

A Canadian screening program for hepatitis C: Is now the time?

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Hepatitis C virus (HCV) infection causes more lost years of life and illness than any other infectious disease in Ontario, and likely in Canada.¹ It is the leading indication for liver transplantation, and HCV-related morbidity and mortality is projected to rise until 2027, with staggering economic costs.² Infected individuals often remain entirely asymptomatic until liver damage is advanced; they typically present only when symptoms from decompensated cirrhosis or liver cancer develop. However, unlike most chronic viral infections, HCV infection is curable. Successful treatment leads to viral eradication, halting the progression of liver disease and decreasing all-cause mortality.³ Thus, there is a clear rationale to identify and treat HCV infections during the asymptomatic phase. Last year, the United States changed their national policy on HCV screening and, more recently, the Canadian Liver Foundation issued a position statement advocating for birth-cohort screening in Canada.⁴ Here we review many of the issues involved in developing and implementing a national screening program for HCV infection in Canada.

What is the rate of HCV infection in Canada?

In the US, the prevalence of HCV infection is 1.6%; however, it is 3.6% among the “baby boomer” cohort (born 1945–1965), who account for 75% of national cases.^{5,6} The US data are derived from the National Health and Nutrition Examination Survey, which prospectively tests sentinel populations for HCV, providing robust population-level data. Based on these data and their own cost-effectiveness analysis, the Centers for Disease Control and Prevention (CDC) recommends routine screening of all baby boomers for HCV, in addition to screening based on risk factors.⁷

In Canada, less is known about the prevalence of HCV infection. The Public Health Agency of

Canada (PHAC) estimates that about 250 000 Canadians, or 0.8% of the population, are infected with HCV. This estimate is based on mathematical modelling of the prevalence in at-risk populations coupled with the estimated number of people in each group.² British Columbia has collected the most comprehensive Canadian data and estimates that 1.5% of Canadians are infected with HCV.⁸ These data raise the question of whether the modelling approach used by PHAC has led to an underestimation of the prevalence for 2 reasons. First, the prevalence estimated by PHAC for BC was only 1.2%. Second, and more importantly, the prevalence in the rest of the country would have to be less than half that in BC, or about 0.7%, which seems unlikely.⁸ Studies including samples from the Canadian population as a whole are limited in both size and design, but these studies have estimated the prevalence to be between 0.5% and 2.8%.^{9,10} Clearly, more robust population-based data at the national level are needed to guide Canadian policy decisions.

Are Canadian data accurate?

Even more important than the prevalence of HCV infection is the prevalence of undiagnosed infections. Using the number of positive test results (192 225) and the estimated number of Canadians with HCV infection (242 521), PHAC reported in 2007 that 50 296 (21%) individuals with HCV remain undiagnosed.² This estimate is

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KEY POINTS

- Hepatitis C virus (HCV) infection has an enormous impact on population health in Canada and is likely underdiagnosed.
- A national strategy to screen for and treat HCV infections would substantially reduce HCV-related morbidity and mortality.
- Birth-cohort screening of people born between 1945 and 1975 coupled with a strategy for follow-up treatment and education is probably the best method to identify and provide care to affected people in Canada.
- Population-level data on the prevalence and health impact of HCV infection are needed in Canada.

markedly lower than in countries with active surveillance programs for HCV, and, if correct, would place Canada among the top countries in the world at diagnosing HCV infections despite not having a national screening program. The CDC estimates that 63% of Americans with HCV are unaware of their infection,⁷ and underdiagnosis is highly prevalent even among people with insurance and access to care.¹¹ Data from Europe show a similar pattern. Before introducing an intensive national program, 75% of infected individuals in France were unaware of their infection; after introduction of this program, the rate decreased to 44%.¹² Given that it took a major national effort in France to get the diagnosis rate to 56%, it seems unlikely that Canada's estimate that 79% of infected individuals are aware of their diagnosis is correct.

The Canadian data may be inaccurate for 2 major reasons. First, diagnosed cases may have been inadvertently counted more than once. Second, and more importantly, the overall prevalence may be considerably higher than estimated, particularly because groups at high risk of HCV infection are often undersampled. With the same number of positive test results, a higher prevalence would lead to a lower diagnosis rate. If Canadian data are similar to those in countries with comparable health care systems (e.g., France), the rate of underdiagnosis is likely much higher than 21%, and strategies to decrease this rate are needed.

What are the benefits and risks of screening?

Hepatitis C virus meets the criteria for a condition for which screening specific populations is potentially useful. There are many benefits: HCV is a major cause of morbidity and mortality; the prevalence of HCV is increased among baby boomers; many individuals are unaware that they are infected; and HCV infection is curable, with early intervention leading to improved overall health outcomes. Patients whose infection has been eradicated before cirrhosis develops have a life expectancy similar to that of uninfected people.¹³ If cirrhosis develops before treatment, viral eradication eliminates the risk of liver failure and markedly reduces the risk of hepatocellular cancer.^{3,13}

There are potential risks associated with screening, including individuals feeling stigmatized by being "targeted," false positive results and a lack of capacity to treat the volume of newly diagnosed cases. The potential psychological harms of screening can be mitigated with

pretest counselling and by developing systems to manage newly diagnosed cases. The CDC argues that even for patients who cannot access treatment, identification of HCV infection has potential adjunct health benefits, including receiving alcohol counselling and vaccinations.¹⁴ In considering their recommendations, the CDC used the widely accepted GRADE (Grading of Recommendations, Assessment, Development and Evaluations; www.gradeworkinggroup.org) criteria to weigh the benefits and risks of a screening intervention; the CDC found that the benefits significantly outweigh the potential harms.¹⁴

Who should be screened?

To maximize the information obtained by screening, populations with a potentially high burden of disease and a low current rate of diagnosis should be targeted. Using such rationale, the CDC identified people born between 1945 and 1965 as an ideal population for routine screening. Based on PHAC modelling, the prevalence of HCV infection in this age group is estimated to be 1.3%, accounting for 58% of all HCV infections.² If people born up to 1970 are included, up to 69% of infections would be captured, and extending the age group to include those born up to 1975 would capture 77% of infected individuals; this is the basis for the Canadian Liver Foundation's recommendation to screen people born between 1945 and 1975.^{2,4}

To date, Canada has advocated for the risk-factor-based screening of 2 groups: people who engage in risk behaviours or have potential exposures to HCV; and those with clinical signs or symptoms that suggest HCV infection.¹⁵ There are no data on the effectiveness of this strategy in Canada. Unfortunately, data from other jurisdictions suggest that risk-factor-based screening is largely unsuccessful for many reasons.¹⁶ Primary care providers may be unaware of the risk factors for HCV infection, or they do not have time or knowledge to provide counselling,^{17,18} and patients may underreport risk behaviours. Hepatitis C virus is still found in screened blood from Canadian blood donors, despite donors being asked about risk factors before donation.¹⁹

Targeting immigrants from endemic countries for screening is likely effective, but this idea has met with resistance because of concerns about stigmatization and possible effects on immigration decisions.²⁰

Many patients with HCV infection have no identifiable risk factors. Any strategy to broaden screening should not replace risk-factor-based

screening, but should augment it because incident infections commonly occur among people with recognized risk factors such as injection drug use.

At the population level, birth-cohort screening (1945–1975) is likely the best strategy in Canada. A recent survey by the Canadian Liver Foundation reported that, despite this group having the highest prevalence of HCV infection, people born between 1945 and 1965 are the least likely to have been tested for HCV.²¹ Birth-cohort screening would thus capture a large proportion of undiagnosed cases, is easy to implement via clinical decision-support modules within electronic medical records, and aligns with existing age-based screening programs.

Birth-cohort screening is also cost-effective. Two detailed economic analyses of birth-cohort screening compared with risk-based screening in the US found that birth-cohort screening was cost-effective, with incremental cost-effectiveness ratios of US\$35 700 and \$37 700 per quality-adjusted life-year gained; these estimates are similar to those for mammography screening for breast cancer among women over age 50 (incremental cost-effectiveness ratio US\$35 500).^{7,22,23} It would certainly be helpful to apply Canadian cost data to formally evaluate birth-cohort screening for HCV, but given the lower treatment costs and universal access to care for those with end-stage liver disease, it is likely to be even more cost-effective.

Which screening test should be performed?

In current clinical practice, screening is performed by use of a third-generation enzyme-linked immunosorbent assay for antibodies to HCV. This test has high sensitivity (97.2%–100%) and specificity (> 99%);^{24,25} however, a positive result indicates only exposure to the virus. Up to 30% of people spontaneously clear HCV within 6 months of infection.²⁶ To document active infection, patients must have evidence of HCV viremia. Thus, reflex confirmatory testing to document viremia for all first-time positive antibody tests should be considered. Although this would add cost and require coordination in the laboratory, the potential benefits include fewer referrals to specialists and reduced anxiety for those with spontaneously resolved infection.

Screening for HCV RNA as an initial test would be too costly, and using alanine aminotransferase alone would miss 35%–50% of cases.²⁷ Other tests that document active infec-

tion, such as HCV core antigen testing, could be explored, but reduced sensitivity may render them inadequate.²⁸

How will we care for all the individuals identified by HCV screening?

Before adopting wide-scale screening, we must have a plan in place to care for infected individuals. This plan should include an effort to improve education about the condition across health professions and to provide universal access to emerging treatments.

Current HCV therapy is not universally effective and is usually prescribed only by specialists. Treatment is costly (Can\$65 000 per complete course), cures about 65%–70% of cases, involves weekly injections, and is resource-intensive and difficult to tolerate.²⁹ However, HCV treatment is rapidly evolving. The first direct-acting antiviral agents for HCV, boceprevir and telaprevir, are approved in Canada, and many other agents are in late-phase testing. It is probable that within 3–5 years, well-tolerated oral treatments with cure rates above 90% will be available.³⁰

Although treatment today requires specialized oversight, treatment in the future may not. Thus, any screening program should be coupled with education and support to enable primary care providers to treat HCV infection. Beginning now is sensible, so that we will be ready to expand access to care as soon as new treatments are available. It will be critical that new agents are approved and the costs are reimbursed in a timely manner so that the increased rates of diagnosis translate to improved health outcomes.

Can we afford population screening?

Screening populations is expensive. A properly executed birth-cohort screening program will be more expensive than risk-based screening in the short term, but it will reduce morbidity and mortality in the long-term, thereby saving future HCV-related costs. In the US, it is estimated that over 15 000 liver transplants and nearly 121 000 deaths will be prevented by birth-cohort screening.¹⁴ Although treatment for HCV infection is expensive, the cost of not screening and instead managing end-stage liver disease and liver cancer with transplantation and other treatments is likely to be even higher. The CDC's analysis found that HCV screening was cost-effective

based on standard “willingness to pay” thresholds for the cost per life-year saved.⁷ Overall, it is probable that birth-cohort screening will be more cost-effective in Canada than in the US; however, we must also perform budget-impact analysis to determine whether our health care system can afford to adopt such a policy.

Conclusion

Hepatitis C virus is a major public health problem. Fortunately, treatment is improving. Unfortunately, the lack of robust Canadian data about the prevalence of HCV infection limits our ability to draw strong conclusions about the best screening policy; however, it is likely that the currently reported prevalence and diagnosis rates are underestimates. If we assume that the true Canadian data mirror those in countries with similar health care systems, birth-cohort screening would be a good policy. Canada should follow the lead of the US and begin birth-cohort screening for HCV infection, even if only to collect the data that we need to determine whether we should be screening at all.

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