associations, etc.) are actively involved and aligned. Efforts are under development to bring care closer to patients. A HCV patient registry containing information

on all diagnosed patients is leveraged to track patients, ensuring that they are treated and that their progress is monitored [75].

The above strategies of comprehensive screening and streamlined diagnosis and management procedures based on the primary care system in both middle- and low-income countries and high-income countries are illustrations of valuable experiences in providing efficient diagnosis and treatment of HCV in less developed areas of China, especially in areas with a high disease burden and limited specialist healthcare resources. However, considering that HCV treatment in China is still largely provided in speciality hospitals and that there is a lack of simplified treatment and management procedures and guidelines applicable to primary care, replicating the above experiences is still quite challenging in China. In practice, the integrated HCV prevention and treatment model has been explored in some regions of China, which has formed a closed-loop management of referral, treatment, and follow-up of patients with HCV and even included HCV in the GP services within an integrated medical service system. However, these are only practiced in a limited number of regions and need to be extended to the whole country as soon as possible.

CONCLUSIONS

To promote the achievement of the WHO goal of eliminating HCV in 2030, China has supported the research and development of DAAs for HCV with government funding based on a national strategy of pharmaceutical innovation. The priority review mechanism of the breakthrough therapeutics has greatly accelerated the market entry of DAAs. The subsequent inclusion of the national health insurance after price negotiations resulted in an approximately 20-fold reduction in treatment costs within 4 years. The innovative health insurance payment methods have abolished the reimbursement cap for outpatient care, further reducing patients' financial burden and improving the efficiency of health insurance fund utilization. These are the unique experiences and advantages of China that have played a key role in the overall

prevention and control efforts and have provided useful experiences for other countries to reduce the financial burden of HCV treatment.

Nevertheless, compared with the other middle-income countries, there is still much room for China to achieve universal free screening, diagnosis, and treatment based on the streamlined disease management procedures. A stronger role for primary care within an integrated healthcare delivery system and integration of HCV programs with other public health programs are other initiatives on which China may focus its efforts.

Considering China to be a developing country with a large population, a more practical approach to the elimination of HCV may be the "micro-elimination" strategy, with focuses screening and proactive diagnosis and treatment for vulnerable populations. At present, although the use of locally developed DAAs has challenged the monopoly position of the multinational pharmaceutical companies, continued efforts are needed to fully overcome the intellectual property barriers to SOF and to make the pan-genotype DAA combinations based on the locally developed DAAs more competitive. Meanwhile, the safety net for patients in economic hardship needs to be further strengthened. More importantly, it is necessary to promote patients' willingness to initiate and comply to standard treatment through increased awareness of HCV among the public and primary care professionals, to increase detection of hidden and missed infections, to increase diagnosis and treatment appropriately. The development of an integrated healthcare delivery system, a patient management procedure which is suitable for primary care, and full compliance of the primary care providers are also important aspects to achieve effective cascade care management.

HCV is a disease that can be cured with 3 months of oral treatment with DAA. As a country with a strong pharmaceutical research and development framework and production capacity that has undergone 10 years of health system reform, China is well-positioned to achieve the WHO goal of eliminating HCV by 2030. Further, as a developing country that carried a heavy burden of HCV, China's

successful responses may provide an example to other developing countries and have significant implications for the achievement of the global goal of HCV elimination.

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Data Availability. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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