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## Commentary

# Screening for Hepatitis C Virus: How Universal Is Universal?



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### ABSTRACT

In March and April of 2020, public health authorities issued major updates to screening recommendations for hepatitis C virus infection. With the rise in cases driven by injection drug use coupled with access to highly effective therapies promising a cure, all adults aged  $\geq 18$  years should receive one-time hepatitis C virus antibody screening in any health care setting. Although the recommendation is dubbed “universal,” this commentary reviews the details of the recommendations and discusses the high-risk populations not entirely captured with these changes. (*Clin Ther.* 2020;42:1434–1441) © 2020 Elsevier Inc.

**Key words:** baby boomers, hepatitis C virus, injection drug use, pregnant women, screening, young adults.

### INTRODUCTION

With the world's attention being focused on the ongoing coronavirus disease 2019 pandemic, a recent public health policy update has received little attention. In March and April of 2020, public health agencies recommended major changes in our national approach to screening for hepatitis C virus (HCV) infection. The US Preventive Services Task Force (USPSTF) and the Centers for Disease Control and Prevention (CDC) now recommend that all adults aged  $>18$  years should be screened at least once for HCV infection.<sup>1,2</sup> There are subtle differences in the policies, which are reviewed later in the article, but this change has long been advocated for by many in the HCV field due to tremendous changes in the epidemiology and treatment of HCV that have occurred in the last 10–15 years.

The present article reviews the prior HCV screening policies, the changes in HCV epidemiology that rendered that strategy ineffective, the new recommended screening strategy, and what gaps still exist in our public health policy toward eradicating HCV.

### THE PRIOR POLICY

In 2012, the USPSTF issued HCV screening guidance that recommended “age-based” universal screening for all adults born between 1945 and 1965.<sup>3</sup> This recommendation was prompted by the high HCV seroprevalence among these “baby boomers” and the poor performance of the prior policy, which focused on assessment of risk factors to prompt the need for HCV screening.<sup>4,5</sup> By changing to universal screening of this age cohort, many thousands of cases of cirrhosis and liver cancer were predicted to be prevented with appropriate subsequent therapy.<sup>3</sup> This change in strategy did not affect the recommendations for all other age groups, which still emphasized an attempt to assess for established risk factors for HCV (receipt of blood transfusion or organ/tissue transplant before 1992; infants born to mothers with known HCV infection).

What was the impact of this policy change? In short, it offered great progress in identifying more people with undiagnosed HCV.<sup>6</sup> Like any recommendation, it has taken persistent efforts to align actual practice with the desired outcome. As the advances in treatment options discussed in this article were introduced incrementally after the age-based

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screening recommendations, public health efforts in the years focused on improving screening rates and referring patients for prompt treatment.

## HOW DID THINGS CHANGE BETWEEN 2012 AND 2020?

Two major changes in the world of HCV created the urgency for modifying our screening strategy: (1) dramatic increases in cases associated with injection drug use; and (2) highly effective antiviral therapy became available that offered the promise of cure from HCV in the vast majority of patients.

### MAJOR CHANGES IN HCV EPIDEMIOLOGY

As the decade of the 2010s progressed, there was an increasing recognition of the overwhelming opioid epidemic that swept across much of the United States.<sup>7,8</sup> Many stories of overdose deaths, particularly in rural communities, received widespread media attention. A widely publicized outbreak of HIV in Indiana brought the problem of infectious disease outbreak to the forefront of public consciousness.<sup>9</sup> With the injection drug use epidemic came an associated rise in HCV cases, primarily in adolescents and young adults.<sup>10,11</sup> State after state reported major changes in the patient populations they were seeing with newly diagnosed HCV: primarily young adults in nonurban communities.<sup>10,12,13</sup> One paper from the CDC predicted an expected surge in HCV based on these trends in cases, a prediction that has proven to be frighteningly accurate.<sup>11</sup> Appalachian states were identified as an epicenter for HCV cases associated with injection drug use, but the increase in HCV cases was observed across the United States in virtually all regions of the country.<sup>10</sup> These young adults with HCV posed many public health challenges that became increasingly apparent: they usually did not access health care until an actual overdose occurred or when seeking treatment for their addiction; these young adults included women of childbearing age, who were now delivering a whole birth cohort of infants exposed to HCV; and based on their age, they were screened based on their risk factors, which was already known to miss cases.<sup>14,15</sup> To address some of the shortcomings of the existing screening recommendations, some states severely affected (eg, Kentucky) passed their own

laws requiring universal HCV screening for pregnant women.<sup>16</sup>

These shifts in epidemiology exposed the flaws of the age-based screening strategy for HCV. One study examined the rates and/or cases of HCV reported by state public health agencies and compared young adults with baby boomers.<sup>17</sup> The study showed that in several states such as Pennsylvania and Ohio, the estimated HCV rate in young adults surpassed those seen in baby boomers. In several more states such as Connecticut and Wisconsin, the rates were equal between the 2 groups. In several of the most populous states such as California, New York, and Florida, the HCV rate was still higher in baby boomers, but the rate in young adults was rising rapidly. These changes resulted in a bimodal distribution of HCV cases across the age spectrum with a peak in young adults and a peak in baby boomers (figure).<sup>18</sup> The 2012 screening strategy recommended universal screening for one age group peak (“baby boomers,” black box) and risk-based screening for the other peak group in young adults (gray box). It is an important caveat that the figures for the young adults from these state surveys resulted from risk-based screening or from those with acute symptoms of hepatitis, and thus the alarmingly high rates are likely to be an underestimate of the true prevalence in this population. If risk-based screening was previously abandoned in baby boomers because of the concern for missed cases, then with an equal HCV burden, risk-based screening should also be abandoned when screening young adults.

### HIGHLY EFFECTIVE HCV ANTIVIRAL THERAPY

The other major change that occurred initially in 2011 and on through the rest of the decade was the revolution in HCV treatments that offered the promise of cure for virtually all patients. Boceprevir and telaprevir were the initial direct-acting antiviral (DAA) options for HCV; these protease inhibitor drugs were additions to the existing interferon and ribavirin regimens.<sup>19,20</sup> Although these drugs increased response rates considerably, they were limited due to restricted genotype activity, significant side effects and drug interactions, and unwieldy monitoring and stopping rules.<sup>21</sup> The major advance came with sofosbuvir, the first HCV polymerase inhibitor, which allowed for the first successful regimens that did not require interferon.<sup>22,23</sup> With

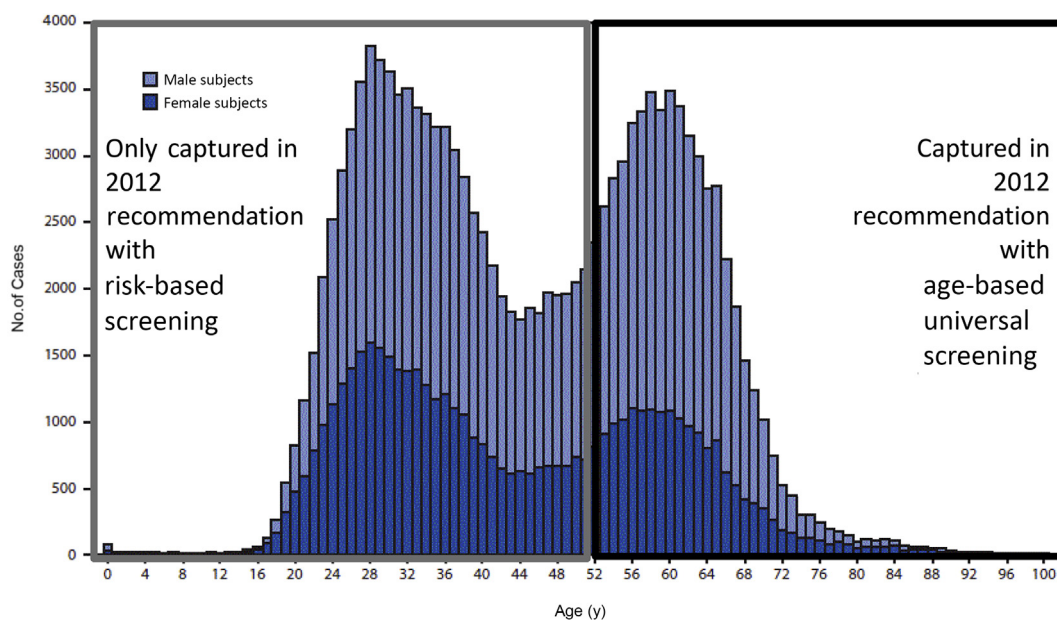


Figure. Data from the Centers for Disease Control and Prevention showing the age distribution of newly identified cases of hepatitis C virus (HCV) from 2018 and the two peaks: one in “baby boomers” and one in younger adults. The outer black box shows that for those individuals born from 1945 to 1965 (ie, the baby boomers), they would be captured in the age-based universal screening. The outer gray box shows that for those individuals in the young adult group, they would be captured by using a risk-based screening strategy. Adapted from Suryaprasad et al.<sup>18</sup>

the addition of drugs that targeted 3 major HCV targets (NS3 protease, HN5b polymerase, and NS5a replication co-factor) and with activity against all the known HCV genotypes (pan genotypes), cure for the majority of patients with HCV infection was now the rule.<sup>24–26</sup> These regimens were oral, once-daily, offered few side effects, and only needed to be given for 8–12 weeks. Although the initial price point for a treatment regimen was more than \$160,000, over time and with increased competition, the prevailing price in 2020 is approximately \$26,000.<sup>27,28</sup>

With the availability of HCV treatment regimens that could cure virtually every patient and a declining cost of treatment, the discussions of HCV public health strategy started to focus on the concept of “microelimination.”<sup>29</sup> The goal of microelimination is to increase the number of patients within various small groups who get tested for HCV, and to promptly refer those individuals who test positive for treatment and subsequent cure. When enough of the individuals in a group are treated and cured in these

small groups, HCV transmission ends, and the virus is eradicated in that group. When a society can achieve microelimination in enough groups, this will eventually lead to eradication across an entire population. This principle is the foundation of the World Health Organization's “Global Health Sector Strategy on Viral Hepatitis 2016–2021” plan, and certain countries (Iceland, Australia, and Egypt) have made tremendous strides in reducing the burden of HCV in their respective populations by widespread access to DAA agents.<sup>30–33</sup> The fundamental need in any eradication strategy is widespread access to HCV testing and reaching as many individuals as possible who can be entered into treatment programs.

With these 2 big changes in the field of HCV, it became clear that the existing screening strategy needed to change accordingly. Proponents for universal screening of all adults began to write about the need to abandon the hybrid risk-based/age-cohort strategy for one that included all adults, including pregnant women.<sup>14,34</sup> Studies found that these

strategies were highly cost-effective when coupled with DAA therapy to cure those patients identified with HCV infection.<sup>35–40</sup> These calls to action led to task forces and subgroups meeting to review how and when the shift in strategy would take place. These discussions ultimately led to the 2 new versions recommending universal screening that were published in the spring of 2020.

### THE NEW RECOMMENDATIONS FOR UNIVERSAL HCV SCREENING

As mentioned previously, both the USPTSF and the CDC issued their recommendations for screening all adults for HCV.<sup>12</sup> Although the spirit of the recommendations is very similar, there are some subtle differences in the guidance that warrant discussion. The USPSTF recommends one-time HCV screening for all adults ages 18–79 years, with pregnant women included in that recommendation.<sup>1</sup> This guidance addresses the shortcomings of the old screening strategy, but the CDC recommendations go a bit further. The CDC guidance does not have an upper age limit and includes those aged >79 years.<sup>2</sup> Although some data suggest that HCV for those in their eighth decade was a population being missed, one would surmise this was an issue of equity and not making any assumptions about any one group.<sup>41</sup> The other most substantial difference is the CDC-recommended screening of pregnant women with each pregnancy, beyond the one-time screening for all other adults.<sup>2</sup> One likely rationale would be risk of subsequent exposure after a first pregnancy. The narrative that accompanies the recommendations does mention this as a concern and cites an internal CDC modeling study that showed cost-effectiveness for HCV screening with each pregnancy.<sup>42</sup> The other issue not mentioned is a practical one that could have created challenges for obstetric providers. One could envision that an inordinate amount of time could be spent trying to assess whether a new patient in an obstetric practice with a prior pregnancy had previously received her one-time HCV screening. Given the many screening tests that are performed during prenatal care for each pregnancy, the addition

of HCV to this menu of tests seems a practical way to ensure that screening actually happens as part of the default process.

### IS UNIVERSAL SCREENING TRULY UNIVERSAL? WHAT ELSE IS REQUIRED TO MAKE THIS POLICY A SUCCESS?

Although the recommendation for universal screening of all adults is a tremendous improvement compared with the previous strategy, there are still gaps that must be acknowledged. Injection drug use and other behaviors that increase the chances for HCV acquisition do not start at 18 years of age. There are many studies that document that burden of HCV in adolescents, and a one-time HCV screening strategy that included adolescents was also predicted to be cost-effective.<sup>37,43</sup> The 2 pan-genotypic DAA regimens that are used first-line (sofosbuvir-velpatasvir and glecaprevir-pibrentasvir) are both now approved by the US Food and Drug Administration for use in children as young as 12 years of age and are predicted to be highly cost-effective.<sup>44–47</sup> Adolescents could be screened as part of school physicals from 15 to 17 years of age, and if found to be positive, could be promptly referred for HCV treatment. Some may argue that an early negative test result could be before a period of risk-taking behavior that would require later screening. The same argument could be made of an 18-, 25-, or 35-year old, however, and thus this is not a valid rationale for excluding adolescents.

The other group that this policy does not directly address is infants exposed to HCV. These infants have always been included in the risk-based screening recommendations, but plenty of studies have shown that the ultimate screening rate for these infants is abysmal.<sup>48–50</sup> Screening at birth has not been shown to be effective, and antibody-based tests cannot be used until after 18 months due to passively transferred maternal antibody. The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America (AASLD-IDSA) HCV Guidance Panel endorsed 2–6 months as an age window during



which the use of an HCV RNA test seemed to offer reliable results to confirm or exclude infection. The CDC recommendations include a discussion of infants in the “Future Directions” section; it is possible, therefore, that this gap will be closed in the near future.<sup>2</sup> Given that the United States has an exceptional infrastructure already in place to screen and follow up infants born to women with HIV infection, it would seem that this infrastructure could be repurposed and funded to expand the focus to include HCV.<sup>51–53</sup>

Those who have been in public health a long time will be quick to acknowledge that recommendations do not equal practice. Behavior takes a long time to change, and the stigma associated with at-risk populations for HCV infection negatively affect the care of these patients. Recommendations have been in place for almost 2 decades for universal HIV screening, and our practice still falls far short of this goal.<sup>54,55</sup> The behavioral economist Dan Ariely often mentions “changing the default” as the easiest and most effective way to change any individual's behavior.<sup>56,57</sup> HCV screening could easily be incorporated into the default order sets for prenatal care, emergency care, and routine primary care.

The success of universal HCV screening hinges on rapidly offering treatment to those testing positive that will cure their infection. The current access of HCV therapies still falls far short of this goal. The State of Hep C ([www.stateofhepc.org](http://www.stateofhepc.org)) is a collaborative project between the National Viral Hepatitis Roundtable and the Center for Health Law and Policy Innovation of Harvard Law School that tracks how each state restricts access to HCV treatment for its citizens. In June 2020, two states received an “F” for their highly restrictive policies for those needing HCV treatment, and another four received a “D+” for slightly less restrictive policies. It is worth noting that many of these grades have improved significantly in recent years as states have worked to lift restrictions and expand access to HCV therapy. The state of Louisiana deserves credit for being the first in the nation to engage in a subscription model of HCV therapy that has been dubbed the “Netflix model.”<sup>57</sup> The state has partnered with a Gilead subsidiary to offer unlimited access for 5 years for eligible patients across the state.<sup>58</sup> Louisiana receives affordable access to therapy while the company receives a guaranteed

revenue stream for providing medication. Washington state has entered into a similar agreement with AbbVie to treat their citizens.<sup>59</sup> This kind of arrangement should serve as a template for other states to increase access to HCV therapy while lowering their overall costs of providing these therapies.

Finally, while increased screening and treatment will help move our society toward eradication, these measures do nothing to solve the upstream factors that promote the risk-taking behaviors that ultimately lead to HCV in the first place. Much more effort and resources must be devoted to helping reduce or eliminate the factors that promote injection drug use and HCV transmission: economic inequality; lack of opportunity; harm reduction/needle exchange; and free and easy substance abuse treatment.

## CONCLUSIONS

The new recommendations for universal HCV screening are welcome and long overdue. They will help accelerate progress in dealing with the challenge of HCV in the United States, but they alone are not enough. When coupled with widespread access to treatment and more robust efforts to address the societal and economic factors that promote HCV transmission, only then can the United States get to the point where eradication of HCV becomes an achievable goal.

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## DISCLOSURES

Dr. Jhaveri currently serves on the AASLD/IDSA HCV Guidance Panel. In the last 36 months, he received support for clinical trial participation from Gilead and AbbVie and a research grant for investigator-initiated studies from Merck; and served as a

consultant for MedImmune/AstraZeneca, Saol Therapeutics, and Seqirus.

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