

## REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

## Global Elimination of Chronic Hepatitis

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**M**AJOR ADVANCES HAVE BEEN MADE IN THE PREVENTION AND TREATMENT of chronic hepatitis C virus (HCV) and hepatitis B virus (HBV) infections. Nonetheless, by causing cirrhosis, hepatocellular cancer, or both, HCV and HBV infections kill more than 1 million persons each year, accounting for as many global deaths as those due to human immunodeficiency virus (HIV) infection, tuberculosis, or malaria (Fig. 1).<sup>1</sup> In fact, by 2040, deaths from chronic hepatitis are projected to exceed the combined mortality associated with HIV infection, tuberculosis, and malaria.<sup>2</sup> Recognizing both the advances that have been made and the continuing threat, the United Nations included the goal of combating viral hepatitis in its 2015 sustainable development goals, and in 2016, the World Health Assembly adopted the Global Health Sector Strategy on viral hepatitis that called for its elimination as a public health threat by 2030.<sup>3,4</sup> In 2017, the World Health Organization (WHO) published a report defining hepatitis elimination and outlining a strategy to achieve that goal by 2030.<sup>5,6</sup> This review considers the goal, the interventions and targets needed to achieve the goal, the progress that has been made, the challenges that remain, and future directions.

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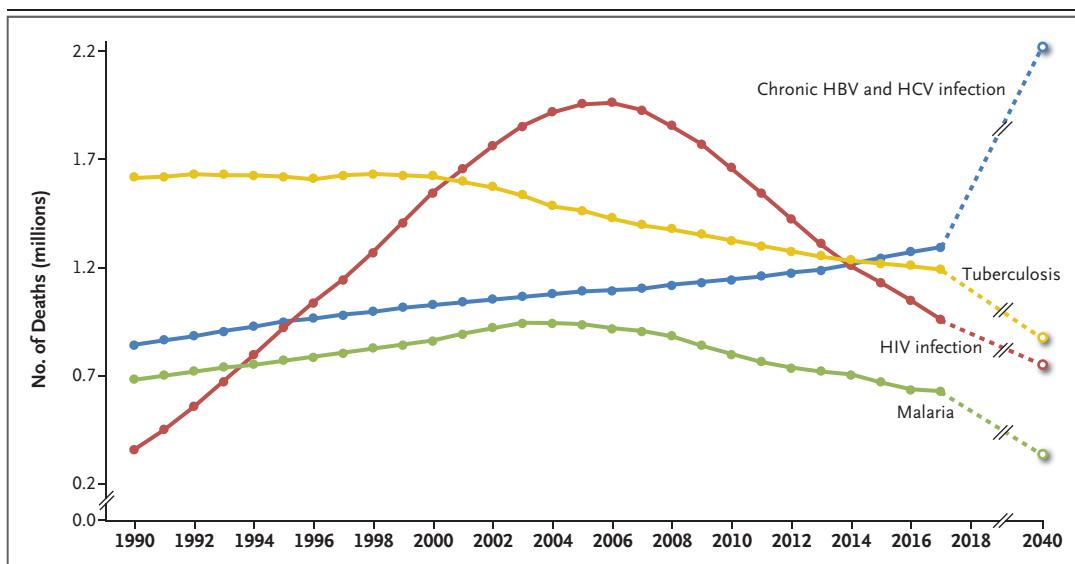
## ELIMINATION INTERVENTIONS AND TARGETS

In global health parlance, elimination of a disease as a public health threat is a goal that falls between complete eradication and regional control. Elimination is the 2030 objective for HIV infection, tuberculosis, malaria, and viral hepatitis. For hepatitis, elimination is defined as a 90% reduction in incidence and a 65% reduction in the number of related deaths from a 2015 baseline (Fig. 2).<sup>5</sup> The 2015 baseline is approximated, and as discussed below, estimates vary widely. Nonetheless, the WHO goal for HCV infection is a decrease from 1.75 million new cases and 400,000 deaths in 2015 to approximately 175,000 new cases and 140,000 deaths in 2030. For HBV infection, 4.7 million new cases and 884,000 deaths in 2015 would decline to approximately 470,000 new cases and 309,000 deaths in 2030. To achieve these goals, the WHO identified key public health interventions and set targets for their achievement<sup>5,7</sup> (Table 1). Since there are considerable differences in the interventions, such as a vaccine to prevent hepatitis B but not hepatitis C and a cure for hepatitis C but not for hepatitis B, I initially discuss them individually.

## HEPATITIS C

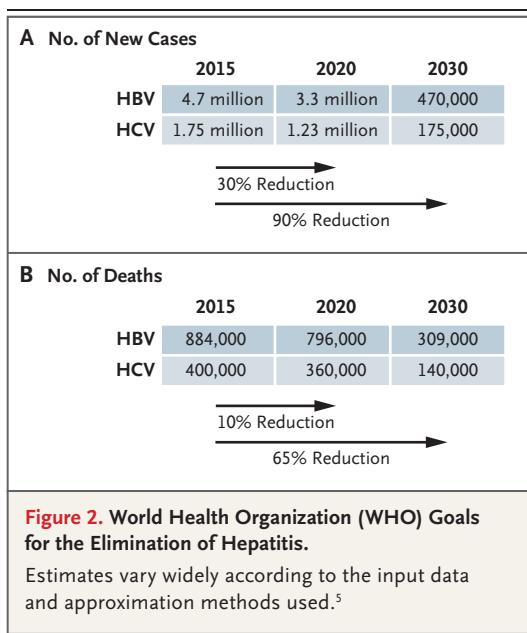
## ELIMINATION OF INCIDENT HCV INFECTION

Most HCV infections are caused by percutaneous exposure to contaminated blood. Unsafe injections, such as reuse of an unsterilized syringe or needle, are a leading source of HCV infection.<sup>5,8,9</sup> It is estimated that 5% of all injections in 2015 were



**Figure 1.** Worldwide Deaths from Chronic Viral Hepatitis as Compared with Deaths from Tuberculosis, Human Immunodeficiency Virus (HIV) Infection, and Malaria.

As the comparative data on deaths show, chronic viral hepatitis is a major public health challenge. Data on deaths from 1990 to 2017 are from the Institute for Health Metrics and Evaluation as of November 14, 2018 (<http://ghdx.healthdata.org/gbd-results-tool?params=gbdpi-%202017-permalink/87c0153764d6e898242b4a9a70cd9c6d>). The projections for 2040 are from Foreman et al.<sup>2</sup>



unsafe, resulting in 315,000 new infections. The target for 2030 is zero, and substantial progress in meeting that target has already been made. Between 2000 and 2010, education and engineering controls that prevent syringe or needle reuse and injuries after disposal reduced new

cases of HCV from unsafe injections by 83%.<sup>9</sup> Continued progress is anticipated, but the target of zero unsafe injections will require intensification in the Eastern Mediterranean and South-East Asia regions.<sup>7</sup> In addition, when infection-control practices are not observed, HCV continues to be transmitted worldwide during conventional health care and by various percutaneous procedures (e.g., circumcision, scarification rituals, and tattooing), which underscores the need to maintain universal precautions.<sup>10</sup>

Transmission of HCV through transfusion has essentially been eradicated where blood donations from volunteers are screened for HCV-specific antibodies and RNA.<sup>11</sup> Nonetheless, in 2015, approximately 3% of transfusions worldwide still were not appropriately screened. Expanded resources, including low-cost, high-sensitivity tests, may help low-income regions achieve the 2030 goal of 100% screening and eradicate transfusion-related transmission.<sup>12</sup>

In most high-income regions of the world, the major source of new HCV infections is injection drug use, which caused approximately 390,000 new cases in 2015.<sup>13,14</sup> Safer injection practices and medication-assisted treatment reduce the incidence of HCV infection.<sup>15,16</sup> The

**Table 1. Targets for the Primary Interventions Projected by the World Health Organization (WHO) to Eliminate Chronic Hepatitis by 2030.\***

Intervention	Indicator	2015 Baseline	2020 Target	2030 Target
HBV vaccination	% of infants with HEPB3 vaccination	84	90	90
Prevention of maternal HBV transmission	% of infants with HBV vaccination $\leq$ 12 hr after birth	39	50	90
Blood safety	% of donations screened with quality assurance	97	98†	100
Injection safety‡	% of unsafe injections	5	0	0
Harm reduction§	No. of syringes or needles distributed/injection drug user/yr	27	200	300
HBV diagnosis	% of infected persons who receive a diagnosis	9	30	90
HCV diagnosis	% of infected persons who receive a diagnosis	20	30	90
HBV treatment¶	% of persons with diagnosed infection who are treated	8	—	80
HCV treatment¶	% of persons with diagnosed infection who are treated	7	—	80

\* Data are from the WHO 2017 Global Hepatitis Report<sup>5</sup> and 2016–2021 Global Health Sector Strategy.<sup>4</sup> The 2015 baseline figures are approximated. For hepatitis B virus (HBV) vaccination, three doses of hepatitis B vaccine (HEPB3) are given with other routine childhood immunizations, often as a pentavalent vaccine. HCV denotes hepatitis C virus.

† The target is given as 95% in the 2017 Global Hepatitis Report<sup>5</sup> and the 2016–2021 Global Health Sector Strategy.<sup>4</sup>

‡ Injection safety is expressed in the 2016–2021 Global Health Sector Strategy<sup>4</sup> as the percentage of injections administered with safety-engineered devices in and out of health care facilities, a practice that began in 2015 at 5% of all injections and needs to rise to 50% and 90% in 2020 and 2030, respectively.<sup>5</sup>

§ Harm reduction is represented by the number of syringes and clean needles distributed to each injection drug user per year but also often includes a comprehensive strategy for expanding medication-assisted treatment.

¶ The need for treatment currently extends to approximately 20% of persons with diagnosed HBV infection and all persons with diagnosed chronic HCV infection. No percentage goals are stated for 2020. Instead, targets for cumulative treatment are 5 million persons with HBV infection and 3 million persons with HCV infection (although more than 3 million HCV-infected persons have already received treatment).

WHO estimates that the number of sterile needles or syringes distributed to people who inject drugs must increase from 27 per person per year to 300 per person per year in order to eliminate new cases of HCV infection.<sup>5,8</sup> Although no target has been established for expanding medication-assisted treatment, it is understood that this also must be included in a comprehensive approach to harm reduction.<sup>4,7,16</sup> There are substantial challenges to reducing the incidence of HCV infection among people who inject drugs. For example, because of the opioid crisis in the United States, the national incidence of HCV infection doubled between 2010 and 2014 and continues to rise.<sup>17,18</sup> Moreover, HCV infections are so widely distributed in rural areas that traditional means of providing conveniently located harm-reduction services are unlikely to work.<sup>19</sup> Elsewhere (including some high-incidence regions), syringe-exchange services are illegal. Thus, other approaches to improving the availability or effectiveness of harm-reduction services or additional tools, such as HCV treatment or vaccination (discussed below), are needed.<sup>6,20</sup>

HCV also continues to be transmitted by other routes. Outbreaks of new HCV infections among HIV-infected men who have sex with men have been reported worldwide and are at least partly due to disinhibition linked to improved prevention and treatment of HIV infection and possibly HCV infection.<sup>21</sup> HCV can also be transmitted perinatally.<sup>22</sup> However, in 2018, neither cesarean delivery nor HCV treatment during pregnancy was recommended to prevent transmission.<sup>23</sup>

#### ELIMINATION OF HCV-RELATED DEATHS

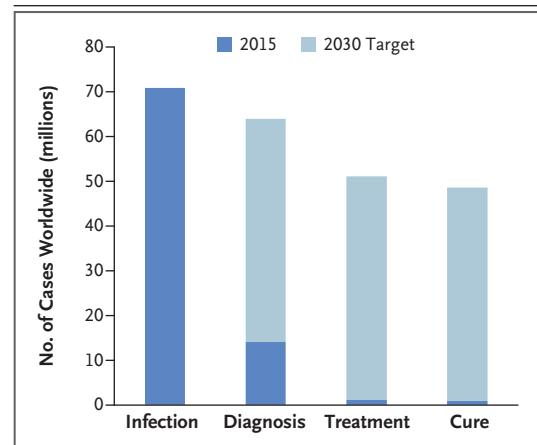
The diagnostic and therapeutic interventions for HCV infection are excellent and justify the goal of reducing HCV-related mortality by 65% among the estimated 71 million persons (range, 62 million to 79 million) who are already infected.<sup>5,24</sup> HCV-specific antibodies can be detected with 96 to 99% sensitivity and specificity, including at the point of care.<sup>25</sup> Ongoing infection is confirmed by additional testing for HCV RNA or core antigen, and such testing has been accomplished in 1 hour with the use of 0.1 ml of blood

collected by fingerstick.<sup>26,27</sup> With recent advances, 8 to 12 weeks of treatment cures more than 95% of persons with HCV infection, thereby reducing mortality and the incidences of liver failure, hepatocellular cancer, and extrahepatic complications of infection.<sup>28-38</sup> Several treatment regimens are effective for all HCV genotypes.<sup>30,31</sup> Although most of these diagnostic and therapeutic interventions existed in 2015, it is estimated that only 20% of the 71 million persons infected received a diagnosis, and only 7% were successfully treated (Fig. 3).<sup>5</sup> Some models suggest that to reduce mortality by 65% by 2030, the percentage of diagnosed cases must increase to 90%, and the percentage of patients treated to 80%,<sup>5,24</sup> although one model suggests that even higher target percentages are needed.<sup>8</sup>

There are many challenges in diagnosing HCV infection and getting infected persons into treatment. HCV infections are generally asymptomatic. One strategy is to screen subpopulations that are disproportionately affected. For example, in the United States and many other high-income regions, the prevalence of HCV infection in the general population is less than 1%, but 50 to 80% of people who inject drugs are infected.<sup>14,15,39,40</sup> Also disproportionately affected are prison inmates, with an estimated 1,546,500 inmates infected worldwide and 227,000 in the United States alone.<sup>40,41</sup> Although nearly all high-income countries recommend testing of people who inject drugs and other high-risk groups, the net effectiveness is diminished, since these groups are often not receiving care.<sup>42</sup> In addition, in regions of the world where infection has typically occurred from unsafe medical exposures, the types of exposures are too common to be useful discriminators for risk-based testing. Age-specific testing is an alternative when the risk is concentrated in a particular birth cohort, such as persons born between 1945 and 1965 in the United States.<sup>43</sup> However, too few of the 71 million persons infected with HCV receive regular care or undergo testing while receiving regular care for these measures to reach the target percentage of diagnosed cases (90%).<sup>24,44,45</sup>

Likewise, there are many challenges to increasing HCV treatment. The need for additional testing after detection of HCV antibodies and additional barriers to treatment make the percentage of cases linked to treatment especially low in many regions.<sup>44,45</sup> The price of treatment may

also create a challenge. Even in a high-income country such as the United States, the price of HCV treatment has led some insurance providers and health care systems (e.g., the Federal Bureau of Prisons and state Medicaid providers) to restrict treatment in contradiction of national guidelines.<sup>23,46</sup> Other high-income nations such as France, Australia, and the Netherlands have absorbed HCV treatment costs in national health plans, which has led to an expansion of treatment that seems likely to exceed the WHO target of treatment for 80% of diagnosed cases.<sup>47,48</sup> In addition, treatment prices in some low- and middle-income countries are as low as \$48 to \$81 (U.S. dollars) per 12-week course. However, even low prices can be a serious impediment in those regions because no large global donors are subsidizing HCV treatment in low-income regions, although treatment for other infections that the WHO has targeted for elimination by 2030 is being subsidized.<sup>48</sup> In addition, although successful HCV treatment reduces the incidence of hepatocellular cancer and liver fail-



**Figure 3. Global Continuum of Care for HCV Infection and 2030 WHO Elimination Targets.**

Conceptually, care for chronic HCV infection declines along a continuum that is shown as beginning in 2015 with an estimated 71 million persons with infection. Approximately 14 million persons receive a diagnosis, and approximately 5 million persons are successfully treated. The 2030 targets correspond to predictions made by the WHO: 90% of infected persons will need to receive a diagnosis, and 80% of those who receive a diagnosis will need to be treated, in order to eliminate HCV.<sup>5</sup> Global data are imprecise but underscore the importance of diagnosis and care in light of the overall effects on public health of the very high efficacy of HCV treatments.

ure, it does not completely remove those risks, especially if treatment is not provided before cirrhosis develops.<sup>34,36-38</sup>

## HEPATITIS B

### ELIMINATION OF INCIDENT CHRONIC HBV INFECTION

Chronic HBV infection occurs in approximately 5% of persons infected in adulthood, as compared with 90% of persons infected in infancy and approximately 50% of those infected in early childhood.<sup>49,50</sup> Thus, the global incidence of chronic hepatitis B is largely driven by mother-to-infant and early-childhood infection, and that is the focus of the WHO elimination plan. The primary intervention is vaccination. Hepatitis B vaccine has been integrated with four other vaccines (for diphtheria, tetanus, pertussis, and *Haemophilus influenzae* type b infection) in a pentavalent formulation. In low-income regions, this vaccine has been funded by GAVI (formerly the Global Alliance for Vaccines and Immunization) and was given to an estimated 84% of infants in 2015.<sup>5,48</sup> Nonetheless, there were still approximately 4.7 million new chronic hepatitis B cases in 2015, and the 2030 goal of reducing that number by 90% requires additional measures.<sup>48</sup>

The intervention that has had the greatest effect is expansion of so-called birth-dose HBV vaccination.<sup>51,52</sup> HBV transmission from an infected mother is more effectively prevented when the first HBV vaccination is given to the infant within 12 to 24 hours after birth than when initially given at approximately 1 month in the pentavalent formulation.<sup>52</sup> Thus, in 2009, the WHO recommended universal birth-dose HBV vaccination. However, by 2015, the practice had been implemented in only 39% of deliveries, and by July 2017, only 9 of the 47 WHO African region countries (19%) had adopted universal birth-dose vaccination.<sup>53</sup> Further expansion requires reaching infants at birth, which is challenging in regions where home delivery is the custom. In 2019, expansion of the subsidy for low-income vaccination to include the monovalent (HBV only) formulations should help increase the use of the birth-dose vaccine.<sup>53</sup>

Treatment of pregnant women with chronic hepatitis B may also diminish perinatal transmission and is recommended for women with HBV DNA levels exceeding 200,000 IU per milli-

liter (in addition to infant vaccination and provision of HBV immune globulin where available).<sup>54,55</sup> Maternal treatment provides relatively little additional benefit when the birth dose of vaccination is given promptly.<sup>56</sup> For example, in one model, expanding coverage for routine vaccinations from 84% in 2015 to 90% in 2030 prevents 4.3 million new cases of HBV infection, and expanding coverage for the birth dose to 80% prevents another 18.7 million cases; adding peripartum antiviral therapy prevents only 0.6 million more cases.<sup>57</sup> The effect of maternal treatment could be greatest in regions where home delivery is customary and the birth dose is missed or delayed.

New cases of chronic hepatitis B also occur in adults through unsafe medical injections, sexual transmission, and transmission through injection drug use, including the unfolding opioid epidemic in the United States. HBV vaccination in infancy prevents chronic hepatitis B in adults, but many persons born before the adoption of universal infant vaccination remain susceptible, justifying efforts to expand adult vaccination to at-risk populations. In addition, reducing to zero the number of unsafe medical injections and expanding harm-reduction services for people who inject drugs will contribute to the elimination of both chronic hepatitis B and chronic hepatitis C.

### ELIMINATION OF HBV-RELATED DEATHS

Testing and treatment are the primary means of reducing HBV-related deaths by 65% for the estimated 257 million to 291 million persons already chronically infected.<sup>5,58,59</sup> Blood tests for the HBV surface antigen (HBsAg) have high sensitivity and specificity and have been developed for use at the point of care.<sup>60</sup> There are also antiviral treatments for HBV infection that reduce the incidence of hepatocellular cancer, cirrhosis, and death.<sup>61</sup> However, in 2015, chronic HBV infection was diagnosed in only 9% of persons with the infection, and less than 10% of persons in need of antiviral treatment received it (Fig. 4).<sup>5,7</sup>

The target of expanding the diagnosis of HBV infection to 90% of cases and treatment to 80% of cases is the same as the target for HCV infection. However, there are notable similarities and differences between HCV infection and HBV infection with respect to this target. Like HCV

infection, HBV infection can disproportionately affect persons in regions with limited primary care services or subpopulations (e.g., injection drug users) that do not regularly receive such services. In addition, ascertainment in those subpopulations is often low, reflecting an astonishing lack of awareness even in regions where HBV infection is a leading cause of death. There are also challenges in linking persons with chronic infection to medical care, and the cost of HBV medications can be an impediment to their long-term use. With both HCV infection and HBV infection, liver-related mortality among those with chronic infection is expected to rise with the aging of infected cohorts.<sup>8,57</sup> Thus, for HBV infection, a 65% reduction from 2015 to 2030 requires a net reduction of more than 72% to bend the natural history arc from more than 1.1 million expected deaths to fewer than 310,000.<sup>57</sup>

Treatment is more complicated for HBV infection than for HCV infection.<sup>55,62</sup> Even the simplest treatment guideline produced by the WHO for HBV infection in low- and middle-income countries recommends detection in blood of alanine aminotransferase activity, a platelet count, measurement of the HBV DNA level (if possible), and detection of hepatitis B e antigen.<sup>62</sup> Ultimately, treatment is indicated in only 10 to 30% of infected persons. In addition (and in contrast to the treatment of HCV infection), treatment rarely cures HBV infection, making an indefinite treatment course necessary in most cases. These complexities and the infrastructure required to maintain treatment are challenges to global escalation of treatment for HBV infection. Fortunately, prevention of HBV infection by vaccination is also an important tool for reducing mortality, as was shown first in Taiwan, underscoring the importance of prevention in eliminating both new cases and deaths from HBV infection.<sup>63,64</sup>

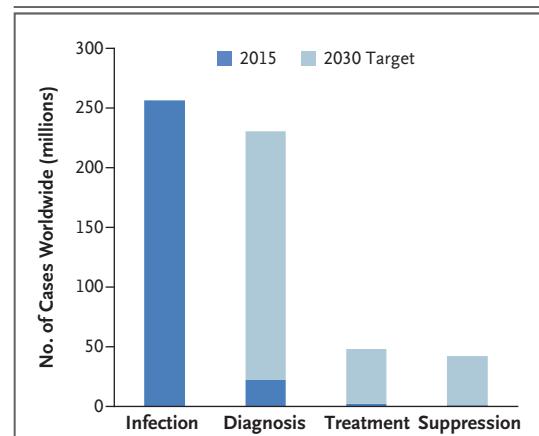
#### PUBLIC HEALTH APPROACH TO THE ELIMINATION OF CHRONIC HEPATITIS

Elimination of viral hepatitis requires a broad public health approach, and the interventions that have been most successful are those that were adopted within the existing public health infrastructure. For example, integration of HBV vaccination with the Expanded Program on Immunization, a public health intervention with global reach and sustainable funding, is expected

to reduce the incidence of chronic hepatitis B by 83% between 1990 and 2020 and to prevent 310 million new cases.<sup>57</sup> Likewise, public health measures are validated when transmission by transfusions and unsafe injections is prevented. In contrast, as astonishing as the breakthroughs in treating HCV infection have been for individual care, the net global effect has been minimal; in 2015, there were as many new HCV infections as there were cases cured by treatment.<sup>65</sup> Thus, the most important question in the field is how to develop and deploy a public health response, especially for the HBV and HCV testing and treatment interventions that have been provided chiefly in individual medical practices.

Reliable epidemiologic data are a cornerstone of a public health response but are generally lacking for hepatitis. Even the core elimination outcomes for hepatitis are poorly measured. Incident HCV infection is almost never recognized, even when there is active surveillance.<sup>66</sup> Likewise, hepatitis-related deaths are difficult to ascertain and are systematically underestimated.<sup>67</sup>

Uncertainty in measures of both interventions



**Figure 4. Global Continuum of Care for HBV Infection and 2030 WHO Elimination Targets.**

Conceptually, care for chronic HBV infection declines along a continuum that is shown as beginning in 2015 with an estimated 257 million persons with infection. Approximately 22 million persons receive a diagnosis, and an even smaller number (approximately 1.7 million persons) receive treatment. The 2030 targets correspond to predictions made by the WHO: in order to eliminate HBV, 90% of all persons who are infected will need to receive a diagnosis, and 80% of those who need treatment will receive it.<sup>5</sup> Currently, only 20 to 30% of infected persons meet treatment guidelines.

and outcomes weakens even the best models used to formulate targets. For example, elimination pivots on reliable estimates of prevalence. However, the best estimate of the number of HCV-infected persons recently changed from a range of 130 million to 170 million persons to 71 million persons. Moreover, the models that link an intervention to an outcome, such as the number of new HCV infections that are prevented for every incremental increase in exposure to syringe-exchange services, are limited by poor primary data sources and differential public health reporting. Improved data should come from WHO sentinel sites, where interventions and outcomes can be reliably measured, with the results generalized in order to marshal resources and adjust strategies for achieving global elimination.

#### MICROELIMINATION

Lessons can also be learned from individual examples of effective public health responses to hepatitis. Although HBV infection was once a major public health threat among Alaska Natives, a vigorous public health approach with universal vaccination, testing, and treatment reduced the incidence of new cases by more than 90% and reduced expected mortality by 65%, effectively eliminating HBV infection.<sup>68</sup> Similarly, in both the Netherlands and Switzerland, testing and treatment for HCV in HIV-infected men who have sex with men were expanded (and funded), resulting in a reduction in the national incidence of HCV infection.<sup>69-71</sup> Likewise, HCV infection was virtually eliminated from one Australian prison by a process of systematic testing, treatment, and prevention.<sup>72</sup> Similar successes have been reported in Egypt, the Republic of Georgia, Australia, and Iceland, as well as by the U.S. Department of Veterans Affairs.<sup>47</sup> Collectively, this so-called microelimination (i.e., elimination in specific subpopulations and even in entire countries) underscores what can occur when the target interventions are expanded and sustained at the population (vs. the individual) level.

#### FROM MICROELIMINATION TO GLOBAL ELIMINATION

Whether global elimination of chronic hepatitis will occur is unclear. Questions remain about the interventions and targets: Can the targets be achieved? Will the achieved target produce the

expected reduction in hepatitis incidence or mortality? One recent model for HCV infection estimates that achieving the intervention targets will reduce the incidence by approximately 65% (as compared with the goal of 90%) and that 95% of all HCV infections will need to be diagnosed to realize the goal of a 65% reduction in mortality by 2030.<sup>8</sup> A model for HBV infection suggests that the elimination goals might be possible if the expanded targets for vaccine coverage and expanded diagnosis and treatment can be achieved.<sup>57</sup> Nonetheless, all predictions underscore the importance of altering the status quo.

Global resources are needed for a public health response. The example of HIV infection is particularly relevant. In 1996, as the threat of acquired immunodeficiency syndrome (AIDS) was sharply rising worldwide, the medical management of HIV infection was suddenly transformed by new interventions that rapidly led to microelimination of HIV infection in specific settings.<sup>73</sup> A public health approach was needed to bring those new medical interventions to the affected populations, and the result was exemplary. By 2018, more than 20 million persons had received a diagnosis of HIV infection and were being treated with antiretroviral therapy, and as shown in Figure 1, there was a sharp bend in the mortality arc. There are obvious analogies with hepatitis, for which there is a similar threat and even better control measures, such as a vaccine for HBV infection and curative treatment for HCV infection. For example, each year since approximately 2016, more than 20 million persons have received 12 months (240 million person-months) of HIV treatment. That yearly allocation of medication for HIV infection exceeds the months of treatment required just once to cure all 71 million HCV-infected persons, who need just 8 to 12 weeks of treatment. The experience with HIV infection shows that infrastructure can be built to scale up testing and treatment interventions from individual clinical care to public health programs.

Resources are especially needed for surveillance and to establish an infrastructure for prevention, testing, and treatment in order to deliver interventions in low-income regions. Even in high-income regions of the world such as the United States, expansion of testing and treatment for HBV and HCV infections will require funding for testing, removal of treatment restric-

tions, and widespread opt-out programs for prisons, such as the initiatives that were developed for HIV infection. Political leadership must also be built and sustained. Elimination of chronic hepatitis has progressed faster in countries with strong political endorsement, such as Portugal, than in other countries, including the United States, which has not yet adopted a specific national elimination plan, despite endorsement of such a plan in March 2017 by the National Academies of Sciences, Engineering, and Medicine.<sup>6</sup>

The sources of funding needed for the elimination of hepatitis remain unclear. Individual interventions are cost-effective in nearly all scenarios, and some will be subsidized by governments and insurance entities.<sup>74</sup> One group estimated that elimination of HCV infection between 2018 and 2030 would cost \$51 billion, with about half the funds coming from existing sources.<sup>75</sup> The more difficult but critical calculation is the total amount that must be invested and the new sources of funding that are needed to achieve elimination and prevent the escalating mortality from hepatitis, which is predicted to exceed the combined mortality from malaria, tuberculosis, and HIV infection in 2040 on the basis of the status quo.<sup>2</sup> It is possible that existing agencies can help, as has occurred with GAVI, Unitaid, and the Clinton Health Access Initiative. However, to achieve the global impact that has been seen with HIV infection, far more global resources will be needed. We need to know the amount and sources of funding and ideally the agency or coalition that will implement, coordinate, and monitor the elimination initiative.<sup>47,48</sup>

Innovation is also needed, including new interventions. For example, vaccinations are the cornerstone of a public health response to infection, and a vaccine to prevent HCV infection would be extremely helpful in high-risk populations such as people who inject drugs.<sup>76</sup> Spontaneous clearance of HCV infection produces immunity against subsequent chronic infection, providing a scientific foundation for the development of a vaccine to prevent chronic hepatitis C.<sup>77,78</sup> The results of a phase 2 trial of a preven-

tive vaccine, funded by the National Institutes of Health, are expected in 2019. However, there has been astonishingly little public or private investment in HCV vaccine development, and WHO elimination strategies do not anticipate the availability of such a vaccine.<sup>79</sup> Better harm-reduction methods are also urgently needed to combat the opiate crisis and blood-borne infections in people who inject drugs. Innovations in diagnostics and treatment that permit public health workers to test for hepatitis infection and deliver treatment at the point of care would be transformative. Long-acting injectable treatments such as those already developed for HIV infection would be especially helpful for HCV infection, which could be detected and potentially cured in a single encounter. This approach is especially effective in regions where the medical infrastructure remains insufficient. Similar advances that simplify the diagnosis and management of HBV infection are also needed. Especially helpful would be treatments for HBV infection that produce functional cure and reduce the need to sustain medical services indefinitely.

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#### SUMMARY

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Chronic hepatitis is a major public health challenge that can be eliminated. There has already been progress toward this goal, especially with the prevention of chronic hepatitis B by vaccination and reductions in the transmission of hepatitis C from transfusions and unsafe injections. There are also potentially potent interventions to detect and treat HCV and HBV infections. However, for the elimination targets to be reached by 2030, substantially more resources and additional innovations are needed to make these interventions widely available. The degree to which elimination of hepatitis is global or focused on select subpopulations will be directly related to the vigor of the international response.

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#### REFERENCES

1. Stanaway JD, Flaxman AD, Naghavi M, et al. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. *Lancet* 2016;388:1081-8.
2. Foreman KJ, Marquez N, Dolgert A, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. *Lancet* 2018;392:2052-90.
3. United Nations General Assembly. Resolution adopted by the General Assembly on 25 September 2015 — Transforming

- our world: the 2030 Agenda for Sustainable Development ([http://www.un.org/ga/search/view\\_doc.asp?symbol=A/RES/70/1&Lang=E%20accessed%206/18/2018](http://www.un.org/ga/search/view_doc.asp?symbol=A/RES/70/1&Lang=E%20accessed%206/18/2018)).
4. Global health sector strategy on viral hepatitis 2016–2021. Geneva: World Health Organization, 2016 (<http://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/>).
  5. Global hepatitis report. Geneva: World Health Organization, 2017.
  6. A national strategy for the elimination of hepatitis B and C: phase two report. Washington DC: National Academies of Sciences, Engineering, and Medicine, 2017.
  7. Hutin YJ, Bulterys M, Hirschall GO. How far are we from viral hepatitis elimination service coverage targets? *J Int AIDS Soc* 2018;21:Suppl 2:e25050.
  8. Heffernan A, Cooke GS, Nayagam S, Thursz M, Hallett TB. Scaling up prevention and treatment towards the elimination of hepatitis C: a global mathematical model. *Lancet* 2019;393:1319–29.
  9. Pépin J, Abou Chakra CN, Pépin E, Nault V, Valiquette L. Evolution of the global burden of viral infections from unsafe medical injections, 2000–2010. *PLoS One* 2014;9(6):e99677.
  10. Patel PR, Larson AK, Castel AD, et al. Hepatitis C virus infections from a contaminated radiopharmaceutical used in myocardial perfusion studies. *JAMA* 2006;296:2005–11.
  11. Stramer SL, Glynn SA, Kleinman SH, et al. Detection of HIV-1 and HCV infections among antibody-negative blood donors by nucleic acid–amplification testing. *N Engl J Med* 2004;351:760–8.
  12. Bloch EM, Vermeulen M, Murphy E. Blood transfusion safety in Africa: a literature review of infectious disease and organizational challenges. *Transfus Med Rev* 2012;26:164–80.
  13. Villano SA, Vlahov D, Nelson KE, Lyles CM, Cohn S, Thomas DL. Incidence and risk factors for hepatitis C among injection drug users in Baltimore, Maryland. *J Clin Microbiol* 1997;35:3274–7.
  14. Page K, Hahn JA, Evans J, et al. Acute hepatitis C virus infection in young adult injection drug users: a prospective study of incident infection, resolution, and reinfection. *J Infect Dis* 2009;200:1216–26.
  15. Mehta SH, Astemborski J, Kirk GD, et al. Changes in blood-borne infection risk among injection drug users. *J Infect Dis* 2011;203:587–94.
  16. Platt L, Minozzi S, Reed J, et al. Needle syringe programmes and opioid substitution therapy for preventing hepatitis C transmission in people who inject drugs. *Cochrane Database Syst Rev* 2017;9:CD012021.
  17. Zibbell JE, Iqbal K, Patel RC, et al. Increases in hepatitis C virus infection related to injection drug use among persons aged ≤30 years — Kentucky, Tennessee, Virginia, and West Virginia, 2006–2012. *MMWR Morb Mortal Wkly Rep* 2015;64:453–8.
  18. Suryaprasad AG, White JZ, Xu F, et al. Emerging epidemic of hepatitis C virus infections among young nonurban persons who inject drugs in the United States, 2006–2012. *Clin Infect Dis* 2014;59:1411–9.
  19. Canary L, Hariri S, Campbell C, et al. Geographic disparities in access to syringe services programs among young persons with hepatitis C virus infection in the United States. *Clin Infect Dis* 2017;65:514–7.
  20. Martin NK, Vickerman P, Grebely J, et al. Hepatitis C virus treatment for prevention among people who inject drugs: modeling treatment scale-up in the age of direct-acting antivirals. *Hepatology* 2013;58:1598–609.
  21. Hagan H, Jordan AE, Neurer J, Cleland CM. Incidence of sexually transmitted hepatitis C virus infection in HIV-positive men who have sex with men. *AIDS* 2015;29:2335–45.
  22. Cottrell EB, Chou R, Wasson N, Rahman B, Guise JM. Reducing risk for mother-to-infant transmission of hepatitis C virus: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2013;158:109–13.
  23. AASLD-IDSA HCV Guidance Panel. Hepatitis C guidance 2018 update: AASLD-IDSA recommendations for testing, managing, and treating hepatitis C virus infection. *Clin Infect Dis* 2018;67:1477–92.
  24. Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. *Lancet Gastroenterol Hepatol* 2017;2:161–76.
  25. Shivkumar S, Peeling R, Jafari Y, Joseph L, Pant Pai N. Accuracy of rapid and point-of-care screening tests for hepatitis C: a systematic review and meta-analysis. *Ann Intern Med* 2012;157:558–66.
  26. Lamoury FMJ, Soker A, Martinez D, et al. Hepatitis C virus core antigen: a simplified treatment monitoring tool, including for post-treatment relapse. *J Clin Virol* 2017;92:32–8.
  27. Lamoury FMJ, Bajis S, Hajarizadeh B, et al. Evaluation of the Xpert HCV viral load finger-stick point-of-care assay. *J Infect Dis* 2018;217:1889–96.
  28. Yoshida EM, Sulkowski MS, Gane EJ, et al. Concordance of sustained virologic response 4, 12, and 24 weeks post-treatment with sofosbuvir-containing regimens for hepatitis C virus. *Hepatology* 2015;61:41–5.
  29. George SL, Bacon BR, Brunt EM, Mihindukulasuriya KL, Hoffmann J, Di Bisceglie AM. Clinical, virologic, histologic, and biochemical outcomes after successful HCV therapy: a 5-year follow-up of 150 patients. *Hepatology* 2009;49:729–38.
  30. Feld JJ, Jacobson IM, Hézode C, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. *N Engl J Med* 2015;373:2599–607.
  31. Puoti M, Foster GR, Wang S, et al. High SVR12 with 8-week and 12-week glecaprevir/pibrentasvir therapy: an integrated analysis of HCV genotype 1–6 patients without cirrhosis. *J Hepatol* 2018;69:293–300.
  32. Calleja JL, Crespo J, Rincón D, et al. Effectiveness, safety and clinical outcomes of direct-acting antiviral therapy in HCV genotype 1 infection: results from a Spanish real-world cohort. *J Hepatol* 2017;66:1138–48.
  33. Ioannou GN, Beste LA, Chang MF, et al. Effectiveness of sofosbuvir, ledipasvir/sofosbuvir, or paritaprevir/ritonavir/ombitasvir and dasabuvir regimens for treatment of patients with hepatitis C in the Veterans Affairs national health care system. *Gastroenterology* 2016;151(3):457–471.e5.
  34. Falade-Nwulia O, Suarez-Cuervo C, Nelson DR, Fried MW, Segal JB, Sulkowski MS. Oral direct-acting agent therapy for hepatitis C virus infection: a systematic review. *Ann Intern Med* 2017;166:637–48.
  35. Terrault NA, Zeuzem S, Di Bisceglie AM, et al. Effectiveness of ledipasvir-sofosbuvir combination in patients with hepatitis C virus infection and factors associated with sustained virologic response. *Gastroenterology* 2016;151(6):1131–1140.e5.
  36. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virologic response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012;308:2584–93.
  37. Saadoun D, Pol S, Ferfar Y, et al. Efficacy and safety of sofosbuvir plus daclatasvir for treatment of HCV-associated cryoglobulinemia vasculitis. *Gastroenterology* 2017;153(1):49–52.e5.
  38. Chou R, Hartung D, Rahman B, Wasson N, Cottrell EB, Fu R. Comparative effectiveness of antiviral treatment for hepatitis C virus infection in adults: a systematic review. *Ann Intern Med* 2013;158:114–23.
  39. Edlin BR, Eckhardt BJ, Shu MA, Holmberg SD, Swan T. Toward a more accurate estimate of the prevalence of hepatitis C in the United States. *Hepatology* 2015;62:1353–63.
  40. Hofmeister MG, Rosenthal EM, Barker LK, et al. Estimating Prevalence of Hepatitis C Virus Infection in the United States, 2013–2016. *Hepatology* 2019;69:1020–31.
  41. Dolan K, Wirtz AL, Moazen B, et al. Global burden of HIV, viral hepatitis, and tuberculosis in prisoners and detainees. *Lancet* 2016;388:1089–102.
  42. Irvin R, Ward K, Agee T, et al. Comparison of hepatitis C virus testing recommendations in high-income countries. *World J Hepatol* 2018;10:743–51.
  43. Smith BD, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Ward JW. Hep-

- atitis C virus testing of persons born during 1945-1965: recommendations from the Centers for Disease Control and Prevention. *Ann Intern Med* 2012;157:817-22.
44. Zhou K, Fitzpatrick T, Walsh N, et al. Interventions to optimise the care continuum for chronic viral hepatitis: a systematic review and meta-analyses. *Lancet Infect Dis* 2016;16:1409-22.
  45. Holmberg SD, Spradling PR, Moorman AC, Denniston MM. Hepatitis C in the United States. *N Engl J Med* 2013;368:1859-61.
  46. Gowda C, Lott S, Grigorian M, et al. Absolute insurer denial of direct-acting antiviral therapy for hepatitis C: a national specialty pharmacy cohort study. *Open Forum Infect Dis* 2018;5:ofy076.
  47. Ward JW, Hinman AR. What is needed to eliminate hepatitis B virus and hepatitis C virus as global health threats. *Gastroenterology* 2019;156:297-310.
  48. Cooke GS, Andrieux-Meyer I, Applegate TL, et al. Accelerating the elimination of viral hepatitis: a Lancet Gastroenterology & Hepatology Commission. *Lancet Gastroenterol Hepatol* 2019;4:135-84.
  49. McMahon BJ, Alward WL, Hall DB, et al. Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. *J Infect Dis* 1985;151:599-603.
  50. Seeff LB, Beebe GW, Hoofnagle JH, et al. A serologic follow-up of the 1942 epidemic of post-vaccination hepatitis in the United States Army. *N Engl J Med* 1987;316:965-70.
  51. Thio CL, Guo N, Xie C, Nelson KE, Ehrhardt S. Global elimination of mother-to-child transmission of hepatitis B: revisiting the current strategy. *Lancet Infect Dis* 2015;15:981-5.
  52. Beasley RP, Hwang LY, Lee GC, et al. Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. *Lancet* 1983;2:1099-102.
  53. Spearman CW, Afihene M, Ally R, et al. Hepatitis B in sub-Saharan Africa: strategies to achieve the 2030 elimination targets. *Lancet Gastroenterol Hepatol* 2017;2:900-9.
  54. Pan CQ, Duan Z, Dai E, et al. Tenofovir to prevent hepatitis B transmission in mothers with high viral load. *N Engl J Med* 2016;374:2324-34.
  55. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018;67:1560-99.
  56. Jourdain G, Ngo-Giang-Huong N, Harrison L, et al. Tenofovir versus placebo to prevent perinatal transmission of hepatitis B. *N Engl J Med* 2018;378:911-23.
  57. Nayagam S, Thursz M, Sicuri E, et al. Requirements for global elimination of hepatitis B: a modelling study. *Lancet Infect Dis* 2016;16:1399-408.
  58. Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *Lancet Gastroenterol Hepatol* 2018;3:383-403.
  59. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet* 2015;386:1546-55.
  60. Amini A, Varsaneux O, Kelly H, et al. Diagnostic accuracy of tests to detect hepatitis B surface antigen: a systematic review of the literature and meta-analysis. *BMC Infect Dis* 2017;17:Suppl 1:698.
  61. Liaw Y-F, Sung JY, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med* 2004;351:1521-31.
  62. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization, March 2015.
  63. Chen HL, Chang MH, Ni YH, et al. Seroepidemiology of hepatitis B virus infection in children: ten years of mass vaccination in Taiwan. *JAMA* 1996;276:906-8.
  64. Chang M-H, Chen C-J, Lai M-S, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. *N Engl J Med* 1997;336:1855-9.
  65. Hill AM, Nath S, Simmons B. The road to elimination of hepatitis C: analysis of cures versus new infections in 91 countries. *J Virus Erad* 2017;3:117-23.
  66. Onofrey S, Aneja J, Haney GA, et al. Underascertainment of acute hepatitis C virus infections in the U.S. surveillance system: a case series and chart review. *Ann Intern Med* 2015;163:254-61.
  67. Manos MM, Leyden WA, Murphy RC, Terrault NA, Bell BP. Limitations of conventionally derived chronic liver disease mortality rates: results of a comprehensive assessment. *Hepatology* 2008;47:1150-7.
  68. McMahon BJ, Bulkow LR, Singleton RJ, et al. Elimination of hepatocellular carcinoma and acute hepatitis B in children 25 years after a hepatitis B newborn and catch-up immunization program. *Hepatology* 2011;54:801-7.
  69. Boerekamps A, van den Berk GE, Lauw FN, et al. Declining hepatitis C virus (HCV) incidence in Dutch human immunodeficiency virus-positive men who have sex with men after unrestricted access to HCV therapy. *Clin Infect Dis* 2018;66:1360-5.
  70. Boerekamps A, Newsum AM, Smit C, et al. High treatment uptake in human immunodeficiency virus/hepatitis C virus-coinfected patients after unrestricted access to direct-acting antivirals in the Netherlands. *Clin Infect Dis* 2018;66:1352-9.
  71. Braun DL, Hampel B, Kouyos R, et al. High cure rates with grazoprevir-elbasvir with or without ribavirin guided by genotypic resistance testing among human immunodeficiency virus/hepatitis C virus-coinfected men who have sex with men. *Clin Infect Dis* 2019;68:569-76.
  72. Bartlett SR, Fox P, Cabatingan H, et al. Demonstration of near-elimination of hepatitis C virus among a prison population: the Lotus Glen Correctional Centre Hepatitis C Treatment Project. *Clin Infect Dis* 2018;67:460-3.
  73. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998;338:853-60.
  74. Chhatwal J, He T, Hur C, Lopez-Olivo MA. Direct-acting antiviral agents for patients with hepatitis C virus genotype 1 infection are cost-saving. *Clin Gastroenterol Hepatol* 2017;15(6):827-837.e8.
  75. World Innovation Summit for Health. Eliminating viral hepatitis: the investment case. Doha, Qatar: WISH, 2018 (<http://www.wish.org.qa/viral-hepatitis/>).
  76. Cox AL. Medicine: global control of hepatitis C virus. *Science* 2015;349:790-1.
  77. Osburn WO, Fisher BE, Dowd KA, et al. Spontaneous control of primary hepatitis C virus infection and immunity against persistent reinfection. *Gastroenterology* 2010;138:315-24.
  78. Mehta SH, Cox A, Hoover DR, et al. Protection against persistence of hepatitis C. *Lancet* 2002;359:1478-83.
  79. Edlin BR. Perspective: test and treat this silent killer. *Nature* 2011;474:S18-S19.

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