COMMENTARY

The 8th Canadian Symposium on Hepatitis C virus: "Improving diagnosis and linkage to care"

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ABSTRACT

Hepatitis C virus (HCV) affects approximately 250,000 Canadians. Although safe and effective (>95% cure rates) antiviral therapies have become available within the past 5 years, chronic HCV infection still remains a major driver of end-stage liver disease and liver transplantation. Both the Canadian Institute for Health Research and the Public Health Agency of Canada recognize the impact of HCV-related liver diseases and support the Canadian Network for Hepatitis C (CanHepC), a National network for the scientific study of hepatitis C that organizes an annual symposium as part of its knowledge translation mandate. At the 8th Canadian Symposium on Hepatitis C Virus in May 2019, basic scientists, clinicians, epidemiologists, social scientists, and community members came together to share their work under the theme of "Improving diagnosis and linkage to care". This symposium also marked the launch of the *Blueprint to inform hepatitis C elimination efforts in Canada*, a policy framework that outlines specific targets, suggested activities, and evidence-based best practices to guide provincial, territorial and federal organizations developing their own HCV elimination strategies.

KEYWORDS: behavioural; biomedical; CanHepC; clinical; epidemiological; hepatitis C virus; people who inject drugs; public health; social sciences; viral hepatitis

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INTRODUCTION

An estimated 250,000 Canadians are living with hepatitis C virus (HCV) (Figure 1) (1,2). Within the past 5 years, safe and effective direct-acting antiviral (DAA) therapies for the treatment of chronic HCV has resulted in high (> 95%) cure rates for all genotypes, yet chronic HCV infection still remains a major driver of end-stage liver disease and a leading indication for liver transplantation in North America (3–5). Reaching the World Health Organization (WHO) targets for HCV elimination will require an 80% reduction of HCV incidence by 2030 (compared with the 2015 baseline) (6). Major challenges remain for HCV elimination efforts, including increasing HCV diagnosis and retaining people within the cascade of care in order to access curative therapy.

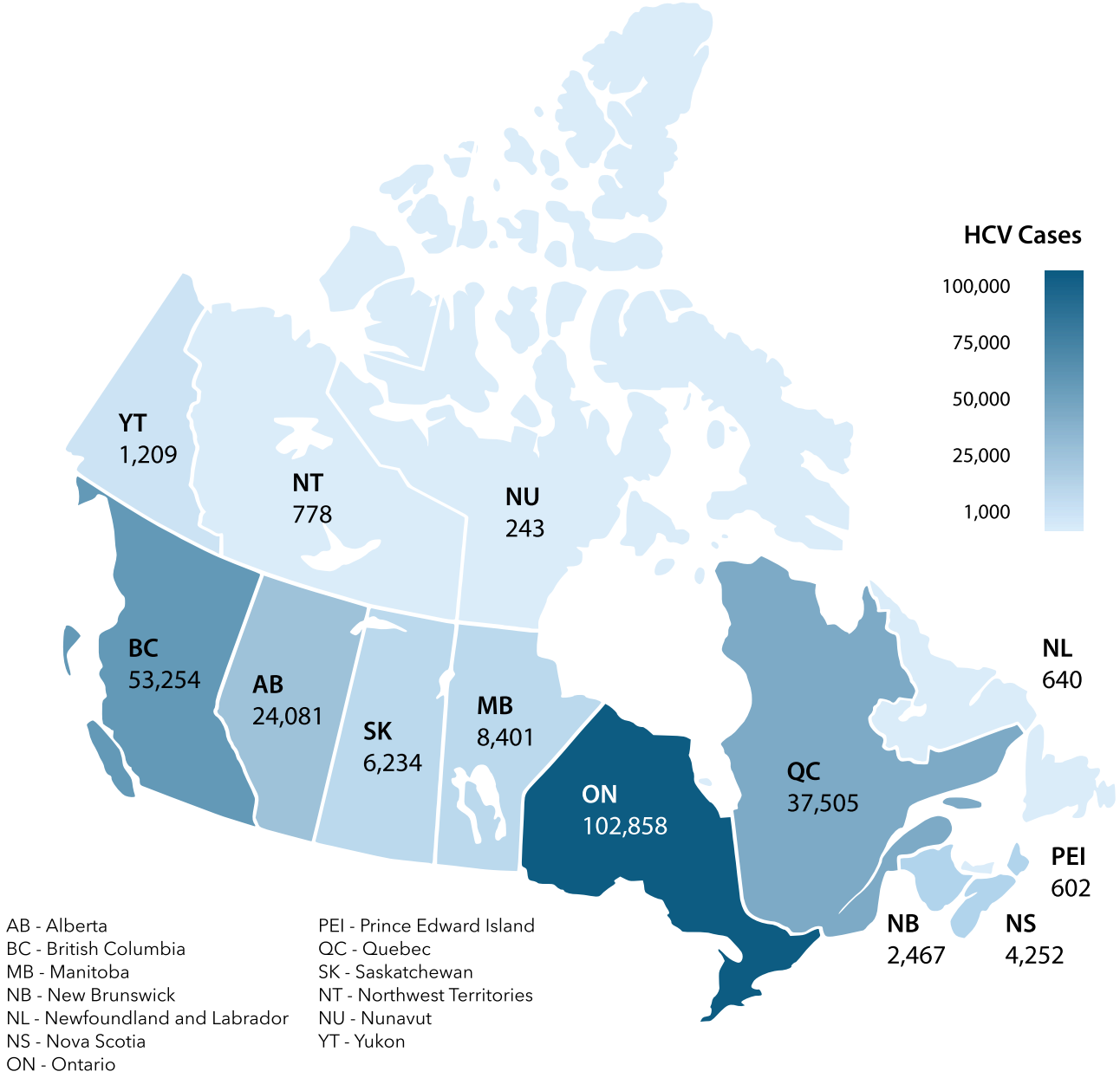

Figure 1: Provincial and territorial HCV estimates in Canada (adapted from (41)).

This commentary summarizes highlights from the 8th Canadian Symposium on Hepatitis C Virus (CSHCV), including insights into: host-virus interactions, liver biology, and liver disease risk post-DAA therapy; the effectiveness of rapid diagnostic strategies; and addressing challenges to improving HCV diagnosis rates. We also highlight the launch of the *Blueprint to inform hepatitis C elimination efforts in Canada*.

THE CANADIAN NETWORK ON HEPATITIS C (CANHEPC)

CanHepC is a National collaborative HCV research network supported by the Canadian Institutes of Health Research (CIHR), the Public Health Agency of Canada (PHAC), as well as non-governmental (e.g. Canadian Liver Foundation), industrial, private and community organizations. It was established in July 2015 to expand the successful training mandate of the pre-existing National CIHR Research Training Program in Hepatitis C (NCRTP-HepC) (2). Since 2003, NCRTP-HepC and CanHepC have supported 116 graduate and postdoctoral fellowships and 86 summer studentships. Currently, CanHepC links 69 researchers and 23 trainees whose research spans the 4 CIHR health research pillars (namely biomedical, clinical, health services, and social, cultural, environmental, and population health research), as well as 7 knowledge users from affected communities.

THE 8TH CANADIAN SYMPOSIUM ON HEPATITIS C VIRUS

For the past 8 years, NCRTP-HepC and subsequently CanHepC has organized the CSHCV to facilitate interdisciplinary HCV research and knowledge translation (2,7–11). This one-day symposium—the second joint conference between CanHepC and the Canadian Liver Meeting (CLM)—was held in Montreal on May 24th, 2019 with the theme of "Improving diagnosis: how to reach the undiagnosed population." The specific aims of the meeting were as follows:

1. To discuss approaches to increase prevention, diagnosis, treatment uptake, and expansion of care across difficult to reach populations with the goal of eliminating HCV in Canada.
2. To facilitate transdisciplinary knowledge exchange and collaborations between Canadian trainees, established researchers, healthcare practitioners, health policy makers, and community-based groups working in the field of HCV.
3. To disseminate symposium findings to support practice change, community awareness, harm reduction, and policy development.

The symposium brought together research scientists, clinicians, nurses, community health workers, patient advocates, community members, and public health officials to discuss HCV diagnosis, research, treatment and care priorities in Canada. The presentations are available on the CanHepC YouTube channel (https://www.youtube.com/channel/UCUgCySYhpXIUuqiaQS_rGJw).

Lessons learned from other hepatitis viruses and mapping the human liver microenvironment

Since the advent of highly effective DAA therapies, HCV research has shifted in focus from the biology of the virus to elucidating host-virus interactions and long-term effects of HCV infection. During the biomedical session of the symposium, presentations highlighted what has been learned—and what can still be learned—from basic research on the molecular biology of persistent hepatitis viruses and the liver microenvironment.

Dr Ralf Bartenschlager (University of Heidelberg, Heidelberg, Germany) opened the session with a reminder that there remain many open questions about the molecular biology of HCV and persistent hepatitis viruses more generally (12). He presented data that compared cellular responses with HCV and to the hepatitis delta virus (HDV) to gain insight into molecular mechanisms employed by these viruses to subvert innate antiviral responses, specifically the cellular interferon (IFN) response. Both HCV and HDV trigger the IFN response, but while HCV can be abolished by IFN therapy, HDV is insensitive to IFN. Dr Bartenschlager reported that both of these viruses are detected by a shared pathway: they are predominantly sensed by the cytosolic RNA sensor MDA5, whose signal is amplified by a related RNA sensor, LGP2 (13). However, this detection by MDA5 is not the only driver of IFN production during infection: HCV, but not HDV, is also detected by the lysosomal RNA sensor, TLR3 (14). Dr Bartenshlager's research suggests that this detection occurs during the recycling process of double-membrane vesicles, a feature of HCV infection and the site of HCV RNA replication in infected hepatocytes. These findings highlight the idea that investigations into diverse hepatitis viruses can generate novel insights that

may resolve open questions regarding the molecular biology of HCV and related hepatitis viruses.

There currently exists no therapy to reprogram a diseased liver into a healthy organ and thereby avoid the need for liver transplantation. Dr Sonya MacParland (University of Toronto, Toronto, Canada) argued that in order to target the liver, we first need to understand what makes up a healthy liver – to know what cell populations exist and their role within the liver microenvironment (15). To characterize liver cell populations at a high resolution, Dr MacParland and colleagues performed single-cell RNA sequencing (scRNA-seq) on healthy liver tissue, which were obtained from caudate lobes removed from five healthy donor livers suitable for transplantation (16). Bioinformatic clustering of the transcriptional profiles revealed 20 distinct cell populations, including several populations of hepatocytes, resident B and T cells, and endothelial cells. It also revealed two distinct populations of liver resident macrophages, corresponding to inflammatory and immunosuppressive macrophages. This data identified cell subtype-specific gene expression patterns, which can be used for immunohistochemical and/or immunofluorescent staining. In all, these transcriptomic and spatial analyses served to generate a map of the healthy human liver microenvironment. This type of data can be used as a platform to study a variety of liver diseases including HCV infection. To this end, the healthy liver scRNA-seq data is publicly available through the Human Cell Atlas program (17) and an interactive visualization tool is available at: http://shiny.baderlab.org/HumanLiverAtlas/.

Improving the HCV cascade of care from diagnosis to monitoring liver disease progression

Despite the existence of curative DAA therapy, chronic HCV infection remains a major etiological driver of end-stage liver disease complications such as decompensated liver cirrhosis and hepatocellular carcinoma (HCC). HCV infection is still the leading indication for liver transplantation in North America (4,5). Thus, the clinical research session focused on two main topics: unmet needs in liver disease progression monitoring post-DAA therapy, and strategies to expand access to therapy.

Dr Hashem El-Serag (Baylor College of Medicine, Houston, USA) opened the session by discussing the importance of HCC in the context of HCV infection (18). Compared with HCV-negative controls, patients with chronic HCV infection have a 25-fold greater relative risk of HCC, with an annual incidence ranging from 3% to 10% among patients with active HCV-induced cirrhosis. Although achieving SVR with DAA therapy leads to a considerable (50%–80%) relative HCC risk reduction over time, patients with liver cirrhosis and DAA-induced SVR still have a relatively high absolute risk of HCC (>1% per year). In contrast, HCC risk is low in almost all patients without cirrhosis, with the exception of those with advanced fibrosis. Based on this data, Dr El-Serag argued that HCC surveillance should be continued for all patients with cirrhosis or advanced fibrosis at the time of SVR. To identify patients with enhanced risk of HCC, Dr Keyur Patel (University Health Network, Toronto, Canada) presented an overview of histologic risk assessment in HCV infection (19). Although liver biopsy is still considered the gold standard for hepatic fibrosis staging, non-invasive tests (such as serum biomarker monitoring and imaging elastography) are increasingly used in clinical practice as first-line tests. While these non-invasive tests have a good diagnostic accuracy for advanced fibrosis stages, Dr Patel emphasized that these tools have limitations: they cannot reliably differentiate adjacent fibrosis stages, and they have not yet been validated for assessment of post-SVR fibrosis regression or for following patients at risk of disease progression.

People who inject drugs (PWID) represent the population with the most new cases of HCV in Canada, yet relatively few PWID engage in HCV care or initiate antiviral treatment (20). To examine the care cascade and linkage to care for PWID, studies were presented that aimed to enhance HCV treatment uptake in this population. Dr Bernadette Lettner (South Riverdale Community Health Centre, Toronto, Canada) evaluated the feasibility of rapid (<1 hour), point-of-care HCV RNA testing and subsequent linkage to care among PWID attending a supervised injection/consumption service in Toronto (21). Of the 112 PWID from whom a valid HCV RNA test was obtained, 41% were HCV positive. Among the clients who tested positive, there was high interest in progressing into the cascade of care with antiviral treatment. Similarly, Dr Shawn Greenan (Health PEI, Halifax, Canada) evaluated the impact of rapid, same-day access to HCV treatment for treatment-naïve vulnerable populations in Prince Edward Island (22). Out of 122 patients on opioid agonist therapy (OAT) or PWID initially referred to this study, 71 initiated treatment and 58

achieved SVR at the time of this presentation. Importantly, individuals who had difficulty attending appointments for OAT before HCV treatment had improved attendance after HCV treatment initiation. Taken together, these studies demonstrate the potential of combining point-of-care testing with immediate linkage to care to enhance HCV treatment uptake among PWID.

Panel discussion: Engaging people with lived experience to improve hepatitis C diagnosis and linkage to care in programming and research

Representatives from Saskatchewan, Québec, and Ontario engaged in a panel discussion examining how people with lived experience of drug use and HCV have unique and valuable expertise, which is an asset to both staff and clients of harm reduction programs. As Dr Barb Bowditch (Access Place, Prince Albert) and Magali Boudon (Dopamine, Montréal) emphasized, both drug use and HCV infection carry a heavy stigma; people with lived experience are in a unique position to avoid prejudice, stereotyping and judgement as they act as a supportive bridge between care providers and clients. By treating clients as a whole person rather than as a disease, and by using proper language and respect, peer workers can decrease clients' perception of being infantilized as they access care. This work is a key component of harm reduction initiatives—and consequently, Martin Pagé (Dopamine, Montréal) argued it is critical that the employees with lived experience who perform this physically and emotionally demanding job be appropriately compensated. Furthermore, as Kate Mason (South Riverdale Community Health Centre, Toronto) remarked, the stigma surrounding drug usage poses a substantial barrier for employment, making job opportunities for individuals with lived experiences in harm reduction services even more important.

Disruptive innovations in HCV diagnostics

Diagnosis is the first step of the HCV care cascade, and therefore the rate limiting step in elimination campaigns (Figure 2) (23). Presentations of the social, cultural, environmental, and population health research session explained the potential of innovative approaches to surmount technological and social barriers to HCV diagnosis.

Dr Stuart Ray (Johns Hopkins University School of Medicine, Baltimore, USA) began this session with a discussion of HCV diagnostic methods (23). Screening begins with testing for antibodies against HCV, primarily due to cost constraints (24). However, approximately 30% of people with HCV antibodies do not have active HCV infections, either due to spontaneous clearance or to successful treatment. As elimination campaigns progress, the proportion of antibody-positive but HCV-negative cases will likely rise. Numerous studies

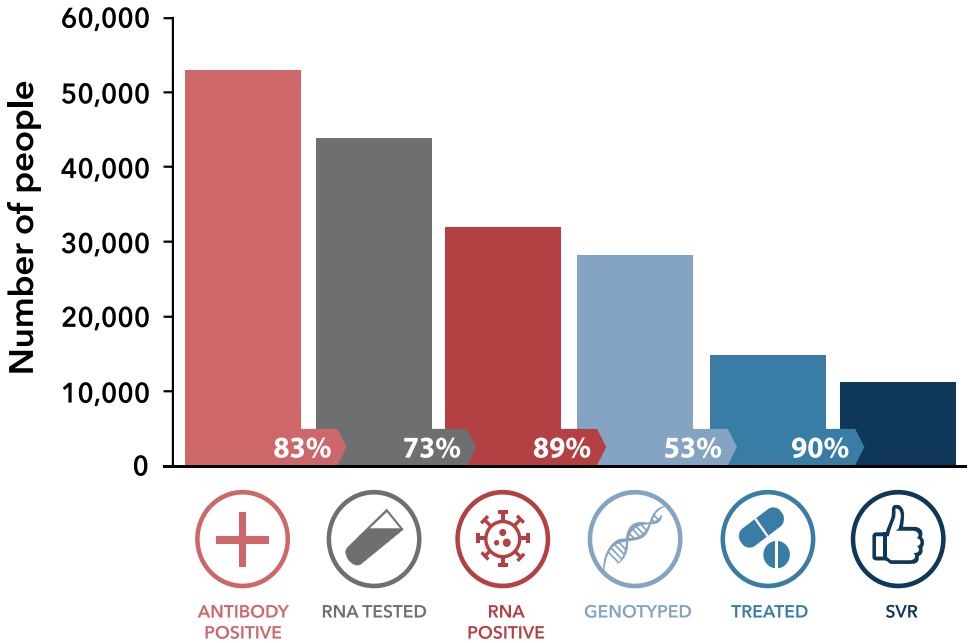

Figure 2: The British Columbia HCV cascade of care (adapted from (26,41)).

worldwide have identified gaps in the HCV care cascade between antibody testing and confirmatory viral RNA testing (25–28). Closing this gap will thus require Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment-free and Deliverable to end-users (ASSURED) diagnostics for HCV (29). While current RNA tests have limits of detection as low as 20 IU/mL, this sensitivity is not necessary for widescale screening purposes, since HCV typically displays a high level of viremia (99.8% of chronically-infected individuals have HCV RNA > 1000 IU/mL) (30). To optimize HCV elimination, inexpensive tests for HCV (such as HCV core antigen testing and qualitative RNA testing) should replace high barrier HCV diagnostics. However, this will require advocacy for people who influence guidelines to change the status quo.

Dr John Kim (Chief of the National Laboratory for HIV Reference Services at the National Microbiology Laboratory, Winnipeg, Canada) extended the discussion on HCV diagnostics by specifically addressing the barriers to HCV testing among people of First Nations (31). These barriers include: 1) proximity to health services; 2) patient perceived stigma; and 3) widespread racism. Dr Kim emphasized the need to revolutionize diagnostic testing by "disruptive innovations"—an innovation that creates a new market and eventually disrupts an existing market by displacing established products (32). He spoke of his recent engagement with several First Nations communities to increase testing opportunities for blood-borne infections using dried blood spot testing. This type of testing fulfills an unmet need, specifically among Indigenous populations across Canada, as the procedure is simple, inexpensive, and can be performed by anyone. He presented work that uses novel models of engagement and ownership to ensure community uptake, which includes Chief/council approval and training of local healthcare workers in the collection of dried blood spot tests. The goal of this model is to address empowerment, stigma, racism, and reduce health inequities associated with inadequate access to HCV testing.

Targeted screening strategies to increase HCV diagnosis

The main theme of the Health Services session revolved around cost-effective approaches to increase rates of HCV diagnosis to meet the WHO's elimination targets, such as by developing targeted HCV screening strategies. Dr Jagpreet Chhatwal (Harvard Medical School, Boston, USA) opened the session with a warning that the rising HCV incidence rates driven by the opioid epidemic will be an added challenge to HCV elimination (33). Model-based projections using data from the United States suggest that even the expansion of current HCV screening efforts to universal screening as well as the removal of all treatment restrictions would only result in cure rates of ~62% by 2030, substantially below the WHO's elimination target of 80% (34). Without additional interventions such as outreach activities that focus on improving annual screening rates, meeting the WHO targets is highly unlikely (35). Furthermore, while HCV treatment is cost-effective over the long term, the high costs of diagnosis and treatment continue to pose a significant barrier to accessing therapy (35). In certain high-prevalence countries such as Pakistan, the cost of HCV testing is greater than that of DAA therapy; thus, to meet elimination goals, there is a need for innovative approaches to lower testing costs (36). Without additional outreach activities to improve screening rates, the availability of cheaper diagnostics alone will not be sufficient to meet the HCV elimination targets (35).

As for how to improve screening rates, Dr Camelia Capraru (Toronto Centre for Liver Disease/VIRCAN, University Health Network, Toronto, Canada) compared HCV screening strategies implemented in three different settings: emergency departments, medical walk-in clinics, and community outreach programs (37). Screening efforts in settings with higher HCV prevalence (such as emergency departments and targeted outreach programs) resulted in higher diagnostic yields and linkage to care. The topic of outreach activities for high-risk groups also emerged as Dr Christina Greenaway (McGill University, Montreal, Canada) spoke about HCV testing and linkage to care strategies among Canadian immigrants (38). In Canada, approximately one-third of foreign-born individuals come from countries with a high or intermediate HCV prevalence, and these patients often face delays in diagnosis and barriers in accessing care (39). Developing optimal strategies to engage with this heterogeneous group therefore needs more attention, since increased engagement through community-based organizations with linguistically and culturally appropriate outreach activities could help improve HCV diagnosis.

LAUNCH OF THE BLUEPRINT TO INFORM HEPATITIS C ELIMINATION EFFORTS IN CANADA

To conclude the 8th CSHCV, Dr Jordan Feld (Toronto General Hospital, Toronto, Canada) presented the *Blueprint to inform hepatitis C elimination efforts in Canada*, a policy framework developed by CanHepC to guide strategies and measure progress towards the elimination of HCV as a public health threat in Canada (40).

In 2016, the Canadian government endorsed the World Health Organization's global HCV elimination targets by 2030. Yet, as a country, we are currently not on track to reach these targets, despite effective prevention strategies, simple diagnostic methods and the arrival of highly effective and safe treatments against HCV.

Recognizing that the HCV context and response varies across different regions of the country, CanHepC, with the help of several partners (CATIE, Prisoners HIV/AIDS Support Action Network, Action Hepatitis Canada, Canadian Liver Foundation, Canadian Aboriginal AIDS Network and more), developed the *Blueprint* to provide guidance to provinces and territories as they establish their own action plans to eliminate HCV. This document was shaped by a writing committee and four working groups that comprised Canada's leading researchers, clinicians, and community representatives of priority populations (including people with lived experience), through an extensive bilingual consultation process that started at the 7th Canadian Symposium on HCV in 2018.

The *Blueprint* is designed to complement the *Pan-Canadian Framework for Action to Reduce the Impact of Sexually Transmitted and Blood-borne Infections (STBBI)* and is structured around its main pillars: prevention, testing and diagnosis, care, and treatment—each linked to objectives and time-bound, measurable targets (Table 1). Every pillar outlines research gaps to address good practices and suggested activities to help reach its targets, as well as indicators and metrics to monitor progress towards these goals. A fourth pillar is entirely dedicated to addressing the specific needs of the Priority populations most affected by HCV, with tailored recommendations and considerations that are also integrated into the three other pillars. The *Blueprint* includes specific recommendations to decrease HCV-related stigma, and further outlines the surveillance systems that should be implemented or strengthened to close our gaps in knowledge about Canada's HCV epidemic. Finally, overarching recommendations actionable at the federal level are also summarized.

The session ended with a panel engaging *Blueprint* Writing Committee members Julie Bruneau (Université de Montréal, Montreal, Canada), Melisa Dickie (CATIE, Toronto, Canada), Lindsay Jennings (Prisoners HIV/AIDS Support Action Network), Marina Klein (McGill University, Montreal, Canada) and Mel Krajden (University of British Columbia, Vancouver, Canada), to discuss the next steps and challenges facing the development of action plans in different regions of the country. One emerging priority is the need for a forum convening national, provincial and territorial stakeholders where progress, good practices, lessons learned, successes, and challenges can be shared. Further, as stressed by Jordan Feld, this is only the beginning of a critical endeavour in Canada to put the blueprint into action, impact clinical practice and policy, and achieve the WHO HCV elimination targets.

OUTCOMES OF THE 8TH CSHCV

The 8th CSHCV was an interdisciplinary meeting of scientists, clinicians, trainees, policy makers, and affected community members under the theme of "Improving diagnosis and linkage to care." The biomedical research session presentations described novel resources to facilitate future studies of viral hepatitis and liver biology, which may be useful to answer the open questions in HCV-induced liver disease progression discussed during the clinical research session. Clinical research presentations demonstrated the potential of combining point-of-care HCV testing with immediate linkage to care, a strategy that would benefit from the rapid, robust, and affordable diagnostic tools addressed during the social, cultural, environmental and population health research session. The health systems research session underscored the need for targeted and culturally appropriate screening efforts in order to reach the not-yet-diagnosed. Finally, the symposium marked the launch of the *Blueprint to inform hepatitis C elimination efforts in Canada*, a policy framework to help guide provinces and territories to develop their own tailored action plans to eliminate HCV—a document built on the foundation laid by previous symposia. Eliminating HCV as a public health threat in Canada in the next decade is an ambitious

Table 1: The *Blueprint*'s objectives and targets (adapted from (41)).

OBJECTIVES	2025 TARGETS	2030 TARGETS
Hepatitis C virus (HCV) prevention		
Reduce new HCV infections	**80%** ↓ incidence *	**80%** ↓ incidence*
Increase the number of sterile needles and syringes provided per person who injects drugs (PWID) per year	**500** sterile needles/syringes	**750** sterile needles/syringes
Increase the number of PWID accessing opioid agonist therapy (OAT)	**40%** of PWID receive OAT	≥40% of PWID receive OAT†
HCV testing and diagnosis		
Increase the number of people living with HCV who have been diagnosed	**70%** of people living with HCV have been diagnosed, all with confirmation of active infection	**90%** of people living with HCV have been diagnosed, all with confirmation of active infection
Increase the number of people with a positive HCV antibody test who receive testing for active HCV infection (e.g. HCV RNA)	**90%** of people with a positive antibody test have received HCV RNA testing	**100%** of people with a positive antibody test have received HCV RNA testing
HCV care and treatment		
Increase the number of people diagnosed with HCV who are linked to care, treatment and ongoing support	**50%** linked to a provider who is familiar with HCV	**90%** linked to a provider who is familiar with HCV
Increase the number of people with HCV who are initiating DAA treatment	**50%** of those living with HCV have initiated DAA treatment	**80%** of those living with HCV have initiated DAA treatment
Ensure high treatment completion rates and documentation of sustained virologic response (SVR)	**95%** treatment completion with 85% documentation of SVR	**95%** treatment completion with 85% documentation of SVR
Reduce HCV prevalence	**50%** ↓*	**90%** ↓*
Reduce HCV-related liver transplantation	**30%** ↓*	**65%** ↓*
Reduce HCV-related mortality	**30%** ↓*	**65%** ↓*

** compared with 2015;*
† Target to be revised according to mathematical modelling studies.

goal – but one that can be made possible by safe and effective antiviral therapies, simple diagnostic methods, effective prevention strategies, and by continuing to share insights across research disciplines to inform policy.

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