Eliminating the Public Health Problem of Hepatitis B and C in the United States: Phase One Report

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Committee on a National Strategy for the Elimination of Hepatitis B and C

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **Robert B. Wallace**, University of Iowa, and **Don Eugene Detmer,** University of Virginia School of Medicine. They were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

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CONTENTS

ACRONYMS

AASLD	American Association for the Study of Liver Diseases
ACIP	Advisory Committee on Immunization Practices
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
anti-HBe	antibody to HBeAg
anti-HBc	antibody to HBcAg
anti-HBs	hepatitis B surface antibody
ART	antiretroviral therapy
cccDNA	covalently closed circular DNA
CDC	Centers for Disease Control and Prevention
DNA	deoxyribonucleic acid
HBcAg	hepatitis B core antigen
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HHS	Department of Health and Human Services
HIV	human immunodeficiency virus
IDSA	Infectious Diseases Society of America
IgG	immunoglobulin G
IgM	immunoglobulin M
IHS	Indian Health Service
IOM	Institute of Medicine
LDL	low-density lipoprotein
MELD	Model for End-Stage Liver Disease
mRNA	messenger ribonucleic acid
NHANES	National Health and Nutrition Examination Survey
PAHO	Pan American Health Organization
PWID	people who inject drugs
R_0	basic reproduction number
RNA	ribonucleic acid
SVR	sustained virologic response

TB	tuberculosis
TORCH	toxoplasmosis, other, rubella, cytomegalovirus, herpes simplex
VA	Department of Veterans Affairs
WHO	World Health Organization

Summary

Every year, hepatitis B and C account for more than 1 million deaths worldwide, 78 percent of world's hepatocellular carcinoma, and more than half of all fatal cirrhosis. In 2013 viral hepatitis, of which hepatitis B virus (HBV) and hepatitis C virus (HCV) are the most common types, surpassed HIV and AIDS to become the seventh leading cause of death worldwide.

The world now has the tools to prevent hepatitis B and cure hepatitis C. A vaccine against HBV confers greater than 95 percent immunity in three doses; new direct-acting antiviral treatments for chronic hepatitis C can cure[1] infection in more than 95 percent of patients. Together these advances have encouraged a global momentum for action against the epidemics of hepatitis B and C. The World Health Organization (WHO) has made viral hepatitis a priority; the United Nations Sustainable Development Goals mention combatting viral hepatitis. At the 2016 World Health Assembly, member states will consider a resolution to eliminate hepatitis B and C by 2030.

The United States has clear goals for combatting hepatitis B and C. The interagency action plan for viral hepatitis emphasizes increasing diagnosis of HBV and HCV, ending mother-to-child transmission of hepatitis B, and reducing incidence of HCV. The goals are the special purview of the Division of Viral Hepatitis at the Centers for Disease Control and Prevention (CDC) and the Office of Minority Health in the Department of Health and Human Services (HHS). Both offices are involved in the global discussion about hepatitis B and C elimination and requested that the National Academies of Sciences, Engineering, and Medicine convene a consensus committee to analyze the question of hepatitis B and C elimination in the United States. The sponsors commissioned this work in two parts. The first task, addressed in this report, was to determine if national elimination of hepatitis B and C is a feasible goal and to describe barriers to meeting this goal. The second phase of the project will set a strategy and recommend action to eliminate the public health problem of hepatitis B and C, and will end in a consensus report by the same committee, to be published in 2017.

This report discusses the feasibility of eliminating *the public health problem* of hepatitis B and C from the United States. Though historically disease elimination refers to complete termination of any incident infections in a population, elimination of a public health problem can be a less absolute goal. The WHO has accepted a non-zero target in its work against viral hepatitis. The organization's provisional target is a 90 percent reduction in incidence and a 65 percent reduction in mortality by 2030. These are global targets, however. The disease burden and epidemiological features of HBV and HCV in individual countries should determine the national elimination strategy.

Perfect vaccination could eradicate HBV, but it would take two generations. In the meantime, there is no cure for the millions of people already infected. Conversely, there is no vaccine for HCV. New direct-acting antivirals can cure nearly all chronic infections, though cost of these drugs and the burden of undiagnosed HCV infection mean that only a small fraction of all chronically infected people can access them. The committee considered these questions in its

[1] In this document sustained virologic response is used synonymously with cure. When interferon treatments were standard of care for hepatitis C this was defined as negative viral load 24 weeks after cessation of therapy, though with direct acting antivirals negative viral load after 12 weeks is considered sustained virologic response.

assessment of the feasibility of hepatitis B and C elimination in the United States, weighing the motivational power of a disease elimination goal against the danger of over-promising. **It concluded that hepatitis B and C could both be eliminated as public health problems in the United States, but that this would take considerable will and resources; disease control might be more manageable in the short-term.** (Disease control, in the committee's deliberations, refers to a reduction in the incidence and prevalence of hepatitis B and C and their sequelae with ongoing control measures, while elimination refers to cessation of transmission in the United States, allowing that the disease itself may remain, but particularly undesirable clinical manifestations prevented entirely.) For the committee's purposes, a public health problem may be defined as a disease that by virtue of transmission or morbidity or mortality commands attention as a major threat to the health of the community.

Broadly speaking, eliminating the public health problem of hepatitis B and C in the United States is a matter of ending transmission and preventing morbidity and mortality among people with chronic infection. There will be room for disagreement as to exactly what constitutes a public health problem, however. To some extent, that determination must be informed by accurate information on the magnitude and distribution of infections in the population. Hepatitis B and C are both largely asymptomatic until the late stages. Less than a third of people with chronic hepatitis B and about half of those with chronic hepatitis C are aware of their infection. Clinical management for these conditions requires designated staffing case management and strong laboratory infrastructure. Viral hepatitis is not a well-funded target for public health surveillance, however. The CDC only funds seven jurisdictions for comprehensive viral hepatitis surveillance. It is difficult to even count deaths attributable to HBV and HCV, as death certificates usually only note cirrhosis or hepatocellular carcinoma without mention of the root cause.

Both HBV and HCV tend to be asymptomatic until their later stages. They can both end in liver fibrosis, cirrhosis, and cancer. Otherwise, the diseases are very different. Therefore, this report discusses HBV and HCV separately, and identifies separate critical factors for supporting their elimination.

ELIMINATING THE PUBLIC HEALTH PROBLEM OF HEPATITIS B

After analyzing the problem of hepatitis B in the United States, the committee concluded that control is feasible in the relatively short term. Eliminating the public health problem of hepatitis B will take more time, and require considerable public will, resources, and attention to the barriers mentioned in Table S-1.

Ending Transmission of HBV

The first step in eliminating hepatitis B is ending transmission of the virus. HBV is transmitted three main ways: from an infected mother to her child, from direct contact with infected blood, or from unprotected sex with an infected partner. All could be prevented with universal immunization; HBV vaccine confers long-lasting, 95 percent immunity in three doses. HBV vaccine coverage is good in most of the world. About 82 percent of the world's infants receive all three doses, but coverage of the birth dose, essential for ending perinatal transmission, is only 38 percent. Support for immunization, especially in the HBV endemic countries of Asia and sub-Saharan Africa could do much to reduce the world's pool of chronic hepatitis B. Action

in endemic countries would also reduce future disease burden in the United States since most chronic HBV infections are imported.

A dose of HBV vaccine at birth and completion of the full vaccine series can help prevent transmission of HBV from mother to child, but better protection is offered by combining the vaccine with hepatitis B immune globulin within 12 hours of birth. It is therefore important to identify women with chronic HBV infection during pregnancy so their babies can receive full and prompt prophylaxis and post-vaccination serologic testing. Mother-to-child transmission of hepatitis B is rare, but not unknown, in the United States. Better screening and surveillance could help avert the 800 to 1,000 infections per year passed from mother to child.

There is room for improvement in the general childhood HBV vaccination in the United States. Only about 64 percent of infants receive the HBV vaccine within 1 day of birth and about 72 percent receive it within the first 3 days, but childhood catch-up is possible. Vaccination of adults is more complicated, as there is no comprehensive system for immunization after school age. Targeting high-risk populations, through routine vaccination at prisons or in sexually transmitted disease clinics, might be an efficient way to reach HBV-susceptible adults.

Reducing Morbidity and Mortality Attributable to Chronic Infection

The at least 700,000 to 1.4 million people in the United States with chronic HBV infection need life-long monitoring for disease progression In the immune tolerant phase, hepatitis B does not require antiviral therapy, but still needs regular monitoring to ensure the patient has not entered the immune active phase when treatment is beneficial. Immune active hepatitis B is treated with highly potent antivirals with low risk of resistance. Treatment is not curative, but sustained treatment response prevents disease progression and deaths from cirrhosis and liver cancer. Once antiviral therapy is started, it is not discontinued lightly. Drug cessation can cause HBV reactivation, liver flares, and hepatic decompensation. The clinical management of HBV infection also requires screening for hepatocellular carcinoma and monitoring co-factors of liver disease progression, such as excessive alcohol intake and use of herbal or dietary supplements and acetaminophen. Providers have to screen for liver cancer, and choose appropriate treatments to control chronic hepatitis B, but none of the treatments currently available cures the infection.

Chronic or resolved HBV infection in patients who are not on antivirals can reactivate when drugs used to treat cancer, organ transplantation, or autoimmune disease suppress the immune system. Reactivation can lead to acute liver injury, liver failure, and death. Antiviral prophylaxis can reduce this risk, but it is not clear in which patients or for how long, nor is the relationship between reactivation and different chemotherapy regimens.

Barriers to Hepatitis B Elimination

There are various barriers to eliminating the public health problem of hepatitis B in the United States that would affect both ending transmission and reducing the complications of chronic infection. Limited disease surveillance is one these barriers. If state and local health offices cannot identify acute or chronic infections, then there will be an incomplete understanding of the epidemic and the strategies to combat it.

There are many serum markers of hepatitis B infection. Full characterization of infection requires analysis of a panel of indicators. Inconsistencies in laboratory testing can impede the

investigation of suspected outbreaks. In some health departments surveillance includes follow-up with the infected person to facilitate testing and vaccination of his or her close contacts, although such follow-up exceeds the staff capacity at many health departments. This strategy could be more effective if vaccine registries were designed to share data across state and local boundaries, something not currently possible.

Feelings of shame and depression in HBV-infected people can also hold back progress on elimination. Fear of a positive test result can cause people to avoid screening. HBV stigma is particularly severe among East Asians, an essential target group for screening and treatment. Education can affect social norms and help reduce stigma, but such a process takes time. In the meantime, testing and screening for the HBV, especially among people born abroad, will be essential. Screening foreign-born people who are uninsured or undocumented presents challenges, however. Foreigners must reside in the United States for 5 years to qualify for many state Medicaid programs; the Affordable Care Act also restricts care for temporary residents and undocumented arrivals. Screening puts an onus on the screener to link infected patients to care, something that some HBV-infected people will not have access to.

It is difficult to ensure that anyone identified through HBV screening campaigns is enrolled and retained in care. The burden of HBV care lies largely on the managing provider, some of whom are not familiar with the long term management of chronic hepatitis B. Electronic patient files and team-based care have the potential to improve care, but more research is needed to define how this could work. More research on hepatitis B would benefit any elimination strategy. Important research topics include reactivation and development of curative therapy.

ELIMINATING THE PUBLIC HEALTH PROBLEM OF HEPATITIS C

After analyzing the problem of hepatitis C in the United States, the committee concluded that control is feasible in the relatively short term. Eliminating the public health problem of hepatitis C will take more time, and require considerable public will, resources, and attention to the barriers mentioned in Table S-2.

Ending Transmission of HCV

HCV is transmitted through contact with infected blood, and, less commonly through sexual contact or from mother to child. There is no vaccine for HCV, so preventing transmission becomes a matter of both reducing the likelihood that someone with hepatitis C will transmit the virus and reducing the risk that someone uninfected will contract it. The people at greatest risk of contracting HCV are young and inject drugs. This can be a difficult group to reach, but some evidence suggests that programs such as needle exchange can reduce their vulnerability. Preventing substance use disorders could also lower transmission by reducing the number of people at risk for contracting the virus. Even delaying HCV infection can provide valuable time to change the course of addiction in young drug injectors. The scientific literature offers many examples of harm reduction (programs such as needle exchange) for people who inject drugs, but most of these programs took place in densely populated cities. Injection drug use is becoming more common in rural areas and small towns, adapting programs to these settings while still reaching enough people to have meaningful effect on behavior could be challenging.

Treating people who inject drugs with curative HCV therapies could also reduce transmission, and elicit a reduction in disease prevalence of 20 to 80 percent. But only a fraction

of people with chronic HCV infection actually transmit the virus. People most likely to transmit the virus are actively injecting drugs; they are young and frequently imprisoned. Although HCV passes only infrequently from mother to child, pregnant women can transmit the virus to their infants. Among people with HIV and HCV, the risk of sexual transmission of HCV rises, so people infected with both viruses are also considered high risk. In general, the people driving most transmission are otherwise healthy, so curing their infection prevents no immediate deaths. Preventing imminent deaths means treating people at risk for cirrhosis. These tend to be older people, who are far less likely to pass the virus through drug use or sexual contact, and are usually beyond childbearing age. Though curative treatment can both prevent deaths from HCV and interrupt transmission, meeting these goals requires attention to different populations.

Eliminating Chronic HCV Infection

Chronic hepatitis C disproportionately affects people born between 1945 and 1965 and African-Americans, as well as people in jail and prison. Better screening and referral to treatment could help reach more infected patients, many of whom would be candidates for direct-acting antiviral treatment to eliminate their chronic infection. These drugs are expensive. Both Medicaid and private insurers have responded to the cost by restricting access. The restrictions complicate the provider's job and may harm the patient–provider relationship.

The direct-aging agents are new and the possibility of drug resistance is not well understood. Poor adherence to treatment may cause drug resistance and reduce the likelihood of treatment response.

Reducing Morbidity and Mortality from Hepatitis C

HCV infection substantially raises risk of death, especially when the infection has progressed to cirrhosis. In the near term, cirrhotic patients have the most to gain from HCV cure, as the nature of their disease puts them at the highest risk of death. Curing HCV infection in patients with decompensated cirrhosis can avoid the need for liver transplantation; cure after transplant prolongs graft survival. Progression of HCV is linked to severity of fibrosis, something that is difficult to measure. Liver biopsy is considered the most accurate measurement, but it is an invasive and expensive procedure that yields, at best, incomplete information. Certain patient characteristics also predict progression to fibrosis. Alcohol use, fatty liver disease, diabetes, and dyslipidemia can all speed progression to fibrosis, but estimating any patient's risk of fibrosis is uncertain because of poorly understood interactions between the virus and host.

Curing HCV before progression to advanced fibrosis can prevent deaths from chronic infection. New curative treatments can elicit sustained virological response in 94 to 99 percent of patients, likely reducing the risk of cirrhosis and hepatocellular carcinoma. Sustained virological response can in turn restore liver function in patients with decompensated cirrhosis. Ending illness and deaths from hepatitis C depends on both stopping the disease's progression in its early stages, and, ideally, reversing the course of advanced disease.

Barriers to Hepatitis C Elimination

As with HBV, some of the barriers to elimination of HCV would hold back progress across the board, be it in ending transmission, eliminating chronic infection, or reducing the complications of chronic infection. Incomplete surveillance is the first example of such a barrier.

Few jurisdictions in the United States have funding for viral hepatitis surveillance, so there is little information about the true incidence and prevalence of infection. Identifying acute cases through surveillance is an imprecise process; the case definition required for inclusion national statistics may be overly restrictive. Reporting of chronic hepatitis C is more straightforward, but the volume of infections and the amount of laboratory testing required to confirm them produces more information than the health department can currently capture. Chronic hepatitis C requires long-term follow-up, something infectious disease surveillance systems are not always designed to track.

Prompt identification of hepatitis C cases is challenging in part because the disease is largely asymptomatic until its later stages. Universal screening among people born between 1945 and 1965 could give a better understanding of the true disease prevalence, but so far, the screening guideline is observed more in the breach than in practice. While people born between 1945 and 1965 account for the majority of chronic hepatitis C in the United States; most new HCV infections in the United States are associated with injection drug use. People who inject drugs are difficult to reach with traditional screening methods; surveys tend to systematically undercount them and other marginalized groups including the homeless and incarcerated. Community screening could improve the proportion of chronically infected people diagnosed, but requires a way to enroll patients in care with minimal losses to follow-up. Managing and retaining HCV patients in care over time is challenging, especially for primary care physicians who are already working at full capacity. Strategies to improve patient retention could include the use of patient navigators and attention to Wagner's chronic care model.

Despite the efficacy of direct-acting agents, only about 1 out of every 10 chronically infected patients receives them. The prices of drugs are high, putting pressure on the budgets of public and private insurers. Insurers have responded to these prices by restricting access. The restrictions are not supported by current treatment guidelines, and appear motivated entirely by cost. Even with restrictions in place, these drugs accounted for a third of the sharp rise in prescription drug spending between 2013 and 2014. Such dramatic increases are uncommon and make insurers reluctant to provide unrestricted access to these expensive products.

The new HCV drugs are expensive, but they are still cost effective compared to older interferon-based therapies. The benefits of treatment to both society and to the health system still outweigh the costs. Eliminating chronic infections is possible, and treatment would do much to reduce transmission as well, but would require near universal access to treatment. Such access appears unfeasible in the current pricing and policy environment.

Through its association with drug use and incarceration, HCV infection carries a social stigma. This stigma can cause feelings of shame and depression in chronically infected people, leading them in turn to avoid medical care, a poor outcome for the patients and for society. Stigma can also prevent HCV from being a public priority. Prisons are a promising venue in which to treat HCV, but treating HCV is expensive for the prison system. The cost of the direct-acting antivirals is high and the staff time required to manage an inmate in treatment often far exceed the available resources.

Although ending the public health problem of hepatitis B and C in the United States is feasible, it is not necessarily likely without considerable attention to the barriers discussed in this report. The strategy needed to address the critical factors and mitigate the barriers laid out in

Tables S-1 and S-2 will be discussed in phase two of this project, in a report to be released in 2017.

TABLE S-1 The Feasibility of Eliminating Hepatitis B as a Public Health Problem in the United States with Critical Factors for Success and Crosscutting Problems

Goal		Feasibility	Critical Factors	Crosscutting Barriers
Ending Transmission	Perinatal	Highly feasible	• Identifying HBV-infected mothers • Consistent birth dosing with HBV vaccine	• Surveillance is sporadic and underfunded. • Vaccine tracking across jurisdictions is poor. • Stigma keeps people from screening and care. • Foreign-born adults can be difficult to reach with screening and treatment programs. • Much of the burden for managing chronic hepatitis B falls on overworked primary care providers. • There is a need to better understand the virus and the management of chronic HBV infection.
	Children	Highly feasible	• Consistent vaccination and attention to catch-up dosing	
	Adults	Feasible	• No system for vaccinating adults • Undiagnosed, asymptomatic chronic infections a reservoir for infection	
Reducing morbidity and mortality attributable to ongoing infection	Slowing progression to cirrhosis	Feasible	• Need for physicians trained in the management of chronic HBV infection • The threat of reactivation in chronic or resolved infection • No available treatment eliminates cccDNA or cures the disease	
	Reducing deaths			

NOTE: cccDNA, covalently closed circular DNA; HBV, hepatitis B virus

TABLE S-2 The Feasibility of Eliminating Hepatitis C as a Public Health Problem in the United States with Critical Factors for Success and Crosscutting Problems

Goal		Feasibility	Critical Factors	Crosscutting Barriers
Ending Transmission		Feasible	• No vaccine • Reaching people who inject drugs with harm reduction programs • Comprehensive drug and alcohol programs • Treating those transmitting the virus to prevent new infection • Reducing the possibility of reinfection	• Surveillance is sporadic and underfunded. • Only about half of chronically infected people have been diagnosed. • Most new infection is associated with injection drug use, the group most affected is difficult to screen. • Poor, marginalized, and hard-to-reach populations are difficult to enroll and retain in care. • The high cost of direct-acting antiviral drugs makes universal treatment unfeasible. • Hepatitis C is not a public priority. • Stigma keeps highest risk people away from care. • The limited capacity of prison health systems to treat HCV-infected inmates.
Eliminating Chronic Infection		Feasible	• Increasing access to treatment • The threat of antiviral resistance • Understanding the role of treatment adherence	
Reducing morbidity and mortality attributable to ongoing infection	Slowing progression to cirrhosis	Feasible	• Problems assessing and staging fibrosis • Obesity, HIV, alcohol use can aggravate disease progression • Eradicating the virus before progression to advanced fibrosis can almost eliminate complications and risk of death • Need for reliable models of disease progression	
	Reducing deaths			

NOTE: HCV, hepatitis C virus

1

Introduction

Hepatitis is an inflammation of the liver, often caused by a virus. Hepatitis B virus (HBV) and hepatitis C virus (HCV) cause the majority of hepatitis in the United States and worldwide. The two diseases together account for more than 1 million deaths per year, including 78 percent of the world's hepatocellular carcinoma, the most common type of liver cancer, and 55 percent of fatal cirrhosis (WHO, 2016b). In 2013, viral hepatitis surpassed HIV and AIDS to become the seventh leading cause of death in the world (WHO, 2016a) (see Box 1-1 and Figure 1-1). Table 1-1 gives more information on the key characteristics of the two diseases.

BOX 1-1
10 Leading Causes of Death Worldwide*

1. Ischemic heart disease
2. Cerebrovascular disease
3. Chronic Obstructive Pulmonary Disease
4. Lower respiratory infections
5. Alzheimer's disease
6. Lung cancer
7. **Viral hepatitis**
8. Road injuries
9. HIV and AIDS
10. Diabetes

* Based on 2013 data.
SOURCES: Cooke et al., 2013; IHME, 2015; WHO, 2016a.

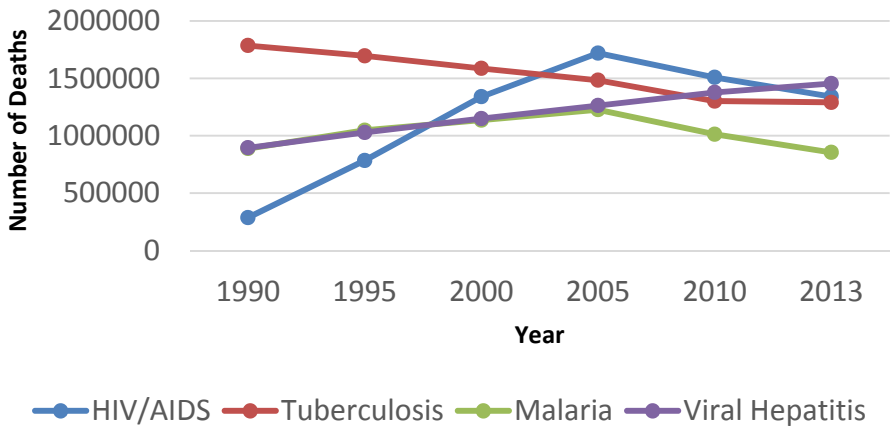

FIGURE 1-1 Estimated deaths worldwide from viral hepatitis, HIV/AIDS, malaria, and TB, 1990-2013.
SOURCE: IHME, 2016.

TABLE 1-1 Key Characteristics of Hepatitis B and Hepatitis C

	Hepatitis B	Hepatitis C
Causative Agent	Partially double-stranded DNA virus Hepadnaviridae family	Enveloped, positive-strand RNA virus *Hepacavirus* genus, Flaviviridae family
Statistics	In the United States, there are an estimated 0.7-1.4 million people chronically infected with HBV, with approximately 19,800 new infections every year.[a]	In the United States, there are an estimated 2.7-4.7 million people chronically infected with HCV, with approximately 29,700 new infections every year.[a]
Routes of Transmission[d]	Contact with infectious blood, semen, and other body fluids; transmitted through[a]: • Birth to an infected mother • Sexual contact with an infected person • Sharing contaminated needles, syringes, or other injection-drug equipment Less commonly through: • Contact with infectious blood through medical procedures	Contact with infectious blood, primarily through[a]: • Sharing contaminated needles, syringes, or other injection-drug equipment Less commonly through[c]: • Sexual contact with an infected person • Birth to an infected mother • Contact with infectious blood through medical procedures
Persons at Risk[d]	• Persons born in geographic regions that have HBsAg prevalence greater than 2%[b] • Infants born to HBV-infected mothers[a] • Household contacts of persons chronically infected with HBV[a] • Sex partners of HBV-infected persons[a] • Injection-drug users[a] • Persons with multiple sex partners[a] • Men who have sex with men[a]	• Persons who have ever injected illegal drugs, including those who injected only once many years ago[a] • • Persons born between 1945 and 1965 • Recipients of clotting factor concentrates made before 1987[a] • Recipients of blood transfusions or donated organs before July 1992[a] • Patients who have ever received long-term

	• Persons at risk for occupational exposure to blood or blood-contaminated body fluids[b] • Residents and staff at facilities for developmentally disabled persons[b] • Patients with signs or symptoms of liver disease • Hemodialysis patients [a] • Persons requiring immunosuppressive or cytotoxic therapy[a] • Travelers to countries that have intermediate or high prevalence of HBV infection[a]	hemodialysis treatment[a] • Persons with known exposures to HCV (e.g., healthcare workers after needlesticks, recipients of blood or organs from donors who later tested HCV-positive[a]) • All persons who have HIV infection[a] • Patients with signs or symptoms of liver disease[a] • Children born to HCV-positive mothers[c]
Potential for Chronic Infection	Among newly infected, persons, chronic infection occurs in[b]: • >90% of infants • 25-50% of children aged 1-5 years • 5% of older children and adults	Chronic infection develops in 75-85% of newly infected persons[c]
Clinical Outcomes	• 15-25% of chronically infected persons will die prematurely from cirrhosis, liver failure, or hepatocellular carcinoma[b] • In the United States, 2,000-4,000 deaths each year are due to chronic HBV infection[b]	• Chronic liver disease[c] develops in 60-70% of chronically infected persons • Cirrhosis develops in 5-20% over a period of 20-30 years[c] • 1-5% will die from cirrhosis or hepatocellular carcinoma[c] • In the United States, about 15,000 deaths a year are due to HCV infection[c]

NOTES: HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus
[d] In no particular order
SOURCES: Adapted from IOM, 2010, with updated information from [a]CDC, 2015e; [b]CDC, 2015a; [c]CDC, 2016.

THE GLOBAL BURDEN OF HEPATITIS B AND C VIRUS INFECIONS

The prevalence of chronic hepatitis B is highest in East Asia and sub-Saharan Africa (see Figure 1-2), where people are commonly infected via mother-to-child transmission at birth, or in early childhood through exposure to infected blood usually from an infected family member or another child. In places with a low prevalence of hepatitis B, such as North America and Western Europe, the virus is more commonly transmitted through injection drug use and unprotected sex, while immigrants from hepatitis B-endemic countries are the major source of chronic infection. Chronic hepatitis C is most prevalent in the Middle East and Asia (see Figure 1-3), where unsafe medical injection and transfusion practices are the major source of infection. In North American and Western Europe, injection drug use is the main transmission route for HCV infection.

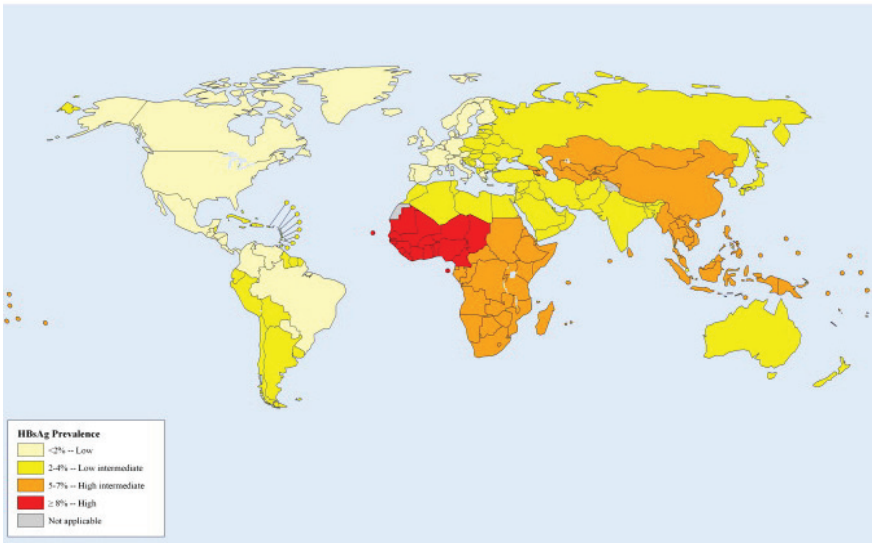

FIGURE 1-2 Global distribution of chronic hepatitis B infection in adults 19-49 years old as indicated by HBsAg seroprevalence, 2005 data.
SOURCE: Ott et al., 2012.

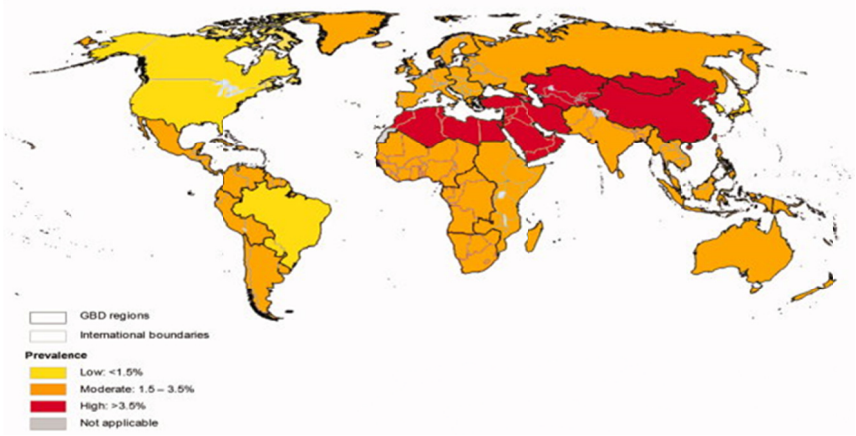

FIGURE 1-3 Global distribution of hepatitis C as indicated by anti-HCV seroprevalence.
NOTES: Estimates are derived from a meta-analysis of data from 232 studies published between 1997-2007 and NHANES data up to 2010. Point prevalence estimates are calculated using regional population age weights.
SOURCE: Mohd Hanafiah et al., 2013.

Viral Hepatitis in the United States

In the United States hepatitis B and C accounted for about 20,000 deaths annually between 2009 and 2013 (CDC, 2013). The CDC estimates that between 700,000 and 1.4 million people have chronic hepatitis B in the United States; the same source gives a chronic hepatitis C prevalence of 2.7 to 3.9 million, though both estimates are thought to be low (CDC, 2011; 2015b).The two diseases together account for over a third of liver transplantations (Luu, 2015). By 2013 estimates, the viruses cause an estimated 61 percent of the nation's hepatocellular carcinoma, the most common form of liver cancer (IHME, 2016). Liver cancer, in turn, is the fastest rising cause of cancer deaths in the United States; its incidence has tripled since the early 1980s (El-Serag and Kanwal, 2014). While Asian-American men have the highest age-adjusted incidence of liver cancer, other ethnic groups have seen rapid proportional increases, as have people aged 45-60, and people in southern states (see Figure 1-4).

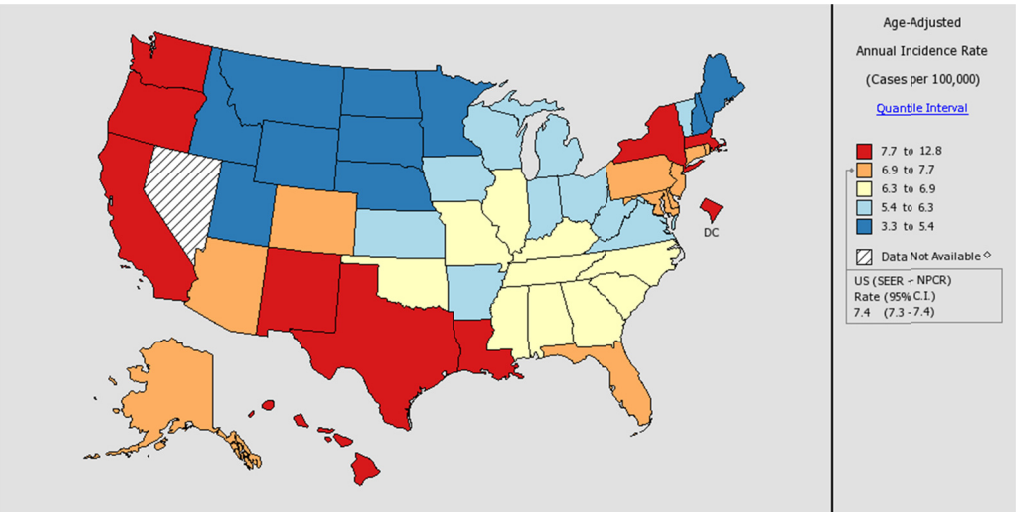

FIGURE 1-4 Incidence rates of liver and bile duct cancer for the United States, 2008-2012.
NOTES: Created by statecancerprofiles.cancer.gov on 01/11/2016 8:58 am. Data on the United States does not include data from Nevada.State Cancer Registries may provide more current or more local data. Data presented on the State Cancer Profiles website may differ from statistics reported by the State Cancer Registries.
† Incidence rates (cases per 100,000 population per year) are age-adjusted to the 2000 US standard population (19 age groups: <1, 1-4, 5-9,… , 80-84, 85+). Rates are for invasive cancer only (except for bladder which is invasive and in situ) or unless otherwise specified. Rates calculated using SEER*Stat. Population counts for denominators are based on census populations as modified by National Cancer Institute. The 1969-2013 population data is used incidence rates.
□ Data not available for this combination of geography, statistics, age and race/ethnicity.
SOURCES: State Cancer Registries, 2016; U.S. Cancer Statistics Working Group, 2016.

Action against hepatitis B and C is difficult, in part because the diseases are often asymptomatic until the later stages. Research suggests approximately two-thirds of people infected with hepatitis B are not aware of their condition (Cohen et al., 2011; Lin et al., 2007). Similarly, about half of those infected with hepatitis C are unaware of their condition (Volk et al., 2009). Without medical management and appropriate antiviral treatment, chronic hepatitis B carries a 15 to 25 percent risk of serious liver conditions (CDC, 2015a). Over time, chronic

hepatitis C greatly increases risk of death. Over 18 years of follow-up, the liver-related mortality rate for chronically infected HCV patients is more than 12 percent, compared to less than 1 percent for people without chronic HCV infection (Lee et al., 2012). Chronic hepatitis B or C also increases the risk of liver cancer (Lai and Yuen, 2013).

To complicate the matter, chronic hepatitis B and C take a disproportionate toll on minority groups and the foreign-born, for whom there may be barriers to seeking treatment. Half of all hepatitis B patients in the United States are Asian-American or Pacific Islander, though this group accounts for only about 5 percent of the population; among African immigrants the prevalence of infection is about 1 in 10 (HHS, 2014; Hoeffel et al., 2012; Mitchell et al., 2011). Hepatitis C infection shows similar disparities. American Indians and Alaskan Natives have the highest incidence of acute hepatitis C of any racial or ethnic group, and African-Americans, who make up only 12 percent of the US population, account for 22 percent of chronic hepatitis C infections (CDC, 2013; HHS, 2014). Viral hepatitis can affect people marginalized in other ways. The use of injection drugs is the principle risk factor for hepatitis C (Zibbell, 2015). Though it is difficult to estimate the disease burden among people who inject drugs, recent surveys among active drug injectors suggest about a third of those under 30 and as many as 70 to 90 percent of those over 30 have chronic hepatitis C (CDC, 2016).

A vaccine against hepatitis B has been available since the 1980s, though the most recent national survey suggests adult coverage rates of only 25 percent (CDC, 2015d; Chen, 2010). Developments in curative therapy for hepatitis C are more recent. As of 2014, oral, direct acting antiviral regimens of relatively short duration make cure[1] possible in 95 percent of patients and are associated with few adverse effects (Feld et al., 2015; Foster et al., 2015). Together these advances have encouraged global interest in action against viral hepatitis, reflected in the United Nations' Sustainable Development Goals, which mention viral hepatitis, along with HIV, tuberculosis, and malaria, as a disease to be actively combatted by 2030 (United Nations, 2014). The World Health Assembly has issued two statements on viral hepatitis in only three years; in 2014 member states requested that the World Health Organization (WHO) examine the feasibility of hepatitis B and C elimination (World Health Assembly, 2014). By January 2016, 24 countries had developed national viral hepatitis actions plans; 19 other countries have plans in development (WHO, 2016a).

THE COMMITTEE'S CHARGE

The elimination of hepatitis B and C is a topic of particular concern to the Division of Viral Hepatitis at the Centers for Disease Control and Prevention (CDC) and the Office of Minority Health in the Department of Health and Human Services (HHS). The US government's 2014 interagency action plan on viral hepatitis lays out four national goals to be achieved by 2020, shown in Box 1-2. Both offices are involved in the global discussion on hepatitis B and C elimination and also work on elimination programs for specific populations, including the elimination of hepatitis C from the Cherokee Nation and the Republic of Georgia (Mitruka et al., 2015). Given this context and the growing international momentum for action against viral

[1] *Sustained virologic response* and *cure* are used synonymously. When interferon treatments were standard of care for hepatitis C, sustained virologic response was defined as negative viral load 24 weeks after cessation of therapy. With direct acting antivirals, this timeframe is shortened to 12 weeks. The 12-week mark is recognized as the endpoint for cure by the Food and Drug Administration because of the high concordance between sustained virologic response at 12 and 24 weeks (FDA, 2013).

hepatitis, the offices sought guidance from the National Academies of Sciences, Engineering, and Medicine on the feasibility of eliminating hepatitis B and C from the United States.

The study sponsors directed the committee to work in two phases and produce two reports. This report, the first of the pair, examines the feasibility of hepatitis B and C elimination in the United States. The phase two report, to be published in 2017, will outline a strategy for meeting the elimination goals discussed in this report. Box 1-3 shows the statement of task for both projects, though this report is limited to the phase one task.

BOX 1-2
National Goals for Reducing the Burden of Viral Hepatitis by 2020

- Increase in the proportion of persons who are aware of their hepatitis B virus infection, from 33% to 66%
- Increase in the proportion of persons who are aware of their hepatitis C virus infection, from 45% to 66%
- Reduce by 25% the number of new cases of HCV infection
- Eliminate mother-to-child transmission of HBV

SOURCE: (HHS, 2014)

The Committee's Approach to Its Charge

To address the charge laid out in Box 1-3, the committee reviewed the available evidence on the burden of hepatitis B and C, the screening, treatment, and management of chronic infection, and scientific and logistical obstacles to elimination. They drew on published literature and presentations from expert speakers as well as information about federal and state viral hepatitis programs. Members of the public submitted written testimony to the committee, which was also taken into account (available from the National Academies' Public Access Records Office, PARO@nas.edu).

The committee met twice to prepare this report; see Appendixes A and B for the meeting agendas. In closed session, the group evaluated the evidence and deliberated on the feasibility of eliminating hepatitis B and C from the United States; members discussed the implications and feasibility of disease control, elimination, and eradication goals. Based on expert opinion, the committee came to conclusions regarding the feasibility of disease elimination. As the two diseases have widely different viral origins, natural histories, epidemiological features, and clinical management, the committee dealt with the elimination question separately for each disease. The remainder of this chapter gives background and context for understanding disease elimination and explains the committee's conclusions about a suitable disease elimination goal. Chapter 2 discusses hepatitis B elimination, and the critical factors necessary to end transmission and reduce morbidity and mortality from the disease. Chapter 3 deals with the same questions for hepatitis C.

BOX 1-3
Statement of Task

PHASE I

The National Academies of Sciences, Engineering, and Medicine will conduct a literature review and convene two meetings of the committee, one of which will include a two part workshop, one part focused on hepatitis B virus (HBV) and one focused on hepatitis C virus (HCV) to determine whether HBV and HCV elimination goals for the United States are feasible and to identify possible critical success factors. A brief report containing the committee's conclusion regarding the feasibility of setting elimination goals and possible critical success factors shall be prepared.

PHASE II

The committee will prepare a consensus report containing committee conclusions and recommendations, specifically identifying:

1. the appropriate hepatitis reduction or elimination goal(s) and specifying a plan of action to achieve the goal(s) including, but not necessarily limited to: medical and substance abuse services, community-based services, and correctional health services;
2. barriers to achieving the goal(s) such as access to treatment and related policy issues; public health infrastructure resources for screening, education and outreach; and surveillance;
3. potential solutions to the barriers identified; and
4. specific stakeholders and their responsibilities to achieve the goal.

The report will be sponsored by the Centers for Disease Control and Prevention (CDC) and addressed to CDC, state and local health departments, the medical community, and others.

DISEASE CONTROL, ELIMINATION, AND ERADICATION

The elimination of important infectious disease from society is a goal dating to at least the eighteenth century, when Edward Jenner envisioned ridding the world of smallpox through widespread vaccination. Programs initiated in the early and middle parts of the 20th century to eradicate yellow fever, yaws, and malaria, while unsuccessful, improved understanding of the epidemiological and biological features that make a disease a candidate for eradication. When, in 1966, the World Health Assembly resolved to eradicate smallpox from the Earth, it was clear that *eradication* meant preventing any new cases of smallpox in the world; the surveillance and documentation system developed to support that goal left no room for a single infection.

Smallpox eradication emboldened policy makers; it seemed at the time that other human and animal diseases might be equally susceptible (Hopkins, 2009). In 1988, the International Task Force on Disease Eradication began systematic evaluation of the qualities that make a disease eradicable (The Carter Center, 2016b; Tulchinsky and Varavikova, 2009). In addition to scientific characteristics of the disease and available counter-measures, the group weighed social considerations such as political will and perceived burden of disease (see Box 1-4). After

BOX 1-4
International Task Force for Disease Eradication

Criteria for Assessing Eradicability

- **Epidemiologic vulnerability** assessed by factors such as the existence of nonhuman reservoir, ease of spread, natural cyclical decline in prevalence, naturally induced immunity, ease of diagnosis, and duration of any relapse potential
- **Availability of an effective, practical intervention,** such as a vaccine or other primary preventive, curative treatment, or vector control intervention. Ideally, the intervention should be effective, safe, inexpensive, long-lasting, and easily deployed.
- **Demonstrated feasibility of elimination** particularly in documented elimination demonstration projects from islands or other geographic units. Political will and popular support are essential.
- **Perceived burden of the disease** includes factors such as extent of burden and deaths. Other effects include possibility of true burden may not be perceived, the reverse of benefits expected to accrue from eradication, and the relevance to rich and poor countries.
- **Expected cost of eradication,** especially in relation to perceived burden of disease.
- **Synergy of aligning with other interventions** and potential for added benefits, savings, or spin-off effects (e.g., polio eradication and the expanded program on immunization coverage; guinea worm and the Water and Sanitation Decade; yaws and primary health care)
- **Necessity for eradication rather than control**

SOURCE: CDC, 1992.

reviewing 94 infectious diseases, they found only six[2] suitable for eradication (CDC, 1993). None of these has since been eradicated, though guinea worm disease is close (The Carter Center, 2016a). The discussion also quickly made it clear that different people could have widely different ideas of what disease eradication, elimination, and control might mean, raising interest in standard definitions of the relevant terms.

Clarifying the hierarchy of different public health efforts was a goal of the 1998 Dahlem Conference, which proposed mutually exclusive definitions for terms relevant to disease eradication. These definitions overlap with those of the earlier task force, especially in their understanding of disease eradication and control (both shown in Box 1-5). The Dahlem definitions emphasize the zero goal of disease elimination, while the earlier understanding left room for controlling the disease to the point of no longer being a public health problem.

In 2010, another expert panel revisited the concepts of disease elimination at the request of the WHO Executive Board (WHO, 2010). But since that meeting, the use of the terms defined in Box 1-5 has grown only more inconsistent. Such confusion causes problems in program evaluation. Without a clear idea of the level of control sought, it is difficult to judge a program's

[2] Guinea worm disease, polio, lymphatic filariasis, mumps, rubella, and pork tapeworm

BOX 1-5
Definition of Terms

The International Task Force for Disease Eradication 1989-1992

Eradication: Reduction of the worldwide incidence of a disease to zero as a result of deliberate efforts, obviating the necessity for further control measures. True eradication usually entails eliminating the microorganism itself or removing it completely from nature.

Elimination: Refers to cessation of transmission of a disease in a single country, continent, or other limited geographic area, rather than global eradication (e.g., polio in the Americas). It is also theoretically possible to "eliminate" a disease in humans while the microbe remains at large (e.g., neonatal tetanus). Although a disease itself may remain, a particularly undesirable clinical manifestation of it may be prevented entirely (e.g., blindness from trachoma) or new transmission interrupted (e.g., infectious yaws). Control of a disease or its manifestations to a level that it is no longer considered "a public health problem," as an arbitrarily defined qualitative (e.g., onchocerciasis in West Africa) or quantitative (e.g., leprosy incidence below one case per 10,000 population) level of disease control.

Control: Reduced incidence or prevalence of a disease or condition; control measures are still required.

The Dahlem Conference, 1998

Control: Reduction of disease incidence, prevalence, morbidity or mortality to a locally acceptable level as a result of deliberate efforts; continued intervention measures are required to maintain the reduction

Elimination of diseases: Reduction to zero of the incidence of a specified disease in a defined geographic area as a result of deliberate efforts; continued intervention measures are required to maintain the reduction.

Elimination of infection: Reduction to zero of the incidence of infection caused by a specific agent in a defined geographic area as a result of deliberate efforts; continued measures to prevent reestablishment of transmission are required.

Eradication: Permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts; intervention measures are no longer needed.

Extinction: The specific infectious agent no longer exists in nature or the laboratory.

SOURCES: CDC, 1993; Dowdle, 1998.

progress, or even know what information the surveillance system should supply. In the smallpox example, the goal of no new cases without continued vaccination was possible because of the disease's recognizable clinical presentation, the lack of chronic infection or silent transmission, the absence of a non-human reservoir in nature, and the availability of a highly effective vaccine. On the other hand, the Pan American Health Organization's measles elimination program, which aimed to end measles transmission in the Americas, recognized that endemic measles in other parts of the world would inevitably lead to periodic re-introduction to the Americas (Andrus et al., 2011). The program therefore needed a sensitive surveillance system and a laboratory network for distinguishing endemic cases from imported ones. Similarly, ongoing work in global

polio eradication struggles with asymptomatic infection and silent transmission, to say nothing of the difficulty distinguishing wild-type virus infection from vaccine-derived infection. Measuring the success of both measles and polio eradication depend on sophisticated virological surveillance.

The elimination of viral hepatitis poses its own challenges, both in defining what qualifies as elimination and in monitoring progress toward the goal. Both HBV and HCV can be cleared after introduction by the host's immune response. Among those people who acquire chronic infection, the majority of cases become clinically apparent only decades later. For these reasons, as well as those discussed earlier (the diseases' different origins, natural histories, epidemiological features, and clinical management), it is necessary to consider the feasibility of eliminating acute infection, chronic infection, and the clinical sequelae of such infections (including liver disease, liver cancer, and death) separately for each disease.

It is also important to remember that both viruses are endemic abroad, so their elimination from the United States would exist against a background of constant re-importation. Perfect vaccination could, in theory, eliminate transmission of HBV, but it would take two generations. In the meantime, there is no cure for the millions of people already infected. The new direct-acting antivirals that cure HCV infection are increasingly available, but still unlikely to reach all of the world's hepatitis C-infected people anytime soon. Any strategy to eliminate hepatitis B and C from the United States would also have to account for the imported cases and for transmission attributable to people born abroad.

In setting elimination goals for hepatitis B and C, the committee considered the challenges of identifying prevalent and incident cases and the related problem of monitoring progress toward the goal of disease reduction. It also acknowledged the devastating consequences of both infections and the power of the global momentum for action against viral hepatitis. With this in mind, the committee concluded that disease control—defined as a reduction in the incidence and prevalence of hepatitis B and C and their sequelae with ongoing control measures required—is feasible in the relatively short term. It also saw value in setting a goal to eliminate the public health problem of these diseases; in this case, elimination refers to cessation of transmission in the United States, allowing that the infections may remain but their particularly undesirable clinical manifestations prevented entirely. In its discussion of elimination the committee emphasized reducing the manifestations of HBV and HCV infection to a level that is *no longer a public health problem*. For the committee's purposes, a public health problem may be defined as a disease that by virtue of transmission or morbidity or mortality commands attention as a major threat to the health of the community.

The committee's reliance on the 1998 interpretation of disease elimination is made in consideration of the epidemiological and clinical presentation of hepatitis B and C, and in an effort to balance the momentum for disease elimination against the real limitations of surveillance and treatment of these infections. The flexible target, already clear in the WHO plan, is more suitable to this question than a hard target of zero incidence or prevalence. For reasons discussed later in this report, hepatitis B patients can expect to live long lives with chronic infection and die of unrelated causes; ending deaths from hepatitis C could be managed far more easily than completely ending transmission of the virus. Disease elimination, or in this case elimination of the public health problem, is still a powerful motivator and one that can be embraced without over-promising or setting the program up for failure.

The committee appreciates the simplicity and motivational value of a zero-target elimination program. Barring major unforeseen scientific advances in treatment or prevention in both the United States *and* the world's HBV and HCV-endemic countries, such a hard goal does not seem feasible. The point at which hepatitis B and C are no longer public health problems might be somewhat open to interpretation. Not every state health officer or politician will have the same view of what constitutes a public health problem, but identifying cut points for such a determination is outside the scope of this report. In any case, to understand when a disease ceases to be a public health problem depends entirely on knowing the disease burden in the population. Monitoring any progress toward the elimination of hepatitis B and C will depend on better systems for surveillance.

Strategies for Hepatitis B and C Surveillance

Disease surveillance systems provide essential intelligence on the magnitude and distribution of a disease. Such data informs strategies for prevention and allocation of treatment resources. A functional disease surveillance system allows health departments to estimate the burden of disease, where and who it strikes, and to describe its natural history. Surveillance systems can monitor for the evolution of mutations or changes in virulence, identify outbreaks, evaluate prevention and control programs, and identify future research priorities (Thacker, 2000).

When surveillance systems are strong, potential outbreaks can be averted. Poor disease surveillance, in contrast, can cause public health disasters such as the 2014 Ebola outbreak and the re-emergence of polio in parts of Africa (Hagan et al., 2015). Surveillance failures happen in rich countries too. In January 2015 state health officers identified an outbreak of HIV in rural Indiana (Conrad et al., 2015). Injection drug use drove the outbreak, and 84.4 percent of cases were found to be co-infected with HCV (Conrad et al., 2015). It is possible that better attention to hepatitis C surveillance might have helped identify this outbreak earlier. Reporting new cases of viral hepatitis, or any infectious disease, to the state or local health department allows for an accurate understanding of disease burden, eases case management, contributes to a better understanding of the disease's transmission routes, and helps to identify outbreaks and monitor progress toward public health goals (Kirkey et al., 2013; Thacker, 2000).

Viral hepatitis is not a well-funded target for public health surveillance (CDC, 2013). Only seven jurisdictions in the United States (five states and two cities) have CDC funding for viral hepatitis surveillance (CDC, 2015c). The CDC and Council of State and Territorial Epidemiologists set national guidelines on classifying and reporting acute and chronic infections, but state and local health departments are responsible for implementing these guidelines in the field and for feeding information to the national surveillance network (Church et al., 2014). Not all jurisdictions require reporting of chronic HBV or HCV infection, and when they do the reporting format is not standardized so valuable data are often missing (Church et al., 2014). Some health departments use automated, web-based systems, but such systems are expensive to buy and to maintain. Even when different jurisdictions use the same system, the configuration is adapted to local reporting policies. The CDC's standardized reporting system is a good base program, available across the country, but it does not allow for more advanced surveillance practice.

Underreporting is common in cases of viral hepatitis, in part because the diseases affect people who may be out of contact with the health system: people born abroad, racial and ethnic

minorities, people who inject drugs or have been in prison. The building, global momentum for elimination of hepatitis B and C is cause enough to revisit the barriers.

Without better understanding of the burden of viral hepatitis, it will not be possible to make efficient use of the resources available to fight it. Expanded sentinel surveillance in high-risk clinical practices would give better understanding of current trends. Technology can also complement surveillance data. Geospatial imaging and mining of electronic health data has potential for disease surveillance, especially in hard-to-reach populations.

Key Findings and Conclusions

- Viral hepatitis is the seventh leading cause of death in the world. Hepatitis B and C cause the majority these deaths. The two diseases account for over a million deaths a year, about 20,000 of which are in the United States.
- Hepatitis B and C infections are asymptomatic until the later stages. About two-thirds and half of people infected with hepatitis B and C respectively do not know of their condition.
- Both infections are borne disproportionately by racial and ethnic minorities and by socially marginalized groups such as people who inject drugs.
- HBV vaccine conveys 95 percent immunity in three doses. New HCV treatments can cure 95 percent of infections. Taken together, these developments have encouraged international momentum for action against viral hepatitis.
- The elimination of hepatitis B and C poses challenges, both in defining what qualifies as elimination and in monitoring progress toward that goal.
- It is feasible in the relatively short term to control hepatitis B and C—meaning to reduce their incidence and prevalence.
- Eliminating the public health problem of hepatitis B and C—meaning that the diseases may remain but transmission will stop and the most undesirable manifestations prevented completely— is also feasible, but considerable barriers face any elimination program.

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2

The Elimination of Hepatitis B

After analyzing the problem of hepatitis B in the United States and reviewing relevant literature, the committee concluded that eliminating the public health problem of this disease is feasible with certain conditions. This chapter lays out the committee's logic in coming to this decision. First, it describes the epidemiology and natural history of the infection, then makes a brief statement on the committee's conclusion regarding elimination. Next, the chapter discusses ending transmission of the virus; then it deals with preventing deaths among people already infected. The last sections lay out critical factors that would influence progress toward the elimination goal and possible barriers to this goal. A discussion of the strategies that might be employed in an elimination program is outside the scope of this report, but can be expected from phase two of this project.

EPIDEMIOLOGY OF HEPATITIS B

Hepatitis B virus (HBV) is the most prevalent cause of chronic viral hepatitis and hepatocellular carcinoma in the world. Recent estimates suggest about 250 million people have chronic HBV infection, causing about 780,000 deaths per year (Schweitzer et al., 2015; WHO, 2015b). The burden of disease is heaviest in East and Southeast Asia, sub-Saharan Africa, the Amazon Basin, and parts of Eastern Europe. In these areas, lifetime risk of HBV exposure is nearly universal and prevalence of chronic infection in adults is about 5 to 10 percent. Prevalence of chronic adult infection is generally lower in the Middle East and South Asia (about 2 to 5 percent) and lower still (less than 1 percent) in North America, Western Europe, and Australia (Evans et al., 2014; Sobeslavsky, 1980; WHO, 2014, 2015b).

HBV is transmitted though contact with blood and bodily fluids of an infected person. Sexual contact and injection drug use drive most HBV transmission among American adults (63 and 16 percent respectively) (Mast et al., 2006). People whose occupations put them in contact with blood or blood products are also at risk, as are household contacts of infected persons, and people travelling in endemic countries, but those routes of transmission account for only about 5 percent of cases (Mast et al., 2006). Sometimes the means of transmission is unclear. About 16 percent on newly-infected hepatitis B patients report no particular risk factors for infection (Mast et al., 2006)

Preventing transmission of HBV to vulnerable newborns and children is a pillar of all global and national HBV prevention strategies. In the United States, the Advisory Committee on Immunization Practices first recommended universal HBV vaccination in 1991among infants (CDC, 1991). By 2013, estimated national coverage of three or more doses among children 19 to 35 months of age was 90.8 percent (95 confidence interval [CI]: 88.8 to 92.8 percent), and 74.2 percent (95 CI: 71.5 to 76.9 percent) of newborns received the first dose with three days of birth (Elam-Evans et al., 2014b). Full immunization among adolescents aged 13 to 17 years, was 93.2 percent (95 CI: 91.8 to 94.6 percent) in 2013 (Elam-Evans et al., 2014a). The proportion of the population that has received the vaccination and is immune will improve over time, as children gradually age.

As a result, the United States has made encouraging progress against transmission of HBV, especially among children and adolescents. Reports of acute hepatitis B have declined

from 8,036 cases in 2000 to 3,050 cases in 2013, a decrease largely attributable to infant and child immunization (CDC, 2013c). Acute hepatitis B is now rare in children, but remains a problem among unvaccinated adults. Adjustments for underreporting suggest an underlying incidence of acute infection at almost 20,000 cases in 2013 (CDC, 2013c). The decrease in incidence of acute hepatitis B has resulted in a decrease in new cases of chronic, domestically-acquired chronic infection. The CDC estimates that immigration from HBV endemic countries accounts for most new chronic infections (see Figure 2-1).

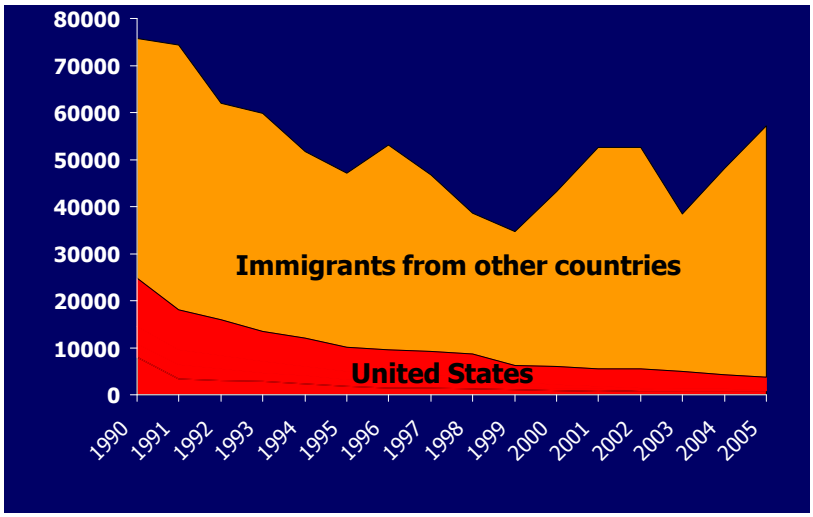

FIGURE 2-1 Estimated new chronic HBV infections by place of acquisition, US 1990-2005.
SOURCE: Hu, 2008.

Although the CDC estimates put the prevalence of chronic hepatitis B infection between 700,000 and 1.4 million, other estimates suggest more than 2 million (CDC, 2015b; Cohen et al., 2007; Kowdley et al., 2012; Wasley et al., 2010). The wide margin reflects the fact that chronic infection is often asymptomatic and borne disproportionately by immigrants from HBV-endemic countries in Asia and sub-Saharan Africa (Amiteye, 2015; Chen and Dang, 2015). Population surveys and other tools to estimate disease prevalence tend to undercount foreign-born people, who may not be proficient in English and often face barriers to accessing care (Chen and Dang, 2015; Rossi et al., 2012). It is also difficult to count the deaths attributable to hepatitis B, as its end-stage consequences (liver cirrhosis and hepatocellular carcinoma) tend to appear on death certificates without mention of the root cause (Ly et al., 2012; Manos et al., 2008).

The Hepatitis B Virus

Hepatitis B virus is a partially double-stranded, circular DNA virus surrounded by a nucleocapsid and outer envelope (Dienstag, 2008; Ganem and Prince, 2004). It replicates by reverse transcription of an RNA intermediate (Seeger et al., 1986). Measuring HBV DNA levels repeatedly over time is central to the clinical management of hepatitis B (EASL, 2012; Lok and McMahon, 2007; Terrault et al., 2016). HBV replication stimulates the host immune response, which in turn drives hepatic inflammation and progression of liver fibrosis (Bertoletti and Ferrari, 2012; Bertoletti et al., 2010). HBV DNA can integrate into the host hepatocyte genome, promoting development of hepatocellular carcinoma even without cirrhosis (Lok and McMahon, 2007; Simonetti et al., 2010; Trépo et al., 2014).

Within the nuclei of infected hepatocytes, HBV maintains a stable pool of transcriptional templates known as covalently closed circular DNA (cccDNA). These templates are essential for viral persistence. HBV cccDNA may remain at low levels after recovery from chronic infection is thought to be responsible for HBV reactivation, however rare, during acquired immunosuppression, a phenomena discussed later in this chapter (Fattovich, 2003; Locarnini and Zoulim, 2010).

The Natural History of Hepatitis B Virus Infection

HBV infection is highly variable in both presentation and severity. Some people clear the infection spontaneously, while others suffer a lifetime of chronic complications, including hepatitis, cirrhosis, and cancer. About 70 percent of acute infections in healthy adults are asymptomatic. In the remaining 30 percent, patients have complaints such as jaundice, abdominal pain, nausea, and malaise, largely indistinguishable from other liver ailments. Severity of symptoms varies greatly, and the acute infection usually resolves without sequelae. Around 1 to 5 percent of acute infections are characterized by overwhelming liver injury leading precipitously to liver failure (called fulminant hepatitis), a likelihood increased by infection with other forms of viral hepatitis (Belongia et al., 2008; Heymann, 2014; Sako et al., 2011). Still, most HBV infection is clinically silent at the start. The serious consequences such as chronic hepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma become apparent only years, even decades, later. In the meantime, people with untreated, chronic hepatitis B are a reservoir of infection to the unvaccinated (Evans et al., 2014).

People infected with HBV often carry certain antigens and antibodies in serum. Collectively these markers are called serological markers of infection. They include HBV surface antigen (HBsAg) the hallmark of active infection; HBV e antigen (HBeAg) a marker of active viral replication; HBV e antibody (anti-HBe) which reflects loss of HBeAg synthesis that can coincide with immunologic containment of infection or that can occur when viral gene mutations interfere with HBeAg synthesis; HBV core antibody (anti-HBc) a marker of past or current infection; and HBV surface antibody (anti-HBs) the marker of recovery from acute infection or immunity from vaccination (Dienstag, 2008; Lok and McMahon, 2007). Anti-HBc immunoglobulin M (IgM) appears as an antibody to the HBV core antigen during acute infection, with levels typically decreasing within 6 months despite persistence of infection (University of Washington, 2013). These markers can define different stages in clinical progression, as shown in Figure 2-2 and explained in Box 2-1.

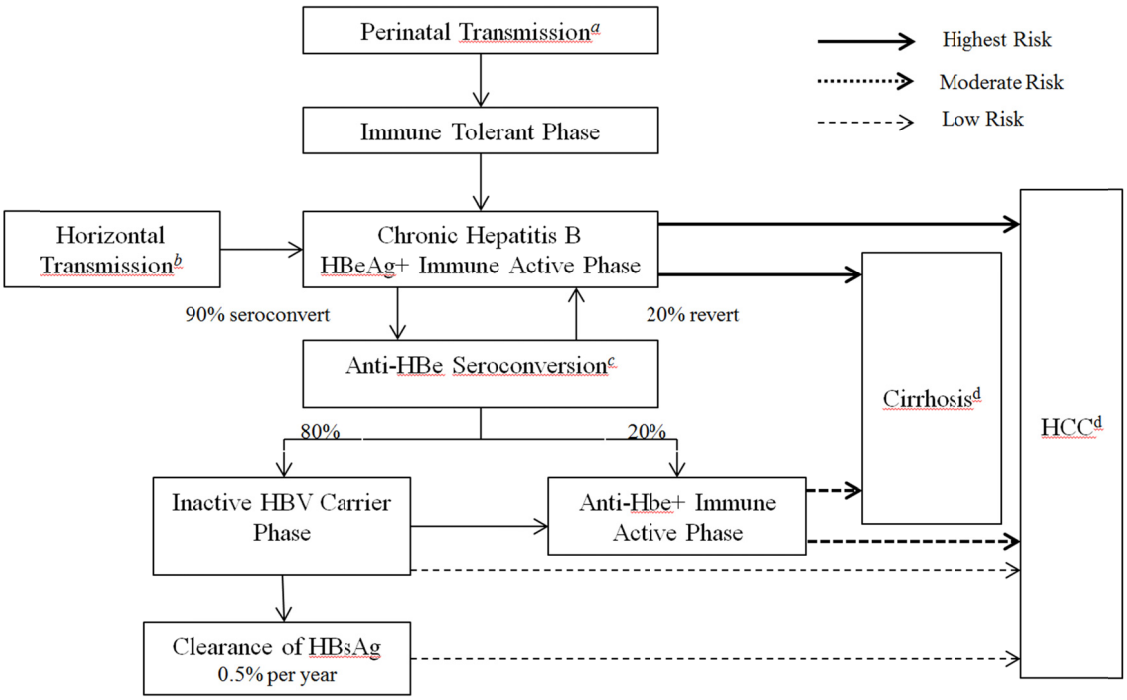

FIGURE 2-2 Natural history of hepatitis B virus infection.
NOTES: Anti-HBe, antibody to hepatitis B e antigen; HBeAg+, hepatitis B e antigen positive; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

[a]Transmission occurs in 90% of infants of HBsAg+/HBeAg+ mothers and 15% of infants of HBsAg+/anti-HBe+ mothers.

[b]30% of those infected from the age of 1–5 years and under 7% of those infected at the age of 6 years or older.

[c]About 50% of patients by 5 years and 70% of patients by 10 years will seroconvert to anti-HBe.

[d]15-25% risk of premature death from cirrhosis and HCC.

SOURCE: IOM, 2010.

BOX 2-1
Phases of Chronic Hepatitis B Virus Infection

Immune tolerance, the initial phase of chronic HBV infection is seen in perinatally-acquired infection and characterized by the presence of HBsAg, high HBV DNA levels, minimal (or no) alanine aminotransferase (ALT) elevations, and no clinical symptoms. HBeAg usually present.

Immune clearance (or immune active), a phase of chronic HBV infection is typically the initial stage in adult-acquired infection. It is characterized by the presence of HBsAg, elevated HBV DNA levels, increased ALT levels, and potentially symptomatic disease (e.g., abdominal pain, jaundice). HBeAg may be present or absent. Persistent elevations in HBV DNA and liver aminotransferase levels with unsuccessful immune clearance increase the risk of cirrhosis and hepatocellular carcinoma (Fattovich et al., 2008; Trépo et al., 2014). When HBsAg has been present for 6 months or longer the infection is said to be chronic.

Low replicative (or inactive) HBV carrier, a phase of chronic HBV infection dinstinguished by loss of HBeAg (if present) and development of anti-HBe with suppression of HBV DNA and normalization of liver aminotransferase levels. This phase is notable for the persistence of HBsAg with low or undetectable HBV DNA levels and normal or very mildly elevated ALT levels. A recent meta-analysis found that significant liver disease was rare in those who had HBV DNA levels ≤20,000 IU/mL and persistently normal liver aminotransferase levels (Papatheodoridis et al., 2012)

Resolved HBV infection, occurs when chronically infected HBV patients become HBsAg-negative. The yearly rate of spontaneous clearance of HBsAg is 0.5-1 percent (Simonetti et al., 2010)

Occult HBV infection, defined as the presence of HBV DNA in the serum or liver tissue of individuals with anti-HBc in the absence of HBsAg (Lo Re et al., 2007; Torbenson and Thomas, 2002). The mechanisms responsible for occult HBV remain unclear but may stem from mutations in the HBV genome that prevent production of HBsAg, host immune dysfunction that permits low-level HBV viremia, chronic hepatitis C virus coinfection that inhibits HBV replication (Brechot et al., 2001). The long-term clinical effects of occult HBV remain unclear, but observational studies suggest that it does not increase the risk of liver aminotransferase elevations (Lo Re et al., 2007, 2008).

Reactivation, usually a resurgence of HBV replication and liver injury in patients who were inactive carriers. Since cccDNA remains in the nuclei of infected hepatocytes, certain stressors such as withdrawal of antiviral therapy or with development of immunosuppression, can trigger viral transcription. Reactivation can result in increased HBV DNA levels, ALT elevations, and symptomatic disease (Fattovich, 2003). In such patients, the risk of reactivation following immunosuppressive therapy is high and dangerous. In patients who has resolved acute or chronic HBV infection, the risk of reactivation is low (Pita et al., 2014).

In general, presence of HBsAg (sometimes called HBsAg positivity or written HBsAg+) indicates current viral infection; in the absence of HBsAg, the presence of anti-HBc indicates prior infection. The presence of anti-HBs indicates immunity, either natural (with anti-HBc) or vaccine-induced (without anti-HBc). An anti-HBs titer of $\geq$10 mIU/ml is considered adequate for

HBV immunity, though lower titers may also be protective. Table 2-1 shows patterns of different serum indicators and their clinical significance.

Predictors of Disease Progression

After exposure to HBV infection, progression from acute to chronic disease depends mainly on age and immunity. Without intervention, up to 90 percent of infants born to HBV-infected, HBeAg+ mothers become chronically infected at birth; but chronic infection develops in 5 to 20 percent of infants born to HBV-infected, HBeAg– mothers (Ko et al., 2014; Mast et al., 2006). Similarly, chronic infection develops in 90 percent of children under five with acute HBV, but only 5 percent of acutely infected adults (Ko et al., 2014; Villeneuve, 2005).

TABLE 2-1 Serological Markers of HBV Infection and Their Usual Significance

	HBsAg Viral Glyco-protein Coat	**Anti-HBs** Antibody to HBsAg	**Anti-HBc** Total Antibody to Viral Core	**IgM anti-HBc** IgM Class Antibody to Viral Core	**HBeAg** e Antigen, Associated with Viral Core	**Anti-HBe** Antibody to HBeAg	**HBV DNA** Viral DNA
Susceptible	–	–	+/–	–	–	–	–
Natural Immunity (past infection)	–	+	+	–	Not Applicable	Not Applicable	–
Vaccine-induced Immunity	–	+ (≥10 mIU/mol considered adequate)	–	–	Not Applicable	Not Applicable	–
Early Acute Infection	+	–	+	+	+	–	+
Chronic Infection	+ Presence for ≥6 months	–	+	–	+/–	+/–	+/–
Resolved or Resolving Infection	–	+	+	–	–	–	–
Occult Infection	–	–	+	–			+/–

SOURCE: Evans et al., 2014.

When infection occurs in the perinatal period, babies are relatively immunologically tolerant to HBV; they generally have high circulating virus but little or no liver injury. This stage of relative immunological tolerance tends to persist for three or four decades (Schiff et al., 2012). Eventually, patients enter a relatively immunologically active phase in which liver damages emerges and persists, leading to cirrhosis and liver cancer. When acute infection occurs in healthy adults, no period of relative immunological tolerance ensues. Instead, immunologically mediated injury of virus-expressing liver cells occurs and, in all but a small proportion of patients, results in clearance of and recovery from HBV infection.

Longitudinal studies in Asia have shown that, among chronic hepatitis B patients, higher HBV DNA levels increase the risk of cirrhosis and hepatocellular carcinoma (Chen et al., 2006; Iloeje et al., 2006). Moreover, while most chronic hepatitis B-related hepatocellular carcinomas develop after cirrhosis, about 20 percent are not preceded by cirrhosis (Trépo et al., 2014). Coinfection with hepatitis C virus (HCV) or hepatitis D virus can further accelerate liver fibrosis progression and increase the risk of hepatic decompensation and hepatocellular carcinoma in chronic infection (Crockett and Keeffe, 2005; Kushner et al., 2015). In the United States, about 5 percent of patients have chronic hepatitis B and D coinfection (Roy, 2015). The proportion of chronic hepatitis B patients coinfected with HCV is less clear, but analysis of Department of Veterans Affairs registries suggests a prevalence 1.3 to 1.5 percent (Tyson et al., 2013).

Virus genotype also influences the course of the infection. There are at least ten[1] known genotypes of HBV, eight of which are frequently studied (Locarnini, 2004). The genotypes have different geographical distributions and varying frequency of mutations associated with clinical outcomes. Because of some genotypes (and sub-genotypes) are found only in certain parts of the world, it is not always possible to study the clinical consequences of different genotypes—the patient populations are usually too different in other ways to allow for valid comparison. In places where such comparisons are possible, usually places of high endemic hepatitis B, the results are intriguing. In Taiwan, genotype C is associated with higher risk of hepatocellular carcinoma than genotype B, partly explained by the fact that genotype B is associated with higher rates of HBeAg clearance (Yang et al., 2010). Among Alaskan Natives, longitudinal studies have shown that genotypes C, D, and F are associated with higher age-specific prevalence of HBeAg compared to genotypes A and B (Livingston et al., 2007). And in sub-Saharan Africa, genotype A subtype A1 was associated with increased risk of liver cancer in younger men (McMahon, 2009).

[1] There are eight major genotypes (A through H), with two additional forms of genotype B (Bj and Ba) (Locarnini, 2004).

Key Findings and Conclusions

- Hepatitis B virus (HBV) is the most common cause of chronic hepatitis and hepatocellular carcinoma in the world. The United States has made encouraging progress against the infection, but between 700,000 and 1.4 million people have chronic hepatitis B; almost 20,000 new acute infections occur every year.
- Chronic hepatitis C is largely asymptomatic and the presentation and severity of infection is highly variable.
- Cirrhosis usually precedes HBV-related carcinoma, but 20 percent of hepatocellular carcinoma in HBV-infected people does not follow cirrhosis.

THE FEASIBILITY OF ELIMINATING THE PUBLIC HEALTH PROBLEM OF HEPATITIS B

In general, disease elimination is a matter of reducing the basic reproductive number of the pathogen (abbreviated R_0, the average number of susceptible persons infected by one infected host, given a fully susceptible population) to a value less than one, and maintaining this rate until no new infections occur. The infectious agent may still live and multiply in its host, creating what is called a reservoir of infection, so ending transmission becomes a matter of sustaining an R_0 less than one until the reservoir of infection is depleted. Hepatitis B has no non-human reservoir and an effective vaccine. Vaccine-induced immunity to HBV is generally long-lasting with some minor age-related decline in immunogenicity. Even decades after vaccination challenge studies show strong anamnestic response with no need for a booster vaccine in otherwise healthy adults (CDC, 2012a). Among chronically infected people, antiviral drugs can reduce HBV replication to levels that dramatically reduce liver injury, disease progression, and infectivity (Osborn and Lok, 2006). Furthermore, there are practical examples of public health programs that have proven effective at interrupting transmission (see Box 2-2). For these reasons, the committee concludes that the elimination of hepatitis B as a public health problem in the United States is feasible with certain conditions.

The conditions of the feasibility of elimination relate to some unique features of the virus. The next section will discuss how HBV can pass from mother to child, an increasingly rare but persistent problem (Ko et al., 2014). The disease is also characterized by long asymptomatic periods of chronic infection, during which time unknowing infected persons could transmit it (Anderson et al., 1992). Vaccinating all susceptible persons could prevent this transmission, but even then, there appear to be genetic factors in the host or the virus that affect the immune response (Anderson et al., 1992).

BOX 2-2
A Case Study on Hepatitis B Elimination in Rural Alaska

In the early 1970s, an epidemiological survey of 3,053 residents in 12 Alaskan Native villages found HBsAg positivity in 6.4 percent of participants, an overall result which masked significant variation (4.6 to 69.9 percent) among villages (Schreeder et al., 1983). Then, in 1981, a field demonstration project of the hepatitis B vaccine found that immunization conferred greater than 97 percent immunity in unexposed Yupik Eskimo adults (Heyward et al., 1985). This success inspired the CDC and the Alaska Native Health Service to begin a comprehensive control program aimed at halting transmission of HBV and reducing deaths from hepatocellular carcinoma (McMahon et al., 1987, 2011). The project had four main components:

1. serological screening of all Alaskan Natives for HBV and at least 90 percent immunization of susceptible persons;
2. screening all pregnant Alaskan Native women, followed by newborn dosing with hepatitis B immune globulin and vaccine to babies born to HBsAg+ mothers;
3. routine hepatitis B vaccination of newborns, with the first dose given before hospital discharge and the second and third doses given at 6 weeks and 6 months respectively;
4. twice yearly testing of all HBsAg carriers for α-fetoprotein, with increased levels triggering cancer evaluation.

More than 53,000 Alaskan Natives of all ages were screened from 1983 to 1986. Patients testing positive for HBsAg were offered further cancer screening, and the 1-year case fatality rate of liver cancer fell by half (McMahon et al., 1987). By 1987, 88 percent of the 44,100 susceptible individuals were undergoing or had completed the vaccine series (McMahon et al., 1987). Acute incidence dropped from 215 per 100,000 at baseline to 14 per 100,000 in 1986 (McMahon et al., 1987).

Twenty-five years after the project's end, hepatitis B vaccination among Alaskan Native children is 93.5 percent (95 percent CI: 87.2-100 percent); the comparable national statistic is only 81.8 percent (95 percent CI: 80.9-82.7 percent) (McMahon et al., 2011). The last case of acute hepatitis B among Alaskan Natives was 1992, their last case of pediatric hepatocellular carcinoma was in 1999 (McMahon et al., 2011).

There are three main points of intervention to eliminate hepatitis B: the infection source or the infected people in the population, the susceptible hosts or those people in a population neither infected nor vaccinated, and the routes of transmission (Chen, 2010). Infection control practices such as the screening of blood, organ, and tissue donations, have done much to reduce HBV spread in the population, and would be an example of an intervention on a route of transmission. Harm reduction services (a combination of needle and syringe exchange and opiate substitution programs discussed in the next chapter) are also a known way to reduce transmission of blood-borne infection, and would be an intervention aimed at the infected people in a population (Strang et al., 2012). Similarly, though antiviral treatment can reduce viral load and therefore lower the likelihood of transmission, antiviral treatment almost never cures HBV infection (Dienstag, 2008). Patient education—simple steps such as informing HBV-infected patients why they should not share razors or toothbrushes and encouraging them to recruit their unvaccinated household members and sex partners for screening and immunization—can also

help stop transmission and would be described as an intervention aimed at the susceptible hosts to the virus.

More broadly speaking, eliminating the public health problem of hepatitis B in the United States is a matter of ending transmission and preventing morbidity and mortality among people with chronic infection. This chapter discusses these two goals in turn and identifies factors critical to the success of such an endeavor. **After analyzing the problem of hepatitis B in the United States, the committee concluded that control is feasible in the relatively short term. Eliminating the public health problem of hepatitis B will take more time and require considerable public will, resources, and attention to the barriers mentioned in Table 2-2.**

Key Findings and Conclusions

- There is no animal reservoir of hepatitis B virus (HBV), and the vaccine conveys 95 percent immunity in three doses, conditions that favor elimination.
- HBV infection is characterized by long periods of asymptomatic infection during which infected people can transmit the virus.
- Elimination of HBV is feasible; ending the transmission of the virus especially so. Eliminating morbidity and mortality from chronic infection is feasible but with more conditions on this feasibility.

TABLE 2-2 The Feasibility of Eliminating Hepatitis B as a Public Health Problem in the United States with Critical Factors for Success and Crosscutting Problems

Goal		Feasibility	Critical Factors	Crosscutting Barriers
Ending transmission	Perinatal	Highly feasible	• Identifying HBV-infected mothers • Consistent birth dosing with HBV vaccine	• Surveillance is sporadic and underfunded. • Vaccine tracking across jurisdictions is poor. • Stigma keeps people from screening and care. • Foreign-born adults can be difficult to reach with screening and treatment programs. • Much of the burden for managing chronic hepatitis B falls on overworked primary care providers. • There is a need to better understand the virus and the management of chronic hepatitis B.
	Children	Highly feasible	• Consistent vaccination and attention to catch-up dosing	
	Adults	Feasible	• No system for vaccinating adults • Undiagnosed, asymptomatic chronic infections a reservoir for infection	
Morbidity and mortality attributable to ongoing infection	Slowing progression to cirrhosis	Feasible	• Need for physicians trained in the management of chronic HBV infection • The threat of reactivation in chronic or resolved infection • No available treatment eliminates cccDNA or cures the disease	
	Reducing deaths			

NOTE: cccDNA, covalently closed circular DNA; HBV, hepatitis B virus

ENDING TRANSMISSION OF HEPATITIS B

For the most part, hepatitis B is transmitted three ways: from an infected mother to her child at birth, from direct contact with infected blood, or from unprotected sex with an infected partner. Transmission from mother to child is known as perinatal transmission; all other routes can be described as horizontal. As mentioned earlier, infection in infancy and early childhood has particularly poor prognosis. Babies born to highly viremic or HBeAg+ women have up to a 90 percent risk for chronic infection (see Figure 2-3). On the other hand, chronic infection develops in less than 5 to 10 percent people infected as adults, although about a third will become ill with symptoms of acute hepatitis (Liang, 2009).

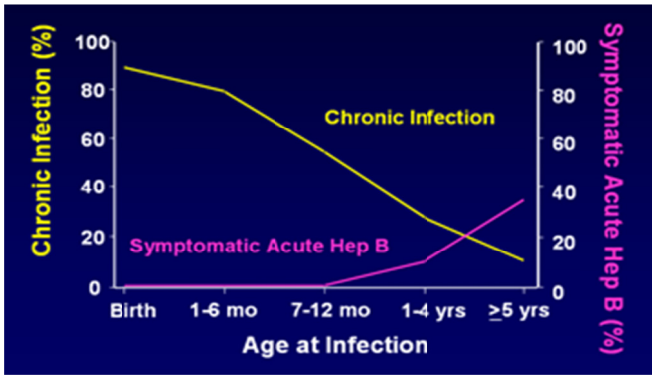

FIGURE 2-3 Outcome of hepatitis B virus infection by age at infection.
SOURCE: Morse et al., 2010.

Hepatitis B is unusual among carcinogens in that a vaccine exists which confers 95 percent immunity in three doses (WHO, 2015b). With perfect vaccination, hepatitis B could be eliminated in two generations (Forcione et al., 2004). In the absence of a cure, any hepatitis B elimination strategy will have to depend heavily the vaccine's ability to interrupt transmission. Children born to HBSAg+ mothers are a particular risk for contracting the virus, and preventing this route of transmission is entirely feasible, as, for similar reasons, is ending transmission to children. Preventing transmission among adults is more complicated, but still possible with attention to vaccine infrastructure and case detection.

Countries that have adopted universal infant and newborn hepatitis B immunization have seen marked reduction in the prevalence hepatitis B infection and the incidence of acute hepatitis B infection in children. In China prevalence of chronic hepatitis B dropped from almost 10 percent in 1992 to 1 percent in 2006 after the vaccination campaign described in Box 2-3. Worldwide, three dose hepatitis B vaccine coverage in infants reached 82 percent in 2014, compared to one percent in 1990 (WHO, 2015a). But the birth dose of HBV vaccine, a crucial intervention for reasons discussed later in this chapter, lags behind. By WHO estimates, only 38 percent of the world's newborns received this intervention in 2014 (WHO, 2015a). The United States could help to reduce the pool of chronically infected people in the world by supporting birth dose coverage abroad. This would also reduce the future domestic burden of chronic hepatitis B, as the majority of the chronic hepatitis B infections in the U.S. are imported (Weinbaum et al., 2008).

BOX 2-3
Case Study Birth Vaccination in China

Countries that have adopted universal infant and newborn HBV immunization have seen a marked reduction in the prevalence of chronic hepatitis B. This trend is perhaps most noticeable in China, where an estimated 9.8 percent of the population is chronically infected. The addition of the infant hepatitis B vaccine to the National Immunization Program reduced chronic hepatitis B in children under the age of 5 from 9.7 percent in 1992 to 1 percent in 2006 (Liang et al., 2009). Modeling estimates indicate that 14 years (1992-2006) of infant immunization prevented 16-20 million chronic infections and 2.8-3.5 million future deaths from liver cancer and liver disease (Liang et al., 2009).

Only 38 percent of children in China born between1992-1997 received the first dose of HBV vaccine within 24 hours of birth—a crucial window for prevention of mother-to-child-transmission (Cui et al., 2010). The Chinese strategy, developed in by the Ministry of Health and Gavi, vastly improved birth dose coverage in China's poorest provinces and may hold transferrable lessons for other countries.

Starting in 2005, the government abolished user fees for recommended vaccines, thereby removing the cost barrier to vaccination. As the national vaccine infrastructure improved, the hepatitis B immunization strategy took shape, with six main points (CDC, 2007):

1. Increasing the proportion of births in hospitals;
2. Preventing vaccine stockouts in hospitals and health centers;
3. Strengthening the relationship between obstetric or midwifery programs and vaccination services;
4. Educating and building awareness about birth dose administration to providers and parents;
5. Improving the training and management of county, city, and village health workers;
6. Paying village health workers to provide vaccines.

China has now met its 2010 goal of reducing chronic HBV infections in children under 5 years to below 1 percent; by 2005 93.4 percent of children completed the full vaccine series (Cui et al., 2010).

Ending Perinatal and Childhood Transmission

Barring early intervention, infants born to HBsAg+ women in the United States have an estimated 36 percent risk of contracting the virus; among women with HBV e antigen in serum, the risk rises to 90 percent (Ko et al., 2014; Smith et al., 2012; Wright, 2006). Infants who contract the virus have 90 percent risk of chronic infection (Lok and McMahon, 2007).

The recombinant vaccine approved in 1986 can prevent perinatal transmission of hepatitis B. In 1991 the CDC's Advisory Committee on Immunization Practices (ACIP) recommended that all newborns receive the first dose of hepatitis B vaccine preferably before discharge from the hospital and no later than 2 months of age (CDC, 1991). The full vaccine series, completed in the first 9 to 18 months of life, confers 95 percent protection against chronic infection (WHO, 2015b). The vaccine has been immensely successful in decreasing incident infections in the United States, with the greatest decline observed among children born since the 1991 guidelines were put into practice (see Figure 2-4). Perinatal transmission of hepatitis B is

now rare in the United States, but not eliminated. Recent models suggest a frequency of 0.80-3.84 percent (Ko et al., 2014; Smith et al., 2012).

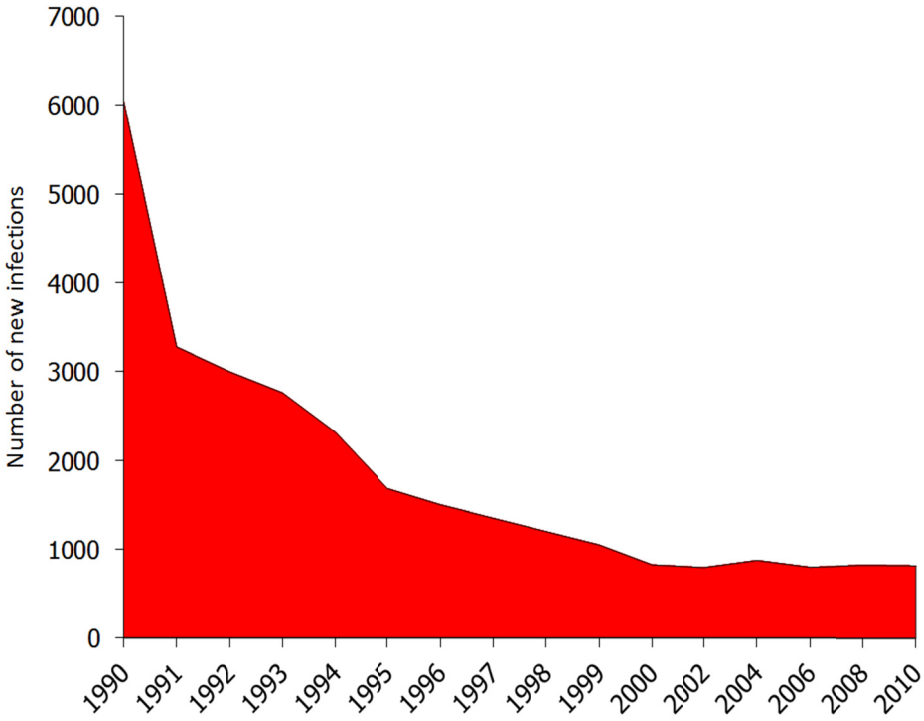

FIGURE 2-4 Estimated new perinatal chronic hepatitis B virus infections in the United States, 1990-2005.
SOURCE: Ward, 2015.

Identifying and Protecting HBV-Infected Mothers

Women with chronic hepatitis B generally have uneventful pregnancies, with no increased risk of premature delivery, fetal loss, low birth weight, congenital anomaly, or perinatal death (Park and Pan, 2014). Without immunoprophylaxis, chronic infection develops in about 40 percent of babies born to HBsAg+ women (CDC, 2015d). ACIP's 1991 recommendations also advised routine screening of pregnant women for HBsAg, so that children of HbsAg+ women would receive a dose of the vaccine plus hepatitis B immune globulin within 12 hours of birth as post-exposure prophylaxis (CDC, 2015d). With proper prophylactic dosing, risk of chronic hepatitis B among these children dropped to between 5 and 10 percent (Tran and Keeffe, 2008).

Current national guidelines require screening all pregnant women, even those who have been vaccinated, with a TORCH titer—a serum test for toxoplasmosis and other pathogens, which usually includes hepatitis B (Ford-Jones, 1999; Mast et al., 2005; Neu et al., 2015). The American Academy of Family Physicians, the American College of Obstetricians and Gynecologists, and the American Academy of Pediatrics all support these recommendations (Lam et al., 2010). Since 1990, the Perinatal Hepatitis B Prevention Program has expanded

screening of pregnant women, and now about half of HBsAg+ women identified in pregnancy are reported to the health authorities and provided case management through this program (HHS, 2016).

High viremia increases the likelihood of perinatal transmission and immunoprophylaxis failure. Even with perfect vaccination and immune globulin dosing, about 9 or 10 percent of women with HBV DNA greater than 100 million copies/mL will pass the virus to their children (Greenup et al., 2014; Pan et al., 2012; Wiseman et al., 2009). Viremia may account for some of the 800-1000 neonates a year in the United States who become chronically infected (Ko et al., 2014). A strategy of prophylactic antiviral therapy at the start of the third trimester if the patient's viral load is above a certain threshold might help eliminate the remaining cases of mother-to-child transmission of HBV, but the possible risks of such a strategy are not yet understood. In 2015 the American Association for the Study of Liver Disease (AASLD) made the conditional suggestion that pregnant women with a HBV viral load greater than or equal 200,000 IU receive prophylactic tenofovir in late gestation (Terrault et al., 2016). At the moment, the addition of prophylactic antivirals is not a CDC or WHO recommendation, and further data and studies are needed to determine the threshold for prophylactic antivirals in addition to immune-globulin and vaccination, as well as the duration of postpartum therapy and the risk of liver flares upon cessation of treatment.

Vaccinating Infants and Children

Timely newborn immunization is essential for stopping perinatal transmission of hepatitis B and for preventing community acquisition in childhood. In 2005, the CDC's ACIP updated its hepatitis B vaccine recommendation, calling for universal birth dosing for all newborns, including children of HBsAg– women (Mast et al., 2005). 2014 data suggest inconsistent observance of this guideline, however. Only 64.0 percent of infants receive the vaccine within 24 hours of birth (95 percent CI: 60.9 to 67.1 percent), though state and local rates vary considerably, from 25.4 percent in Vermont (95 percent CI: 13.1 to 37.7 percent) to 81.7 percent in Alabama (95 percent CI: 68.2 to 95.2 percent) (CDC, 2014b). Nationally, about 71.0 percent of infants receive the birth dose within 2 days of birth, and 72.4 percent within 3 days (CDC, 2014b). Though cases of chronic hepatitis B in infants have declined about 75 percent since 1990, the steady, lingering infection of 800-1,000 infants is evidence for the need for better strategies to expand the birth dose and immuno-prophylaxis (CDC, 2012a; Ko et al., 2014) (see Figure 2-4).

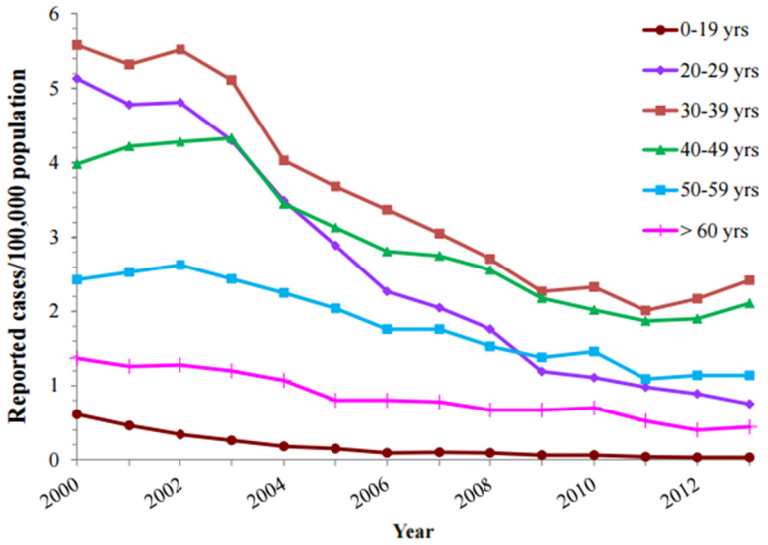

FIGURE 2-5 Incidence of acute hepatitis B, by age group, United States, 2000-2013.
SOURCE: CDC, 2013c.

Infants and children who miss the birth dose of vaccine can begin catch up vaccination at any time, with a minimum 4 week interval between the first and second doses, and a minimum 16 week interval between the first and third doses (CDC, 2015e). Childhood catch up is successful, by 2014 estimates 91.6 percent (95% CI: 89.8-93.4), of children aged 19 to 36 months were fully vaccinated against hepatitis B (Hill et al., 2015). In accordance with ACIP recommendation, 47 states now require hepatitis B immunization of children; 41 states mandate vaccination for children entering daycare, 46 states for school entry, and 39 states for middle school (Immunization Action Coalition, 2015). Widespread childhood vaccination has reduced the incidence of hepatitis B among children and adolescents to less than 1 per 100,000 from 2000-2013 (see Figure 2-5), a reminder that ending transmission of hepatitis B is feasible with sufficient resources and commitment (CDC, 2013c). Universal immunization of infants and children will help end transmission of HBV and protect future generations from cirrhosis and liver cancer deaths caused by chronic hepatitis B infection.

Ending Transmission in Adults

The vaccination of infants and children is clearly a national priority, cited as one of four overarching goals in the Department of Health and Human Services (HHS) *Action Plan for the Prevention, Care, & Treatment of Viral Hepatitis* (HHS, 2015a). As of 1990 federal funds were allocated to the national perinatal hepatitis B prevention program; in 1994, the Vaccines for Children program was established to provide free vaccine for children whose parents or guardians could not afford them (CDC, 2014a; Smith et al., 2012).

The HHS action plan cites a goal of vaccinating all adults and youths at risk for hepatitis B (HHS, 2015a). Sustaining immunity to HBV in all age groups is crucial to eliminating hepatitis B, but, as Figure 2-6 shows, the prevalence of HBV infection increases sharply after adolescence.

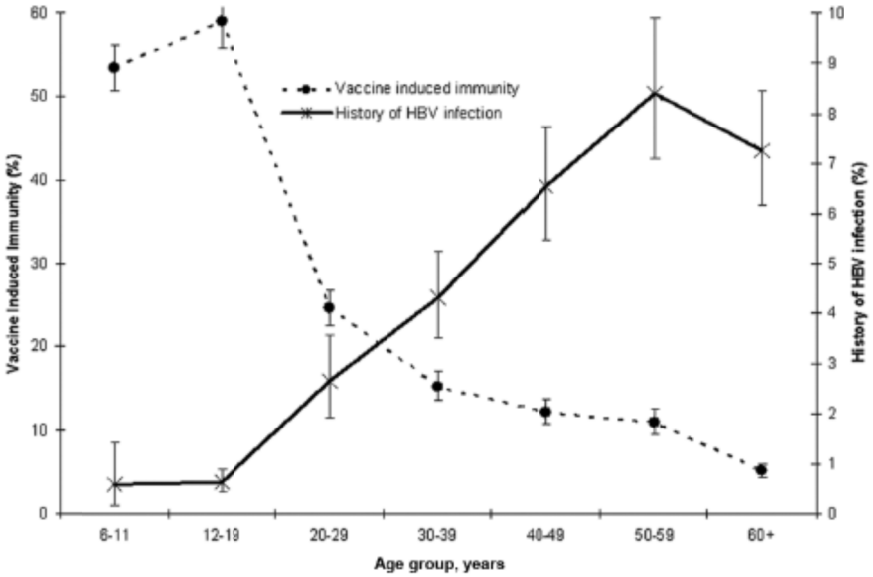

FIGURE 2-6 Crude prevalence of hepatitis B virus infection markers and vaccine-induced immunity by age, 1999-2006.
SOURCE: Wasley et al., 2010.

Vaccination of Susceptible Adults

About 95 percent of new HBV infections in the United States occur in adults (CDC, 2015f). Therefore, the CDC recommends that adults at high risk of coming into contact with HBV be immunized. Box 2-4 lists ACIP's groups of adults recommended to receive HBV vaccination, making clear there are many adults conceivably at risk for infection, but adult vaccination coverage is low. The 2013 National Health Interview Survey conducted found adult vaccination coverage for hepatitis B was only 25 percent (95% CI: 24.3-25.8), down 2.1 percentage points from 2012 results (Williams et al., 2015). Coverage is lower among certain minority groups; the CDC estimates that statistically significantly fewer African-American and Hispanic adults have completed the vaccine series than whites of the same age (CDC, 2013b). Even among health workers, who might be expected to have greater awareness about the importance of HBV immunization, slightly less than two-thirds are fully vaccinated (see Table 2-3).

BOX 2-4
Adults Recommended to Receive HBV Infection

- **Persons at risk for infection by sexual exposure,** including sex partners of HBsAg+ people, sexually active persons not in a long-term, mutually monogamous relationship, persons seeking evaluation or treatment for a sexually transmitted disease, and men who have sex with men.
- **Persons at risk for infection by percutaneous or mucosal exposure to blood,** including current or recent injection-drug users, household contacts of HBsAg+ persons, residents and staff of facilities for developmentally disabled persons, health care and public safety workers with reasonable anticipated risk for exposure to blood or blood-contaminated fluids, and persons with end-stage renal disease.
- **Others,** including international travelers to regions with high or intermediate leaves of endemic HBV infection, such as East Asia and sub-Saharan Africa, persons with chronic liver disease, persons with HIV infection, and all other persons seeking protection from HBV infection.

SOURCE: Mast et al., 2006.

TABLE 2-3 Estimated Proportion of Adults Aged ≥19 Years Who Received ≥3 Doses HBV Vaccine by Age Group, Race or Ethnicity,[†] and Other Selected Characteristics—National Health Interview Survey, United States, 2011

Age Group or Selected Characteristic	No. in sample	% (95% CI)
19-49 years, total	15,568	35.9 (34.9-36.9)
19-49 years, white	8,256	37.8 (36.5-39.2)
19-49 years, black	2,349	33.0 (30.7-35.3)**
19-49 years, Hispanic	3,429	28.9 (27.1-30.9)**
19-49 years, Asian	1,144	40.7 (36.8-44.6)
19-49 years, other	390	44.1 (38.5-49.9)
19-59 years, with diabetes, overall	1,224	26.9 (23.8-30.3)
≥60 years, with diabetes, overall	1,746	12.4 (10.8-14.3)
Health care personnel >19 years	2564	63.8 (61.4-66.2)

NOTES: [†] Race or ethnicity was categorized as follows: Hispanic, black, white, Asian, and other. In this report, persons identified as Hispanic might be of any race. Persons identified as black, white, Asian, or other race are non-Hispanic. Other includes American Indian, Alaska Native, and multiple race. The five racial and ethnic categories are mutually exclusive.

** $p<0.05$ by t test for comparisons with whites as the reference.

SOURCE: Adapted from CDC, 2013b.

Immunization of adults is logistically complicated; there is no good system for vaccinating people after school age. The primary responsibility for ensuring vaccination of people in high-risk groups falls on the health provider. Given the burdens already on providers discussed later in this chapter, it may be unrealistic to expect them to have the time to offer the HBV screening and vaccination to their patients, counsel them on its importance, and oversee the immunization during a brief, routine visit. Offering vaccination though organizations already in

contact with people at high risk for HBV (prisons and clinics for sexually transmitted infections, for example) might be a more efficient strategy.

In Amsterdam, for example, immunization of men who have sex with men elicited a sharp decline in incidence of acute hepatitis B, despite reaching only 30 to 38 percent of the target population (van Rijckevorsel et al., 2013). The researchers attributed the decline in incidence to vaccinating a critical mass of people most likely to transmit the virus (van Rijckevorsel et al., 2013). People at high risk for HBV infection may have relatively regular contact with staff at needle exchange sites and sexually transmitted disease clinics. Research at community health centers in Boston found 31.5 percent of patients seeking testing for HIV or sexually transmitted infection returned to the same center three times, enough to complete the HBV vaccine series (Sharfstein and Wise, 1997). Clients at a mobile needle exchange in New Haven were also amenable to vaccination. Two-thirds completed the six-month schedule for HBV screening and vaccination (Altice et al., 2005). Jails, prisons, drug treatment centers, and clinics are all rife with missed opportunities to vaccinate for hepatitis B (Hershey et al., 2005). In the past, CDC funded state and local health departments to expand vaccination through these organizations, but these funds are now far less available (Hinman, 2005; NACCHO, 2015).

Vaccinating adults for HBV is particularly important now, as spikes in injection drug use may be leading to acute outbreaks (Iqbal et al., 2015). Incident HBV infections increased by 90 percent in Tennessee over the years from 2006 to 2011, with most new infections occurring among Caucasians in their forties and attributable to sharing injection equipment (Iqbal et al., 2015). Medical exposures may also be risk factors for acquiring HBV infection. Research among adults over 55 indicates that recently infected people have vastly increased odds of having had certain medical procedures than matched controls (Perz et al., 2013). Compared to matched controls, cases have 2.31 greater odds of having had surgery (95% CI: 1.14-4.67); 4.26 greater odds of having stayed overnight in a hospital (95% CI: 1.75-10.34); 13.03 greater odds of having had dialysis (95% CI: 1.48-114.59); and 23.43 greater odds of having had a blood transfusion (95% CI: 2.73-201.21) (Perz et al., 2013).

The spread of HBV in medical settings is not well understood. HBV is a highly infectious virus, 50 to 100 times more infectious than HIV, and even slight lapses in infection control can result in patient-to-patient transmission (CDC, 2015c). Some infections occur in the absence of any obvious violation of infection control (Allos and Schaffner, 2007). An analysis of a 2007 case of patient-to-patient transmission at an oral surgery concluded, “the best efforts of well-meaning providers to eliminate these events will likely not completely succeed,” and advocated for universal adult vaccination as the best way to stop transmission (Allos and Schaffner, 2007, 1246).

Treatment as Prevention

Vaccination is clearly the most effective tool to prevent transmission of HBV (Mast et al., 2006). But ending transmission in adults will also require attention to the identification and treatment of chronically infected adults. The CDC recommends contact management and patient education as ways the providers and public health officials can help reduce HBV transmission (Weinbaum et al., 2008).

Eliminating transmission could also be aided by treating those with known HBV infection, a concept known as treatment as prevention. Treatment as prevention gained

prominence as a way to control the spread of HIV, and was shown in a phase three clinical trials reduce sexual transmission of HIV by 96 percent (Cohen et al., 2011b; Montaner et al., 2006). Treatment as prevention is now a cornerstone of AIDS strategy around the world (ONAP, 2015; UNAIDS, 2014).

For treatment to be an effective means of prevention it should reduce viral load in bodily fluids to non-infectious levels. This reduction should be established across many populations and modes of transmission. Also, treatment should be recommended and available for everyone infected. HBV does not meet these conditions.

Nevertheless, some principles of treatment as prevention apply to HBV. Viremia in pregnant women can increase the risk of vaccination failure among children born to HBsAg+ women (del Canho et al., 1994; Ngui et al., 1998). Furthermore, treatment with antivirals has been shown to reduce perinatal transmission (Brown et al., 2016; van Zonneveld et al., 2003; Xu et al., 2009). Treatment during pregnancy has no known harmful effects for mother or child, though the data on safety on treatment in pregnancy is limited (Brown et al., 2016).

Most research on treatment as prevention of HBV applies only to mother-to-child transmission. This is partly because HBV treatment is not recommended for all carriers. AASLD treatment guidelines recommend against antiviral therapy for adults with immune-tolerant chronic infection, despite some evidence of improved intermediate outcomes with antiviral therapy in this population (Lok et al., 2016; Terrault et al., 2016). High viremia, but normal liver enzyme levels and liver biopsy characterize the immune-tolerant phase of chronic infection. Should further research demonstrate health benefits for treating immune tolerant HBV, it would be necessary to consider whether the level of viral suppression was sufficient to reduce or eliminate transmission, and whether this treatment was cost effective.

Given these shortcomings, treatment as prevention is not a strategy to prevent adult transmission of HBV. Patient education, vaccination, and public health management are better options. These strategies rely on early and systematic identification of chronically infected people.

The essence of public health management of HBV is the identification and immunization of susceptible people, with particular emphasis on the sex partners, household contacts, and need sharing partners of chronically infected adults. This strategy is has only been widely applied as part of the perinatal HBV prevention program, and even then only about 26 percent of HBsAg+ women's contacts are identified, tested, and evaluated for immunization (Weinbaum et al., 2008). Few jurisdictions have state or local programs for contact management outside the perinatal HBV program (Holmberg, 2016; Weinbaum et al., 2008). But all states and many local jurisdictions have routine partner follow up for sexually transmitted infections (Dooley, 2008). Such programs might provide a valuable infrastructure for HBV contact management.

Patient education is currently the main method used to reduce transmission of HBV to adults. This includes educating HBsAg+ people on measures they can take to reduce the risk of transmitting the virus to their contacts. Patients are also encouraged to notify their sex partners, household members, and injection drug sharing contacts so that these people can seek testing and vaccination. The actual success of patient education in reducing HBV transmission is not established, however.

Key Findings and Conclusions

- Hepatitis B is mostly transmitted from an infected mother to her child at birth, from direct contact with infected blood, or from unprotected sex with an infected partner.
- Worldwide about 82 percent of infants receive the full course of the hepatitis B virus (HBV) vaccine, but only 38 percent receive the birth dose key to preventing mother-to-child transmission.
- Support for birth dose coverage in the HBV endemic countries of Asia and Africa could help reduce the future domestic burden of HBV, as most chronic infections in the United States are imported.
- Perinatal transmission of HBV is rare in the United States, but there is room for improvement in both birth dose coverage and catch up vaccination of children.
- Universal immunization of infants and children would protect future generations from cirrhosis and liver cancer due to HBV.
- Immunization of adults is logistically complicated, but important, especially among high-risk groups. Vaccination might be made more efficient by offering it at places already in contact with people at risk for HBV, such as prisons or jails.

PREVENTING COMPLICATIONS AND DEATHS AMONG THE CHRONICALLY INFECTED

Any discussion of disease elimination must first consider how to interrupt transmission, but this is not enough to eliminate the public health problem of hepatitis B. The 700,000 to 1.4 million HBV-infected people in the United States need appropriate care to stop the progression of the infection to cirrhosis or worse. Although there is no cure for HBV infection, antiviral treatments and careful monitoring make it reasonable to expect that no one die might from hepatitis B in the United States. This section discusses the management necessary to achieve that goal.

Slowing the Progression to Cirrhosis in Chronic HBV Infection

Action on the part of the health provider can help slow the progression of chronic hepatitis B-associated liver fibrosis progression and reduce the risk of cirrhosis and other liver complications. Patients in the immune-tolerant phase require ongoing monitoring for transition into the immune active phase. Such monitoring allows for early identification of possible hepatocellular carcinomas. It can also identify chronic hepatitis B patients who would benefit from antiviral treatment (Lok and McMahon, 2007; Lok et al., 2016).

It is also important to assess all chronic HBV-infected people for immunity to hepatitis A virus infection (anti-hepatitis A IgM antibody) because acute infection with hepatitis A in those

with underlying chronic hepatitis B could increase the risk of fulminant hepatitis and cause considerable patient suffering (Lok and McMahon, 2007; Vento et al., 1998). Hepatitis A vaccination is therefore recommended for all chronically infected HBV patients who are hepatitis A IgG antibody-negative (AIDSinfo, 2015). Similarly, coinfection with HCV can hasten onset of hepatic fibrosis and increase the risk of fulminant hepatitis and liver complications in chronic hepatitis B, so screening for HCV antibody is also recommended (Crockett and Keeffe, 2005; Lok and McMahon, 2007). Among those patients infected with both HBV and HCV, there is often value in antiviral treatment for the HCV infection (AASLD-IDSA, 2016). Screening for hepatitis D (delta) virus infection is recommended for hepatitis B patients with unusually severe disease and for those from countries where hepatitis D is common (Lok and McMahon, 2007). Hepatitis D only infects patients with chronic hepatitis B and may accelerate liver disease progression (Kushner et al., 2015).

Assessing alcohol intake is crucial to managing chronic hepatitis B. It is not clear what amount of alcohol hepatitis B patients can safely consume, but drinking more than 50 g (about 5 drinks) per day can accelerate progression to hepatic fibrosis; increase the risks of cirrhosis, hepatic decompensation, and hepatocellular carcinoma; and cause poor compliance with treatment (Hassan et al., 2002; Lucas et al., 2002). Providers may need to refer patients who need and want it to alcohol therapy. In the same way, over-the-counter medicines and herbal or dietary supplements can harm liver tissue already weakened by viral hepatitis. Managing these patients requires attention to their consumption of such products and, when necessary, counseling avoidance of them (Goldberg et al., 2015). Acetaminophen can be particularly toxic to the liver; doses in excess of 2 gm in a 24-hour period are discouraged for hepatitis B patients, but even this cut point is somewhat arbitrary (Lee, 2004).

Liver fibrosis is a risk factor for cirrhosis. Cirrhosis requires additional monitoring for esophageal varices and for clinical complications such as ascites, variceal hemorrhage, and hepatic encephalopathy (Benvegnù et al., 2004). While liver biopsy (a painful, risky, and expensive procedure) has been the traditional method to assess liver fibrosis, increasing evidence suggests that non-invasive analysis of serum markers and transient elastography might serve the same end (Lee et al., 2014; Leroy et al., 2014; Mayo Clinic, 2014; Myers et al., 2003; Poynard et al., 2014).

Proper medical management of hepatitis B has a clear goal of averting hepatocellular carcinoma deaths, whether by preventing the cancer or by catching it at an early stage when treatment is most effective. The AASLD guidelines suggest surveillance for hepatocellular carcinoma among certain chronic hepatitis B patients. These are Asian men over 40, Asian women over 50, African or African-Americans of any age, anyone with cirrhosis, and anyone with a family history of liver cancer (Bruix and Sherman, 2011). Caucasian patients with a high HBV DNA levels and hepatic inflammation are presumed to also be at risk for hepatocellular carcinoma, although it is not clear at what age the risk becomes meaningful (Bruix and Sherman, 2011). All screening should be done with radiographic imaging, preferably abdominal ultrasound (EASL, 2012; Lok and McMahon, 2007).

Antivirals in the Treatment of Chronic Hepatitis B Virus Infection

Approved treatments of chronic hepatitis B include pegylated interferon (hereafter interferon therapy) and lamivudine, adefovir dipivoxil, telbivudine, entecavir, and tenofovir (hereafter nucleos(t)ide analogue therapy) (Terrault et al., 2016). Choosing among these treatments is complicated. Interferon, on one hand, has the advantage of finite treatment duration. It does not

select resistant mutants and elicits a more durable response. At the same time, interferon is difficult for patients to tolerate and has less therapeutic success; it is also contraindicated in patients with decompensated cirrhosis (Bhattacharya and Thio, 2010; Lok et al., 2016). Tenofovir and entecavir are the currently preferred nucleos(t)ide analogue therapies because their virologic efficacy is high and risk of resistance is low (Bhattacharya and Thio, 2010; Delaney et al., 2006; Heathcote et al., 2011; Marcellin et al., 2013; Sheldon et al., 2005; Snow-Lampart et al., 2011; Terrault et al., 2016).

None of the treatments currently approved for hepatitis B cure the infection, except in a very small proportion of patients, meaning treatment does not eradicate the virus' cccDNA from the nuclei of infected hepatocytes[2] (Thio, 2009). In the absence of a cure, the goal of therapy is sustained suppression of HBV DNA to an undetectable level. This suppression reduces the likelihood of liver-related complications and the risk horizontal transmission (Lai and Yuen, 2007; Liaw et al., 2008; Lok and McMahon, 2007; Soriano et al., 2008). Therapy can also seek to bring liver enzyme levels to normal, to induce HBeA to anti-HBe seroconversion, to improve liver histology, and clearance of HBsAg (Terrault et al., 2016). Durable suppression of HBV replication has been shown to reverse liver fibrosis in chronic HBV infection (Calvaruso and Craxi, 2014). Still, clearance of HBsAg is unusual on nucleos(t)ide analogue therapy, and reactivation of HBV upon discontinuation of treatment is high , so once started, anti-HBV nucleos(t)ide analogue therapy is often continued indefinitely (Dore et al., 2010; Lok et al., 2016). While lifelong therapy is complicated and expensive, the risks of treatment cessation are real. Drug cessation can cause HBV flare, and risks losing the benefit accrued from prior treatment (Bellini et al., 2009; Dore et al., 2010). It is also a risk factor for hepatic decompensation (Terrault et al., 2016).

While on nucleos(t)ide analogue therapy, HBV DNA should be monitored for viral suppression every 12-24 weeks (EASL, 2012; Lok and McMahon, 2007; Terrault et al., 2016). Ideally, HBV DNA should be undetectable after 24 weeks (EASL, 2012). There is no known resistance to tenofovir so if HBV DNA is persistently detectable providers might need to inquire with their patients about treatment adherence and, if necessary, help identify strategies to support better compliance (Gordon et al., 2013; Snow-Lampart et al., 2011).

Avoiding Reactivation

Reactivation of HBV infection is an important complication of immunosuppressive treatments for cancer, organ transplant, and autoimmune diseases (Hwang and Lok, 2014). Reactivation may promote liver disease progression in patients with chronic or resolved infection (Lo Re and Schuster, 2016). HBV reactivation is characterized either by an abrupt increase in HBV DNA among HBsAg+ patients or by reappearance of serum HBV DNA in those with serological evidence of resolved infection (HBsAg-negative and anti-HBc-positive with or without anti-HBs). Reactivation is usually accompanied by elevations in liver aminotransferase

[2] New antiviral treatments for HBV are currently in development, including several methods targeting cccDNA (Cai et al., 2012; Cradick et al., 2010). Pharmacological elimination of cccDNA could result in virologic cure of HBV since cccDNA serves as the template for transcription of HBV RNA and for translation of HBV proteins. An alternative strategy is to prevent transcription of cccDNA to HBV RNA or to decrease the stability of HBV mRNA (Zimmerman et al., 2008). Several classes of compounds have been shown to interfere with HBV capsid assembly (Feld et al., 2007).

levels (Hoofnagle, 2009). It is a serious complication, and one that can lead to serious acute liver injury, liver failure, and death (Lok et al., 2012).

HBV reactivation occurs because after acute infection the virus establishes cccDNA as a durable miniature chromosome within the nuclei of infected hepatocytes (Dienstag, 2008). The cccDNA may persist after recovery from chronic infection, so subsequent immunosuppression can disrupt the immune system's ability to control the replication of the virus, and the infection becomes active again (Perrillo, 2001).

Many patients living with chronic or resolved HBV infection may at some point require immunosuppressive drug therapy for cancer, autoimmune disease, or organ transplantation, putting them at risk for reactivation. Prophylactic anti-HBV treatment with lamivudine (or better yet, entecavir or tenofovir) can greatly reduce the risk of HBV reactivation in HbsAg+ and HBsAg- and anti-HBc-positive patients on immune suppressive therapy (Loomba et al., 2008). The CDC, American Association for the Study of Liver Diseases, American Gastroenterological Association, Asian Pacific Association for the Study of the Liver, and European Association for the Study of the Liver all recommend screening for HBV infection with HBsAg and anti-HBc in all patients receiving immunosuppressive therapy (Perrillo et al., 2015). Their rationale is that these assays are sensitive, specific, and inexpensive, and that risk-based screening methods can miss many HBV-infected patients.

Antiviral prophylaxis reduces the risk of HBV reactivation among chronic hepatitis B patients receiving immunosuppressive drug therapy for solid or liquid tumors (Dong et al., 2013; Evens et al., 2011; Paul et al., 2016). The benefits of prophylaxis for patients with resolved HBV infection who require immunosuppressive drug therapy remain less clear.

Additional study of HBV reactivation and antiviral prophylaxis is necessary. The risk of HBV reactivation with different chemotherapy regimens is not yet clear, nor is the optimal duration of antiviral prophylaxis. Immunosuppressive therapy can also be prescribed for non-malignant disorders, such as inflammatory bowel disease, rheumatoid arthritis, psoriasis, and other autoimmune conditions, but it is not clear if these treatments pose the same risk for HBV reactivation. A better understanding of these questions is necessary to avoid reactivation and prevent end-stage liver disease from HBV.

Key Findings and Conclusions

- Patients in the immune-tolerant phase of hepatitis B virus (HBV) infection require ongoing monitoring for transition to the immune active stage. This monitoring can identify patients who would benefit from antiviral treatment and allow for early identification of hepatocellular carcinoma.
- None of the treatments approved for HBV usually cure the infection. The goal of therapy is to suppress HBV DNA to an undetectable level. Cure, though not unheard of, is extremely rare.
- Many chronically infected HBV patients eventually require immunosuppressive drugs for cancer, autoimmune disease or organ transplantation. These drugs can reactivate suppressed HB, a serious complication that can lead to liver failure.

CROSSCUTTING BARRIERS TO HEPATITIS B ELIMINATION

Any progress toward the elimination of hepatitis B in the United States, either ending the transmission or improving the prognosis for people already infected, will require attention to various health system and social obstacles that keep people from being tested for HBV, prevent HBsAg+ people from accessing care, and impede the best possible provision of services.

Surveillance

Surveillance for viral hepatitis in the United States in sporadic and greatly underfunded given the scope of the epidemics and the need for accurate data to understand them. Elimination of HBV will rely on state and local jurisdictions being able to identify cases of acute and chronic HBV infection, especially among pregnant women. Identifying cases and understanding the baseline burden of disease in a community is an obvious prerequisite to spotting an outbreak; it is also essential for tracking progress toward elimination. The CDC funds comprehensive viral hepatitis surveillance in only seven jurisdictions, five states and two large cities (HHS, 2015b). The average award for these programs is $475,000; most states are unable to conduct full surveillance for HBV (CDC, 2015a).

Data from the seven comprehensive viral hepatitis surveillance sites reveals other problems with the public health infrastructure for hepatitis B. There are many serological markers of HBV (see Table 2-1), proper characterization of a patient's status involves analysis of a panel of indicators. Inconsistencies in laboratory reporting can make it difficult to analyze a patient's chart, a problem that only grows when multiple laboratories run tests for a single patient (Fleming et al., 2006). When the laboratory data are incomplete, the authorities cannot follow up on suspected outbreaks.

The serological maker IgM anti-HBc, described earlier in this chapter, is crucial to the identification of acute infection, as this antibody signals cases exposed in the previous six months. In people who are asymptomatic during early acute infection are not likely to seek care or be reported to the health department. The acute case definition shown in Box 2-4 also requires reporting of clinical symptoms, information health departments might not be able to obtain. Moreover, the current case classification for chronic hepatitis B requires analysis of multiple serum markers over time. Unless the health department has a highly automated disease surveillance system with synchronized laboratory reporting, tracking any one person's results over time is exceptionally challenging. The case definition of chronic hepatitis B also depends on serological testing (see Box 2-4). Prevalence of chronic HBV infection varies widely among different state and local health departments, following the different distribution of foreign-born people and other high-risk groups. Tracking progress toward eliminating the disease will depend on good local estimates of disease burden. Increased use electronic health and laboratory records may ease case identification and advance this goal, especially if the electronic systems have a highly automated reporting function (Church et al., 2014). Hospitals and clinics also sometimes have large datasets that the health department can use to track cases and validate surveillance data (CDC, 2013a).

BOX 2-4
Council of State and Territorial Epidemiologists
Definitions for Case Classification of Hepatitis B Infection

The case definition for *acute hepatitis B* requires:

- *Clinical evidence:* An acute illness with a discrete onset of any sign or symptom consistent with acute viral hepatitis (e.g., fever, headache, malaise, anorexia, nausea, vomiting, diarrhea, and abdominal pain), and either a) jaundice, or elevated serum alanine aminotransferase (ALT) levels >100 IU/L
  Note: A documented negative HBsAg laboratory test result within 6 months prior to a positive test (either HBsAg, HBeAg, or HBV NAT including genotype) result does not require an acute clinical presentation to meet the surveillance case definition.
- *Laboratory criteria for diagnosis*: HBsAg+ and IgM anti-HBc+
  Note: Serological testing is not always done
- *Case classification:* a confirmed case that meets the clinical case definition, is laboratory confirmed, and is not known to have chronic hepatitis B

The case definition for *chronic hepatitis B* requires:

- *Clinical evidence:* No symptoms are required
- *Laboratory evidence:* IgM anti-HBc- and a positive result on one of the following tests: HBsAg, HBeAg, or nucleic acid test for HBV DNA (including qualitative, quantitative and genotype testing) OR HBsAg+ or HBV DNA positive (including qualitative, quantitative and genotype testing), or HBeAg+ twice at least 6 months apart (Any combination of these tests performed 6 months apart is acceptable)
- *Case classification:* a confirmed case meets either of the above laboratory criteria for diagnosis. A probable case has a single HBsAG+ or HBV DNA positive test (including qualititative, quantitative, and genotype testing), or HBeAg positive lab result and does not meet the case definition for acute hepatitis B

SOURCES: Sweet, 2011a,b.

Public Health Case Management

Ideally, the health department surveillance group has sufficient budget and staffing to allow for case management, which includes immunization, referral to care, counseling, and clinical services. For example, when tests reveal HBsAg in women of childbearing age, the health department follows up with the woman to see if she might be pregnant, and provides intensive case management for any HBsAg+ pregnant woman and her child, a process that has helped make mother-to-child transmission of hepatitis B a rare event (Mast et al., 2005). Avoiding the 800 to 1,000 cases per year of chronic hepatitis B in children could be advanced by better case management in all jurisdictions.

Vaccination Tracking

A strong case management system helps ensure the HBV-infected person is referred to treatment; some jurisdictions also follow up with the cases to help ensure vaccination for their close contacts. As the earlier section mentions, adult vaccination is difficult. Adult outpatient care is rife with missed opportunities for immunization in general, hepatitis B immunization in in particular (Ozisik et al., 2015; Szilagyi et al., 1993).

State immunization registries can be used to identify unvaccinated adults at risk for hepatitis B. Immunization registries are secure, population databases that collect and consolidate vaccination records from various health providers in a given area (Community Preventive Services Task Force, 2015). The systems can generate reminders when an unvaccinated patient makes an appointment; they also can provide reports on vaccination coverage within a practice or a larger geographic area. Automated immunization registries are often designed to include school and daycare immunization data, making them a useful tool to assess vaccination of children (Community Preventive Services Task Force, 2015). Registries depend on widespread enrollment and usually on active participation from providers. A 2004 CDC survey in private practices found that among 56 immunization grantees in 50 states and 6 jurisdictions, only 39 percent were actively submitting data to state or regional registries (Mast et al., 2005). By 2009, little had changed; with 38 percent of private providers participating, though variability ranged from perfect reporting in some states to only 3 percent in Hawaii (CDC, 2009). Local government support for adult registries is uneven, but there is reason to believe it is growing. By 2015, 31 jurisdictions had a law or regulation requiring some degree of reporting to immunization information systems, an almost 160 percent increase over the number of jurisdiction requiring the same in 2000 (Martin et al., 2015). Like electronic laboratory and patient record systems, immunization registries are most effective if they are designed to share information across various state and local boundaries. The ability of the information systems to work together (called interoperability) is limited in practice, however. Different vendors create widely different products, consolidating data from these systems can be impossible, and even when consistent tracking or data merging is possible, data are often labeled inconsistently, impeding aggregate analysis.

The 2009 Health Information Technology for Economic and Clinical Health Act set a national goal of meaningful use of electronic records in health (HHS, 2012). For practical purposes, the Centers for Medicare and Medicaid have identified three stages of meaningful use. The first stage includes the submission of data to an immunization registry (CDC, 2012b). Participating providers establish that their electronic system can send data to public health agencies, and then to begin regular reporting. Regardless of whether the provider works in state with a requirement to report immunizations, government incentives for meaningful use of electronic systems help encourage wider use of the registries and better attention paid to them in practice.

Stigma

HBV-infected people may have a sense of shame about their condition, partly because the virus can be spread by sexual contact or injection drug use, and because liver disease in general is associated with drug and alcohol abuse. Research among cirrhotics bears this out, with younger patients reporting more stigmatizing distress over their condition than older ones (Vaughn-Sandler et al., 2014). Stigma, in turn, can cause feelings of depression and make HBV-infected people more likely to avoid medical care (Vaughn-Sandler et al., 2014). Even before

patients can be brought to treatment, fear of a positive test result decreases likelihood of taking part in HBV screening (Li et al., 2012).

In the United States, most people with chronic hepatitis B come from abroad. Among East Asians, about 1 in 10 of whom have chronic hepatitis B, the stigma of the disease may be particularly severe (Philbin et al., 2012). Canadian research found that 31 percent of HBV-infected East Asians were ashamed to have HBV, and 53 percent were unwilling to discuss their illness with friends or family (Wu et al., 2009). Among Chinese immigrants in Illinois, over 20 percent believed hepatitis B infection would cause discrimination in school or at work; 36 percent felt that that people with hepatitis B bring trouble to their families (Cotler et al., 2012). Perceptions of the disease vary among different ethnic groups, but there is evidence of some consistent discrimination against HBV-infected people. When asked if they believed people avoid someone with hepatitis B, 38 percent of Vietnamese-American respondents, 55 percent of Hmong-American respondents, 47 percent of Korean-American respondents, and 70 percent of Cambodian-American respondents agreed (Maxwell et al., 2012).

It is possible to alleviate the stigma of hepatitis B, but doing so requires education and changes to social norms. As Brian McMahon of the Alaska Native Medical Center explained to the committee, "we don't have stigma in Alaska anymore, and I think that is because people understand hepatitis B. Patients who have it understand that if they meet someone they want to have a relationship with that person can be vaccinated and they can prevent transmission. We really emphasize using barrier methods until the vaccine series is completed, and that helps with stigma. It takes a long time, but eventually people know that they are not going to transmit the disease." It is hard to say if reducing the stigma of HBV in Alaska was a cause or an effect of the elimination program described in Box 2-2, but it is clear that fear and silence are antithetical preventing and managing HBV.

Screening

Identifying adults infected with HBV is crucial to any elimination program. Both stopping transmission and improving prognosis for HBV-infected person depend on knowing who is infected. Though at least 700,000 to 1.4 million people in the United States have chronic hepatitis B, only about 50,000 are in treatment (Cohen et al., 2011a). With this in mind, in 2014 the US Preventive Services Task Force (USPSTF) recommended the screening of high-risk adolescents and adults, and pregnant women at first prenatal visit for HBV infection, thereby removing co-pays and co-insurance charges to people seeking this test (USPSTF, 2016).

In the United States, hepatitis B infection is greatest among people born in the HBV endemic countries of Asia and sub-Saharan Africa. More than 53,000 people immigrate to the United States every year from HBV-endemic countries (Hu et al., 2013). People born abroad are over nine times more likely than those born in the United States to be infected with chronic hepatitis B (Liu et al., 2015). The CDC therefore recommends hepatitis B screening for anyone born in country with HBsAg prevalence ≥2 percent (Weinbaum et al., 2008). Modeling exercises in Canada suggest that screening immigrants could add 1,675 productive life years to society for 250,000 people screened (Rossi et al., 2013).

Nevertheless, HBV screening is not as common as it should be. Evidence suggests that undocumented immigrants may avoid screening out a fear that a positive result, or even the interaction with the health system, could trigger deportation (Hacker et al., 2015). Other

opportunities are missed for more mundane reasons. A retrospective observational study in Boston found that only 36 percent of foreign-born patients were screened for HBV infection (Waldorf et al., 2014). With this in mind, the USPSTF recommended screening for people in the risk groups shown in Box 2-5.

BOX 2-5
The US Preventive Services Task Force Important Risk Groups for HBV Screening in Non-Pregnant Adolescents and Adults

- Persons born in countries and regions with a high prevalence of HBV infection (≥2%)
- US-born persons not vaccinated as infants whose parents were born in regions with a very high
  prevalence of HBV infection (≥8%),such as sub-Saharan Africa and southeast and central Asia
- HIV-positive persons
- Injection drug users
- Men who have sex with men
- Household contacts or sexual partners of persons with HBV infection

SOURCE: LeFevre, 2014.

Improved screening for foreign-born persons would help control the progression of disease in infected individuals and prevent the further spread of infection (Petersen, 2015). Screening foreign-born individuals is a complicated proposition, however. A foreigner must live in the United States for 5 years to qualify for Medicaid; the Affordable Care Act also restricts care for temporary residents and undocumented arrivals. These restrictions mean that many people identified in screening programs may have no way to pursue treatment (Castaneda et al., 2015). The tension between the need for screening and the onus it puts on the screener could be an obstacle to eliminating hepatitis B.

Among foreign-born people, recognized refugees are sometimes in more ready contact with the health system (Rein et al., 2010a). Some health departments screen refugees for HBV (Rein et al., 2010b). When surveyed, only 20 of these health departments were able to account for the number of refugees screened, and 13 were able to calculate the hepatitis B prevalence among refugees in their jurisdictions (Rein et al., 2010b). An analysis of their data suggest that over 2 percent of refugees in the United States have chronic hepatitis B, with prevalence among different national groups widely similar to the prevalence in their home countries (Rein et al., 2010b).

People who are already using primary care may be easier to reach. The USPSTF recommends that primary care providers screen: people born places with endemic infection ≥2 percent; people whose parents were born in regions of very high HBV infection (≥8 percent); HIV+ people; people who inject drugs; men who have sex with men; and the household members or sexual partners of people with HBV infection (LeFevre, 2014). But reaching everyone at risk through primary care might not be realistic, given the demands (discussed later in this chapter) already on the primary care system. Providers are also not always aware that they should be screening. A 2008 survey among providers at federally qualified health centers serving mainly Asian-Americans and Pacific Islanders found that about two-thirds reported regularly screening patients for HBV, even though 89 percent rated hepatitis B as an “above average or

huge" problem for their patients (Caballero, 2012). The limiting factor may be screening guidelines and monitoring protocols, which only half of respondents found to be clear, and resources for treatment and referral, which only 40 percent saw as adequate (Caballero, 2012). A 2012 survey at an academic primary care practice found similar results. Approximately one-third of Asian-American patients were tested for HBV, but the primary reason for testing was usually pre-employment physicals, pregnancy or adoption requirements, and occupational exposures, not routine screening (Loo et al., 2012). And, of course, not everyone sees a primary care provider regularly or at all.

Community screening, whether in a stand-alone campaign or as part of a health fair or other community program, can be an opportunity reach a wider audience, including many of the high-risk groups for HBV who may not otherwise have care. A survey of 55 community organizations in the United States with some involvement in HBV screening found that such screenings reached subpopulations with a 15 to 25 times greater prevalence of HBV than the United States overall (Rein et al., 2010a). Community screening poses its own challenges, however. While most community organization surveys refer HBsAg+ patients to care, only 29 percent were able to provide medical care (Rein et al., 2010a). It is difficult to link patients to care or unvaccinated people to services when the initial contact is not within the formal health system. Such contacts can be lost easily. Screening programs done through community centers may be less able to validate people's receipt of their test results, and the screening would not generally be noted on any formal patient chart (Chen and Dang, 2015).

Enrolling and Retaining Patients in Care

Regardless of whether testing is done in community settings or through primary care, services should be linked to treatment for the patient and vaccination for his or her household contacts (HHS, 2015a). HBV infection requires ongoing, usually lifelong care. Modern medical advances mean that people should no longer die from hepatitis B, but realizing the promise of these treatments will require creative strategies to keep HBV patients in care and adhering to prescribed treatment.

Over half of the chronic hepatitis B patients in the United States are Asian-American, Native Hawaiian, or Pacific Islander, and more than half of Asian and Pacific Islanders with hepatitis B were born outside the United States (Tung, 2012). Managing health care in English can be difficult for these patients, Asian-Americans and Pacific Islanders report more problems communicating with their doctors and less positive interactions with the health system than whites (Islam et al., 2015). Lay health workers, who understand the social context and attitudes of their community, can be effective in helping reach minority patients and keep them in care (Chen and Dang, 2015; Islam et al., 2015). Although a recent systematic review concluded that community health workers are not being sufficiently used in Asian-American and Pacific Islander communities, the authors concluded that the best strategies to employ lay health workers are not clear (Islam et al., 2015).

Though the health worker can be instrumental in screening and patient support, much of the burden of hepatitis B care lies with the managing provider. As the previous section makes clear, hepatitis B is a difficult disease to manage. A 2010 survey of San Francisco-area primary care providers found only 43 percent of respondents familiar with the AASLD guidelines for managing HBV, and about half unclear on liver cancer screening guidelines (Burman et al., 2013). A review of patient records done in conjunction with the provider survey confirmed the

problems. Although about half of the records indicated some attempt at hepatocellular carcinoma screening, only a third of the screenings were done with proper imaging (Burman et al., 2013).

Most of the research documenting primary care physicians' challenges in managing hepatitis B predate the 2014 US Preventive Services Task Force recommendations. This recommendation has been widely publicized (LeFevre, 2014; Mitka, 2014). It is possible that failure to implement the recommendation is a function of the limits of the primary care provider's time. Calculations of 10 years ago (long before the US Preventive Services Task Force recommendations on HBV went into effect) estimated that if every recommend service were provided it would take an estimated 7.4 hours per day of the primary care provider's time (Yarnall et al., 2003).

Electronic medical records hold promise to reduce the burden on providers, although nearly half of physicians responding to the 2014 national survey believed the electronic records impeded their efficiency (The Physicians Foundation, 2014). It is possible that electronic records, and much of the management of hepatitis B in primary care, would be best used to support team-style care. A pilot study at federally qualified health centers used electronic records to identify patients at high risk for HBV. The electronic system linked with the patients previous test results, and generated tools before each visit with information on managing chronic hepatitis B and counseling prevention and immunization for the patient's susceptible contacts (Toyoji et al., 2015). When this information is available to team that includes a health educator, that person can take on some of the patient counseling responsibilities (Toyoji et al., 2015). The pilot program has found a 48 percent improvement in mean monthly HBV testing (Toyoji et al., 2015), consistent with earlier recommendations that that teams of health professionals might be better able to provide recommended preventative services (Ghorob and Bodenheimer, 2012; Ostbye et al., 2005).

Team based hepatitis B care has met with notable success in two practices serving a predominantly Asian-American patient base (Charles B. Wang Community Health Center, 2011; NEMS, 2014). In San Francisco, Northeast Medical Center set a long-term goal of eliminating hepatitis B from its community (Dan, 2012). To meet that goal, the center offers free HBV screening and vaccination, thereby removing financial barriers for their uninsured patients, many of whom are Chinese immigrants (Dan, 2012).The Charles B Wang Community Health Center in New York City has similar programs; provider teams at Charles B Wang created a hepatitis B registry to link their patients' electronic records with their records at other doctors (Dan, 2012). Hepatitis B teams at both centers include primary care physicians, case managers, health educators, and hepatologists (Dan, 2012).

Research

Hepatitis B, though not a neglected disease, would benefit from more targeted research and development. The previous section describes the problem of reactivation in patients with resolved infection, but further research is needed to identify the risk of different chemotherapy regimens as triggers for reactivation. Similarly, as much as the HBV vaccine is effective, its usefulness could be improved if it could be given in fewer or more closely timed doses. A curative treatment for the virus would clearly change the short-term likelihood of elimination. While there is evidence that such treatment may be possible, nothing of the sort is currently available (Kapoor and Kottilil, 2014; Klumpp et al., 2015).

There is also a need for implementation research in hepatitis B. While it is clear that people born abroad account for much of the adult burden of HBV, it is not clear how screening, testing, and treatment might be integrated with the immigration process or targeted services for refugee and asylee patients. These are all important gaps in understanding that would need to be better understood before elimination could be entirely feasible.

Key Findings and Conclusions

- Comprehensive disease surveillance can improve estimates of the incidence and prevalence of hepatitis B, thereby supporting the efficient allocation of resources and prevention measures. It is also essential for tracking progress toward elimination. Hepatitis B virus (HBV) disease surveillance is inconsistent across jurisdictions and not well funded.
- Immunization registries can provide important information on vaccination coverage in a population. Local support for these registries is uneven. Effective sharing of information across registries is limited.
- HBV infection carries a social stigma that could undermine elimination efforts. Education and changes to social norms can alleviate stigma. Such change is possible, but takes time.
- Improved screening could help reduce complications and deaths from HBV, it could also help end transmission. Screening foreign born people would identify new infections, but restrictions on access to care could keep many of the newly identified cases from treatment.
- Screening should be accompanied by a method to enroll and retain patients in care.
- Hepatitis B is a difficult disease to manage and primary care providers are overburdened already. There is a need for better understanding of how to share patient care among teams of health personnel and make efficient use of electronic record systems.
- Research on reactivation, better vaccines, and a treatment to cure infection would facilitate HBV elimination.

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3

The Elimination of Hepatitis C

In its deliberations, the committee analyzed the problem of hepatitis C in the United States and concluded that eliminating the public health problem of this disease is feasible with certain conditions. This chapter will lay out the committee's logic in coming to this conclusion. First, the chapter describes the epidemiology and natural history of hepatitis C virus (HCV), followed by a brief statement on the committee's conclusion regarding elimination. Next, it discusses ending transmission of HCV and eliminating infection in chronic hepatitis C patients. The following section describes the challenges of preventing deaths among people with chronic infection. The last section presents critical factors that would influence the success of any HCV elimination program. A discussion of the strategies that might be employed to eliminate hepatitis C is outside the scope of this report, but can be expected from phase two of this project.

THE EPIDEMIOLOGY OF HEPATITIS C

In 1989, a small enveloped RNA virus was discovered to be the cause of hepatitis C, a transfusion-associated condition that had until then been called non-A non-B hepatitis (after etiologic exclusion of hepatitis A virus and hepatitis B virus [HBV]) (Choo et al., 1989). HCV infects 2.5-4.7 million people in the United States, and more than 185 million people worldwide (Edlin et al., 2015; Mohd Hanafiah et al., 2013). In addition to contaminated blood transfusions, HCV is primarily spread from person to person by injection drug use, and, less commonly, through sex (particularly among HIV positive men who have sex with men) or from mother to child (Ray and Thomas, 2015).

Most HCV infected people are unaware of their condition. About one-third of infections resolve spontaneously in the first year, the rest continue and become chronic (Cox et al., 2005; Mosley et al., 2005). Both people with resolved infection and those with chronic infection test positive for antibodies to HCV, whereas only those with chronic hepatitis C have consistently detectable HCV RNA in the blood (a test often called viral load) at a level of about 3.2 million IU/mL with 96 percent having a viral load greater than 400,000 IU/mL (Afdhal et al., 2014; Ferenci et al., 2014; Kowdley et al., 2014; Thomas et al., 2000b; Zeuzem et al., 2014). Chronic HCV infection can progress to end-stage liver disease, including liver cancer. HCV can also cause serious problems in organ systems other than the liver, including cryoglobulinemic vasculitis, metabolic bone disease, kidney disease, cardiovascular disease, and hematologic malignancies (Cacoub et al., 2015; Lee et al., 2012). In the United States, HCV is the leading cause of end-stage liver disease requiring liver transplantation, and mortality attributed to HCV is expected to continue rising during the next 10 years (Luu, 2015; McNamara et al., 2014). Though effective treatment is now available, its impact will be muted without expanded measures for screening, disease surveillance, enrolling and retaining patients in care, and patient management (Durham et al., 2016).

The Hepatitis C Virus

In human blood, HCV exists as a lipo-viro-particles containing cholesterol-laden lipoproteins. The lipoproteins facilitate the virus binding to low-density lipoprotein receptors on liver cells, followed by more specific interactions between the viral envelope proteins with an array of cell surface proteins (Andre et al., 2002; Ray et al., 2013). Internalization of the virion is

followed by release of the viral RNA genome into the cytoplasm where it functions as a messenger RNA. This viral RNA is translated by ribosomes to produce HCV's polyprotein, which is cleaved by cellular and viral proteases (e.g., NS3/NS4A protease) to form viral proteins that manufacture viral RNA genomes (via the NS5B RNA polymerase) and reprogram the cell's lipid export pathway to assemble infectious HCV particles (dependent on NS5A phosphoprotein), completing the cycle.

HCV's unique life cycle offers several targets for treatment and prevention of infection. The NS3/NS4A protease, the NS5B RNA polymerase, and the NS5A phosphoprotein are essential, and each of these is targeted by one or more of the direct-acting antiviral drug combinations, therapies that make cure or sustained virologic response[1] possible in more than 95 percent of patients (Zoulim et al., 2015). Viral proteins are potential targets of cellular immunity, and abundant human and animal research evidence supports a critical role for T-cell responses in spontaneous resolution of acute HCV infection (Klenerman and Thimme, 2012). B-cell responses to HCV control the infection in an animal model and may have therapeutic or prophylactic potential (de Jong et al., 2014), especially as the B-cell response tends to appear early in people who are clearing their acute infection (Osburn et al., 2014). Spontaneous control of HCV, which occurs in about a third of acutely infected individuals, is associated with cellular and humoral responses that appear to protect against HCV persistence after repeated infection, further evidence that prophylactic vaccination is possible (Lauer, 2013; Osburn et al., 2010).

The Natural History of Hepatitis C Virus Infection

The National Health and Nutrition Examination Survey (NHANES) conducted between 2003 and 2010 reported that approximately 1 percent of the US population, or about 2.7 million people, are infected with chronic hepatitis C virus (HCV) (Denniston et al., 2014). This is likely an underestimate, as the NHANES survey does not include people who are incarcerated, hospitalized, homeless, in the military, or living in nursing homes—groups thought to account for at least 800,000 additional cases (Armstrong et al., 2006; CDC, 2016; Holmberg et al., 2013). More recent estimates peg the US prevalence at approximately 2.5-4.7 million people (Edlin et al., 2015). Because of the large burden of undiagnosed cases, the Centers for Disease Control and Prevention (CDC) estimates that for each new, symptomatic infection reported, an estimated 3.3 cases of symptomatic, acute hepatitis C actually occur (University of Washington, 2016). Furthermore, because of under-reporting and nonspecific symptoms, for every, new, acute, symptomatic infection reported there are an estimated 12.3 actual new HCV infections in the population (Klevens et al., 2014). This ratio suggest about 17,000 people are infected every year, considerably less than the peak new infections of about 230,000 per year seen in the 1980s (CDC, 2010; Klevens et al., 2014; Smith et al., 2012). Effective screening of blood and tissue donors beginning in 1992 vastly decreased the estimated annual incidence of HCV (Alter and Houghton, 2000; Selvarajah and Busch, 2012). But because of high transmission during the 1970s and 1980s, people born between 1945 and 1965 account for more than three-quarters of chronic hepatitis C in the United States (Smith et al., 2012).

[1] *Sustained virologic response* and *cure* are used synonymously. When interferon treatments were standard of care for hepatitis C sustained virologic response was defined as negative viral load 24 weeks after cessation of therapy. With direct acting antivirals, this timeframe is shortened to 12 week. The 12-week mark is recognized as the endpoint for cure by the Food and Drug Administration (FDA) because of the high concordance between sustained virologic response at 12 and 24 weeks (FDA, 2013).

Only about half of chronically HCV-infected people are aware of their condition (Volk et al., 2009). Over time, chronic HCV infection initiates a cascade of inflammation and progressive hepatic fibrosis, which can lead to cirrhosis (D'Amico et al., 2006; Ray and Thomas, 2015). The risk of liver fibrosis increases with duration of infection. Given the aging of the Baby Boomers, by 2020 there should be about one million cases of cirrhosis attributable to chronic hepatitis C in the United States (Davis et al., 2010).

The most recent models suggest that the 2,138 confirmed, acute HCV infections reported to the CDC in 2013 indicate 29,700 incident cases, a 180 percent increase over 2011 estimates (CDC, 2015). Such estimates may be artificially low (Onofrey et al., 2015). As with HBV, surveillance for HCV in the United States is limited; nine states and the District of Columbia do not report acute cases to the CDC (CDC, 2013). There is also a problem of identifying acute infections for a largely asymptomatic disease. Disease elimination programs generally rely on clinically apparent signs of infection or complications. Identifying acute HCV infection requires active testing to identify seroconversion and repeated testing over time, unless a cross-sectional incidence assay becomes available (Patel et al., 2016). Verifying chronic hepatitis C requires attention to a high volume of cases and laboratory test results, exceeding the capacity of the surveillance infrastructure in most jurisdictions. Furthermore, the people at greatest risk for HCV are often marginalized in other ways; they tend to be undercounted in surveys and outside the reach of the formal health system.

Key Findings and Conclusions

- National surveys from 2003 to 2010 estimated hepatitis C virus (HCV) to be about 1 percent prevalent in the Unites States; but these are likely underestimates as the surveys exclude the homeless, incarcerated, and institutionalized. More recent estimates suggest a prevalence of 2.5 to 4.7 million people.
- Most HCV is undiagnosed. The Centers for Disease Control and Prevention estimates 12.3 new infections occur for every new, symptomatic case reported.
- It is difficult to identify acute HCV infection because it is largely asymptomatic disease. Disease elimination programs tend to rely on clinically-apparent signs of infection.
- People with chronic HCV infection are often asymptomatic; they may also be marginalized and hard to reach.
- Even the limited data available suggest a rise in new HCV infections.

THE FEASIBILITY OF ELIMINATING THE PUBLIC HEALTH PROBLEM OF HEPATITIS C

As the previous chapter describes, disease elimination is a matter of reducing the reproductive number (abbreviated R_0) of a pathogen to a value less than one and maintaining this value until new infections cease. HCV has an R_0 of about 2, which is to say its transmission is not especially efficient, and a modest reduction in transmission efficiency could end the public health problem of HCV (Pybus et al., 2001). If a quarter of a million people were treated for HCV in the United States in 2015, the treatment rate would exceed the annual infection rate by about 10-fold (Durham et al., 2016). But as the disease burden falls more on difficult-to-treat populations, this could change. Already the rate of new infections appears to be rising

substantially, probably driven by increasing injection drug use among young people in at least seven states (CDC, 2013; Zibbell et al., 2015).

Biologically, HCV is a tractable target for eradication. There is no known non-human reservoir and, unlike HIV and HBV, there is no latent cellular reservoir (Ray et al., 2013). Pharmacologic treatment with direct-acting antivirals can truly cure an infected person, treatment-based elimination is an option (Pawlotsky, 2014). At the same time, reinfection is a possibility until either risk of transmission can be eliminated or prophylaxis is available via antiviral drug or vaccine. Such risk undermines progress toward HCV elimination (Simmons et al., 2016). Therefore, the committee concludes that elimination of hepatitis C as a public health problem in the United States is feasible, though there are several conditions on this statement.

Although the biology of the virus and medicines available to treat it would seem to favor the feasibility of elimination, there are serious barriers to this goal. Like hepatitis B, Hepatitis C is generally asymptomatic both during the acute and chronic phase. This epidemiological challenge is aggravated by the heavy concentration of HCV infections in difficult-to-reach populations, including people who inject drugs and the homeless, as well as marginalized groups such as the incarcerated. These groups are not generally represented, sometimes systematically under-represented, in national surveillance surveys such as NHANES (Edlin et al., 2015). Also, the curative treatment that holds the best promise to destroy the viral reservoir is exceedingly expensive. This expense raises concerns about the feasibility of widespread treatment (Durham et al., 2016). In any case, a prophylactic vaccination would make elimination more manageable, especially for a disease that disproportionately effects people who have limited access to medical care. A prophylactic vaccine may be an essential missing piece of the effort to eliminate hepatitis C. Similarly, if current trends in incidence continue, a single-dose curative treatment (as opposed to the current 8- to 12-week therapy) could be invaluable in ending chronic infection among patients often out of contact with the health system.

As with hepatitis B, eliminating the public health problem of hepatitis C in the United States is a matter of ending transmission and reducing the burden of disease among people already infected. The curative treatments available for HCV make the elimination of chronic infection another possibility. This chapter discusses each of these goals in turn and identifies factors crucial to the success of each goal. **After analyzing the problem of hepatitis C in the United States, the committee concluded that control is feasible in the relatively short term. Eliminating the public health problem of hepatitis C will take more time, and require considerable public will, resources, and attention to the barriers mentioned in Table 3-1.** Past success with other infectious diseases suggest that a prophylactic vaccine would greatly increase the likelihood and durability of progress toward elimination, especially given the disproportionate burden of HCV among people with the least engagement with the health system. Table 3-1 gives an overview of the committee's main points and the conclusions presented in this chapter.

Key Findings and Conclusions

- There is no animal reservoir for hepatitis C virus (HCV), and no latent cellular reservoir, making it a tractable target for elimination.
- Treatment with direct-acting antivirals can cure infection, but reinfection after cure is a possibility.
- There is no prophylactic vaccine for HCV.
- Eliminating the public health problem of hepatitis C is feasible, but would require considerable public will and attention to the barriers described in this chapter.

TABLE 3-1 The Feasibility of Eliminating Hepatitis C as a Public Health Problem in the United States with Critical Factors for Success and Crosscutting Problems.

Goal		Feasibility	Critical Factors	Crosscutting Barriers
Ending Transmission		Feasible	• No vaccine • Reaching people who inject drugs with harm reduction programs • Comprehensive drug and alcohol addiction programs • Treating those transmitting the virus to prevent new infection • Reducing the possibility of reinfection	• Surveillance is sporadic and underfunded • Only about half of chronically infected people have been diagnosed • Most new infection is associated with injection drug use, the group most affected is difficult to screen • Poor, marginalized, and hard-to-reach populations are difficult to enroll and retain in care • The high cost of direct-acting antiviral drugs makes universal treatment infeasible • Hepatitis C is not a public priority • Stigma keeps highest risk people away from care • The limited capacity of prison health systems to treat HCV-infected inmates
Eliminating Chronic Infection		Feasible	• Increasing access to treatment • The threat of antiviral resistance • Understanding the role of treatment adherence	
Reducing Morbidity and Mortality Attributable to Ongoing Infection	Slowing progression to cirrhosis	Feasible	• Problems assessing and staging fibrosis • Obesity, HIV, alcohol use can aggravate disease progression • Eradicating the virus before progression to advanced fibrosis can almost eliminate complications and risk of death • Need for reliable models of disease progression	
	Reducing deaths			

NOTE: HCV, hepatitis C virus

ENDING TRANSMISSION OF HEPATITIS C

Eliminating hepatitis C will require stopping transmission of the virus. In the United States, people who inject drugs have the highest risk of transmitting the virus (Alter, 1997). A strategy to stop transmission in this group should give attention to both reducing the risk of contracting HCV among people who are not infected and to reducing the likelihood of transmission among those who are (Edlin and Winkelstein, 2014; Grebely and Dore, 2014; Hellard et al., 2014). Preventing infection among people who use drugs was key to reducing incidence of HIV, but appears less effective for HCV (Palmateer et al., 2010; Wright and Tompkins, 2006). This is because HCV is more transmissible than HIV (Alter, 2006). Even without sharing a needle, HCV can be spread through shared equipment such tourniquets (Hagan et al., 2001).

Nevertheless, there is some evidence that HCV transmission can be reduced through primary prevention efforts. In a 2011 review, Hagan and colleagues found little evidence that behavioral interventions, substance-abuse treatment, opioid-replacement therapy, or syringe programs reduced incidence of HCV when any one program was implemented alone (Hagan et al., 2011). However, two studies that employed multiple strategies (both including opioid replacement, one with counseling, the other with syringe exchange) reduced HCV incidence among drug injectors by about 75 percent (Hagan et al., 2011). A pooled analysis from the United Kingdom, however, suggested that syringe exchange and opioid replacement could each be effective in reducing infection by about 50 percent when implemented independently, provided the syringe exchange reached a large amount of the target population (Turner et al., 2011). When these programs were combined, their reduction on HCV incidence was near 80 percent, similar to the estimate in the Hagan review (Turner et al., 2011).

There is reason to believe that needle and syringe exchange programs, counselling, and opioid replacement therapy (collectively called harm reduction services) can help reduce the transmission of HCV especially among younger people and those who have more recently begun injecting (Mehta et al., 2011; Tseng et al., 2007). Cities with strong needle and syringe exchange programs, including New York and San Francisco, have seen significant declines in HCV prevalence (Des Jarlais et al., 2005; Tseng et al., 2007). The higher prevalence of HCV among older injectors and those who have been injecting longer suggests that the programs delayed, but did not prevent, the infection (Mehta et al., 2011). The longer time to infection may also prove a valuable window in which to reach young people who inject drugs with information about preventing infection or treating substance use disorders (Mehta et al., 2011). The recent lifting of Congress' ban on use of federal funds for syringe exchange (with the caveat that the funds cannot be used on needles or syringes) may allow for expanding harm reduction programs.

Comprehensive drug and alcohol programs will be critical to any HCV elimination program. Such programs may be complicated. Injecting drug use is becoming more common in rural areas and small towns, not the just densely populated cities where such programs have a history (Suryaprasad et al., 2014; Zibbell et al., 2015). Adapting harm reduction strategies to rural and suburban areas could be challenging. Mathematical models suggest that high-coverage—referring to both the number of injectors reached in a geographical area and the number of syringes exchanged relative to injections made—is important in needle and syringe exchange programs (Day and Topp, 2011). Furthermore, needle and syringe exchange programs in combination with opioid replacement therapy can reduce HCV prevalence, but it takes many

years to see these effects (Vickerman et al., 2012). In areas where harm reduction programs have been going on for many years, additional reductions in prevalence may be difficult without the introduction of new, more effective interventions, such as widespread treatment or use of a vaccine.

Treatment as Prevention and Reducing Reinfection

The simple, safe, and curative HCV treatments that came onto the market in 2014 changed not only the prognosis for individual hepatitis C patients, but also the strategy for interrupting transmission. Treating infected patients as a way to prevent disease spread is an established clinical and epidemiological principle in HIV (Cohen et al., 2011; Tanser et al., 2013). The promise of direct-acting, combination antiviral treatments for hepatitis C is even better, as these therapies can cure the vast majority of infections and can do so in relatively short time.

Modelling studies, many based on populations outside the United States, indicate that treating hepatitis C in people who inject drugs would reduce disease prevalence by 20 to 80 percent (Durier et al., 2012; Hellard et al., 2012; Martin et al., 2011). In Vancouver, where about 5 out of 1,000 drug-injecting hepatitis C patients are treated per year, treating an additional 71 patients per year would halve the burden of hepatitis C (Martin et al., 2013b). More recent models suggest that a four-fold increase in treatment of hepatitis C (from about 100,000 to 400,000 patients per year) could prevent more than 250,000 deaths and more than 500,000 cases of cirrhosis per year (Durham et al., 2016). As the burden of disease is heaviest among people who inject drugs, a 90 percent reduction in prevalence in the United States would require screening 20 percent of injection drug users and treating about a third of those infected (Durham et al., 2016) (see Box 3-1).

BOX 3-1
Case Study on Cherokee Nation Health Services HCV Elimination Project

The Cherokee Nation in northwest Oklahoma, is home to more than 300,000 people, 131,000 of whom are Cherokees. In the past few years, reported hepatitis C incidence in the community has increased from 263 in 2012 to 945 in 2015. The Cherokee Nation Health Services manages these cases with an electronic health record system developed in partnership with the University of New Mexico, the University of Oklahoma, and the Indian Health Service. They are also the recipient of a $1.5 million grant from the Gilead Foundation for the hepatitis C elimination program with the following goals:

1. **Secure political commitment for hepatitis C elimination in the Cherokee Nation Health Services**

To this end, the Cherokee Nation Principal Chief Bill John Baker has been involved with the program since its start in late 2015, with support from other tribal leaders and staff from various state and federal agencies.

2. **Expand the screening program**

The Cherokee nation has good screening for people born between 1945 and 1965, but poor outreach to other age groups. Therefore, the elimination program aims to screen an additional 84,000 patients, or 65 percent of the Cherokee Nation Health Services population, in 3 years. The screening will be triggered by reminders in electronic health records, and Indian Health Service nurses will be required to ask new patients about their risk factors for HCV.

3. **Establish robust programs to link to care, treat, and cure patients with hepatitis C**

The Indian Health Service estimates that of the more than 4,300 hepatitis C patients in the Cherokee Nation only 274 (about 6 percent) initiated treatment in 2015, with 118 (almost 3 percent) achieving 12-week sustained virologic response. Through expansion of the University of New Mexico Extended Community Health Outcomes Project, new goals were set for treating 85 percent of patients with active hepatitis C infection in 3 years, and curing 85 percent of patients defined by 12-week sustained virologic response.

4. **Reduce the incidence of new hepatitis C infections in the Cherokee Nation Health Services**

Among Cherokee patients, injection drug use, tattoos from unlicensed artists, blood transfusion, and occupational exposure to blood are the most common risk factors for HCV. Tattooing alone is a risk factor seen in almost two-thirds Cherokee hepatitis C patients. Therefore, the Oklahoma State Health Department and the Cherokee Nation Health Services are working on culturally-relevant educational campaigns explaining how hepatitis C is transmitted. The program is also active in contact tracing and using treatment as prevention. The state health department is working with the Indian Health Service to develop a sentinel surveillance system, data from which could also inform modelling of the unique transmission dynamics in the Cherokee Nation.

5. **Model elimination of hepatitis C infection in the Cherokee Nation Health Services**

An advisory committee develops and reviews all of the program's work. The epidemiological data collected as part of the screening and surveillance programs will be used to adjust the long-term goals as necessary.

SOURCES: Baker, 2016; Mera and Drevets, 2015.

Translating these models' promise into tangible results is complicated for several reasons. First, there may be error in the models introduced by the assumption of random mixing[2] among people in a population. In reality, only a fraction of hepatitis C patients are actively transmitting the virus. The most infectious candidates are those currently using injection drugs, a relatively young and frequently incarcerated population (Hagan et al., 2004; Zeiler et al., 2010). Though hepatitis C passes only rarely from mother to child, pregnant women with HCV could transmit it to their children. Among people infected with both HCV and HIV the otherwise low risk of sexual transmission rises, so HIV+ people are also seen as higher risk for transmission. Treating hepatitis C in high-risk transmitters, an otherwise healthy group who could become reinfected, would prevent no immediate deaths. Preventing deaths means treating the patients at greatest risk of cirrhosis and end-stage liver disease: older people, often no longer sharing needles or injecting drugs at all, beyond child bearing age, and with fewer sexual partners (Hagan et al., 2004; Kirk et al., 2013). So while the direct-acting antiviral treatments can both prevent hepatitis C deaths and interrupt new infections, meeting these goals requires attention to widely different patient populations.

[2] Meaning, for example, that a teenager who injects drugs is as likely to trasnmit the virus to a person of middle age as to another teenager.

Furthermore, treatment models assume that cases identified in screening programs would complete a course of treatment under appropriate medical supervision, but national data suggest that only about one-third of people who screen positive for HCV antibody receive any follow-up care (Holmberg et al., 2013). Patients themselves may be reluctant to pursue treatment. Hepatitis C infection is mostly asymptomatic, encouraging the perception that it is not serious especially when weighed against the common and severe side effects of pre-2012 pegylated interferon and ribavirin treatment (Edlin et al., 2005; Mehta et al., 2008). The new direct-acting antiviral treatments are far more easily tolerated, but the misconception may persist, or concern with HCV be simply overshadowed by poverty and the co-morbidities of addiction (Grebely et al., 2008; Mehta et al., 2008; Treloar et al., 2010). Providers may share in the reluctance to treat or even screen people actively using injection drugs out of a belief that they would not cooperate with treatment or be quickly reinfected (Lambert et al., 2011; Osilla et al., 2011).

The Threat of Reinfection

Reinfection is a barrier to using hepatitis C treatment as a tool to end transmission. Curative treatments are new, and research on reinfection after direct-acting antiviral therapy is limited (van de Ven et al., 2015). There is some evidence that risk of reinfection is relatively low, however. A 2013 analysis pooled data from seven studies on reinfection with HCV following treatment-induced sustained virologic response in men who have sex with men and people who inject drugs (Grady et al., 2013). The overall pooled estimate or risk of reinfection was between 0.91 and 6.12 percent per 100 person-years (Grady et al., 2013). The authors observed that the baseline incidence of HCV in the population appeared to influence this rate. So in places where HCV infection was rare, the risk of reinfection in high-risk patients was lower than in places where the background incidence of HCV was high (Grady et al., 2013). It is also not easy to distinguish between relapse after sustained virologic response and true reinfection. Patients from high-risk groups may be more likely to be infected with more than one strain of HCV. In these cases one strain may respond to treatment, while another persists (Grady et al., 2013).

Frequency of infectious contacts after being cured and the background HCV prevalence in the subpopulation both influence the risk of reinfection (Grebely et al., 2012). Phylogenetic analysis indicates that HCV transmission clusters among people with a reported injecting relationship (Sacks-Davis et al., 2012). Treating all infections within an injecting group—accomplished by encouraging patients to bring their friends for treatment—has promise to reduce prevalence among the drug-injecting subpopulation by 7 percentage points more than traditional treatment strategies and is currently being tested in Australia (Hellard et al., 2014, 2015).

Harm Reduction

Active drug users drive the bulk of hepatitis C transmission in the United States (Alter, 2002, 2007; Bruggmann and Grebely, 2015). The expansion of harm reduction services holds particular promise to interrupt transmission in this group. Recent models indicate that preceding hepatitis C therapy with a 40 percent increase in harm reduction services could decrease the treatment rate required to halve chronic hepatitis C prevalence over 10 years (Martin et al., 2013a).

The people most likely to transmit the virus are young and injecting drugs—people who are not well connected to health or social services. Reaching this group will be challenging, but there may be transferrable strategies from HIV (e.g., mobile testing and treatment, community and peer support, cash incentives) to encourage compliance with treatment (Chang et al., 2013). There is also the matter of addressing the root causes of drug addiction, and linking hepatitis C treatment to social and mental health services.

Key Findings and Conclusions

- In the United States, people who inject drugs are most likely to transmit hepatitis C virus (HCV).
- Harm reduction services can help reduce the transmission of HCV especially among younger people and those who have more recently started injecting.
- The effectiveness of harm reduction depends on the number of injectors reached and the number of syringes exchanged relative to total injections made. Most harm-reduction models were designed in cities where coverage was relatively easy to maintain, but injection drug use is becoming more common in rural areas and small towns. Adapting harm reduction to less densely populated places will be challenging.
- Direct-acting antivirals can both prevent hepatitis C deaths and interrupt transmission, but meeting these goals requires attention to widely different patient populations.
- Reinfection after cure is possible, but since the curative treatments are new, research on reinfection is limited.

ELIMINATING CHRONIC HEPATITIS C

There are 2.7 to 4.7 million people in the United States with chronic hepatitis C (Ward and Mermin, 2015). The disease disproportionately affects people aged 40 to 59, the same age group already experiencing the increased burden of chronic disease brought on by age. The burden of HCV is also felt more among the poor and less educated; fewer than half of people with HCV infection have incomes greater than twice the poverty level or education beyond high school (Denniston et al., 2014). Even these estimates might be biased toward the relatively stable and affluent, as prisoners and homeless people, known risk groups for HCV, are not included in national surveys (Denniston et al., 2014).

Managing chronic disease is challenging for reasons discussed later in this chapter. Both the chronic disease patient and his or her providers need to be involved in an ongoing process from diagnosis through continued monitoring and treatment. This process is sometimes called the care cascade or treatment cascade (HHS, 2015b). For people living with chronic hepatitis C, the care cascade starts with diagnosis and links to care. Once in care, patients should have HCV RNA confirmatory testing and genotyping and undergo liver fibrosis staging to help inform their prognosis and make decisions regarding antiviral therapy. Lastly, they must be prescribed HCV treatment and adhere to that treatment to the point of sustained virologic response (Yehia et al., 2014). National guidelines outline the appropriate care for patients along this continuum (Ghany et al., 2009, 2011; Yee et al., 2012).

The concept of a care cascade as a diagram showing the proportion of patients accounted for at every step of treatment, provides a framework for evaluating hepatitis C services over time and within patient subgroups. The effects of new screening efforts or antiviral drugs can be shown clearly on such a diagram (Moyer, 2013; Smith et al., 2012; Thomas, 2012). One recent meta-analysis made clear that the sharpest drop in the continuum from infection to sustained virologic response was in the diagnosis of HCV infection (Yehia et al., 2014) (see Figure 3-1).

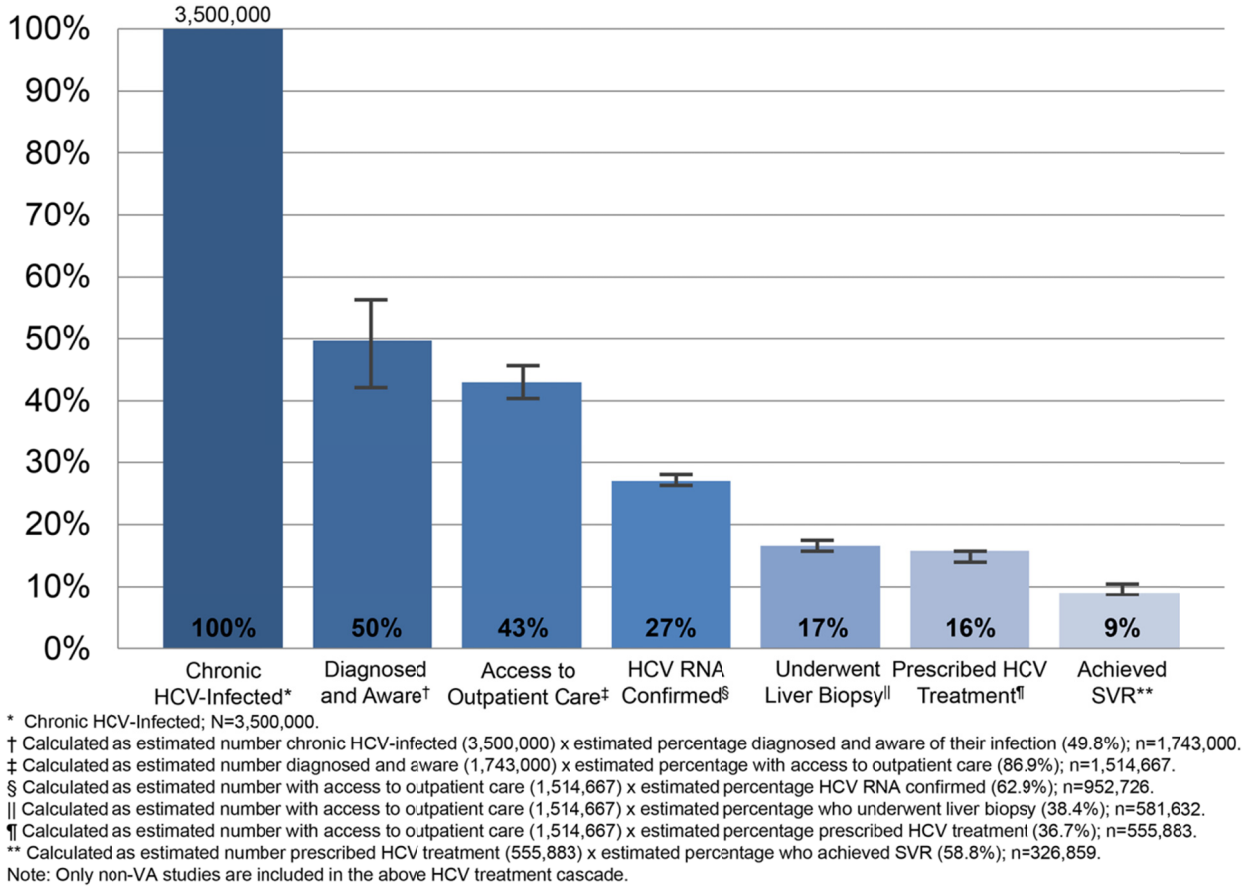

FIGURE 3-1 The treatment cascade for chronic hepatitis C virus infection in the United States.
NOTE: HCV, hepatitis C virus; RNA, ribonucleic acid; SVR, sustained virologic response; VA, Department of Veterans Affairs.
SOURCE: Yehia et al., 2014.

In 2012, the CDC recommended one-time HCV testing for everyone born between 1945 and 1965, regardless of other risk factors, because this group is thought to account for three-fourths of all HCV infections in the country (Smith et al., 2012). The same recommendation called for referral of newly identified HCV-infected people to care (Smith et al., 2012). This recommendation may be better observed in the breach than in practice. CDC and NHANES research suggests that only about half of HCV infected people are aware of their condition (Denniston et al., 2012). Among those who are aware, about 57 percent carry health insurance, compared to 43 percent of those unaware of their infection (Denniston et al., 2012).

As Figure 3-1 illustrates, the prescription of antiviral therapy is another drop-off on the HCV care cascade, though recent developments in treatment may be reducing this decline. A

retrospective analysis of Department of Veterans Affairs data found that the 2011 introduction of boceprevir-based combination therapies nearly doubled the monthly volume of patients treated (Gidwani et al., 2015). The advent of all-oral, highly efficacious, and tolerable direct-acting antivirals has shortened treatment duration. Shorter treatment means less opportunity to lose track of patients during therapy; the better tolerability of the treatments should allow for improved compliance. The best strategies for retaining patients in care are still unclear, however.

Access to Direct-Acting Antiviral Therapies

Direct-acting antiviral drugs make cure possible in 95 percent of chronic HCV infections, but their use is limited. The cost of these treatments is discussed later in this chapter, but briefly, the high cost and anticipated demand for these drugs have led many insurers to restrict access to these medications. Before approving a prescription some insurers need evidence of advanced liver fibrosis or consultation with a specialist (Brennan and Shrank, 2014; Saag, 2014; Steinbrook and Redberg, 2014). Many insurers require patients abstain from alcohol and illicit drugs for a set time before beginning treatment; some request drug screening to confirm sobriety (Grebely et al., 2015). Two recent reports analyzed how these restrictions are put into practice across different state Medicaid programs. They revealed considerable variation in different states' restrictions on treatment, despite the federal Medicaid law's requirement that all states cover drugs in accordance with the FDA label (Barua et al., 2015; Canary et al., 2015).

Wide inconsistencies in insurers' restrictions on access to hepatitis C treatments have created extra work for providers. Insurers now require that the prescribing clinician or collaborating pharmacy submit a request for prior authorization documenting that the patient meets the insurer's criteria for HCV treatment. The insurer reviews the request and either approves or denies it. If prescription is denied, the prescriber can appeal the decision; the insurer will uphold or overturn the denial based on the supporting information presented during the appeal. It is unclear what toll the denial and appeal process might take on clinical outcomes, to say nothing of patient–provider relationships. Further research examining the consequences of treatment denial could inform a more complete understanding of the direct and opportunity costs of treatment.

Adherence to Antiretroviral Therapy

Clinical trials have shown direct-acting antivirals to be highly efficacious and tolerable, but their real-life effectiveness depends on the patient's adherence to treatment (Afdhal et al., 2014; Feld et al., 2014; Sulkowski et al., 2014). As with other chronic viral illnesses, particularly HIV, poor adherence reduces the likelihood of treatment response (Bangsberg et al., 2001; Gross et al., 2001; Nachega et al., 2007). Thus, understanding patients' actual adherence to treatment is crucial when considering the possible elimination of chronic HCV infection.

Before the direct-acting agents were available, better adherence to treatment pegylated interferon and ribavirin was associated with greater HCV RNA declines and higher rates of early and sustained virologic response (Lo Re et al., 2009, 2011, 2013). But these treatments were difficult for patients to tolerate, and adherence tended to decline over the course of therapy. The direct-acting antivirals are easier to tolerate, but to date no studies have evaluated the effects of adherence on serological markers of infection. Given the costs of these therapies and the possible consequences of non-adherence (i.e., drug resistance, continued progression of liver disease, potential to transmit HCV infection), it is important to understand the relationship between adherence and sustained virologic response, the patterns of adherence to different regimens, and

changes in adherence over the 8- to 12-week course of therapy. Such analyses could help clinicians ensure the best possible clinical response (Weiss et al., 2009).

Threat of Resistance to Direct-Acting Antiviral Therapies

When patients do not respond to direct-acting antiviral therapy, there is a threat that unsuccessful treatment can select for HCV variants resistant to these agents (Poveda et al., 2014). The selection of mutations at different positions in the NS3/4a protease, NS5B polymerase, and NS5A replication complex proteins drive the development of resistance to direct-acting antivirals (Sarrazin and Zeuzem, 2010). With the exception of NS5B nucleos(t)ide inhibitors, most direct-acting antivirals have a low genetic barrier to resistance, with significant cross-resistance between agents in the same drug class. Cross-resistance between drugs in the same class seems to be of greatest concern with use of NS3/4A protease inhibitors and NS5A inhibitors (Poveda et al., 2014). A specific mutation profile may be associated with each medication or class and can vary by genotype or subtype (Poveda et al., 2014; Wyles, 2013). There are also resistant mutations existing as natural polymorphisms in certain genotypes and subtypes. In the past, testing prior to antiviral treatment aimed to identify these mutations before treatment. For example, the Q80K polymorphism is frequently found among patients with genotype 1a[3] and is associated with resistance to the NS3/4A protease inhibitor simeprevir (Kieffer et al., 2012; Poveda et al., 2014; Trevino et al., 2011; Trimoulet et al., 2011).

Cure rates for current direct acting antiviral agents exceed 90 percent, but these agents have only been used for a few years. Many questions regarding resistance remain. Current data suggest that pre-existing mutations have a negligible impact on HCV treatment response, and retreatment of patients with treatment-acquired resistance variants can be effective (Afdhal et al., 2014; Feld et al., 2014; Sulkowski et al., 2014). The clinical significance of preexisting resistance mutations for these therapies is largely unknown. Moreover, it is not clear how long existing resistant mutations persist or if NS3/4A or NS5A cross-resistance might be a concern for patients who failed prior treatment regimens with these agents. These are important questions, as the threat of resistance needs to be considered in the management of hepatitis C and the eventual elimination of the disease.

Key Findings and Conclusions

- The direct-acting antiviral drugs that cure hepatitis C virus infection are expensive, so insurers restrict their access, usually asking for evidence of advanced fibrosis or consultation with a specialist, some also require confirmation of sobriety.
- State Medicaid programs have widely different restrictions on treatment.
- Most direct-acting antivirals have a low genetic barrier to resistance, with significant cross-resistance between agents in the same drug class.

REDUCING MORBIDITY AND MORTALITY FROM HEPATITIS C

People living with HCV—especially those with cirrhosis—are at a substantially increased risk of death. HCV-infected people participating in the NHANES survey between 1988 and 1994 and followed though 2006 had a 2.4 times higher all-cause mortality rate and a 26.5 times higher

[3] 19 to 48 percent prevalent.

liver-related mortality rate ration compared to HCV negative people (El-Kamary et al., 2011). Models that assume absence of treatment suggest that incident cases of end stage liver disease among HCV-infected people will peak between 2030 and 2035 with 379,600 cumulative deaths by 2030 and 1,071,229 cumulative deaths by 2060 (Rein et al., 2011).

HCV related cirrhosis is also a leading indication for liver transplantation in the United States. The Scientific Registry of Transplant Recipients from 2012 gives HCV-related cirrhosis as the underlying cause for listing 4612 patients (about 30 percent of the list), resulting in 1,402 liver transplants (OPTN/SRTR, 2014). If untreated prior to liver transplantation, HCV will reinfect the transplanted organ resulting in decreased patient and graft survival. Efforts to cure HCV in patients with decompensated cirrhosis may help avoid need for liver transplantation. If transplantation is still required, HCV cure after transplant prolongs graft survival (Joshi et al., 2014).

HCV also causes considerable morbidity, including complications not related to liver disease. HCV-related cryoglobulinemia has been associated with cutaneous and visceral vasculitis, and glomerulonephritis, as well as B-cell non-Hodgkin's lymphoma (Negro et al., 2015). Because the liver and heart function together to ensure a healthy blood flow, liver damage can cause cardiovascular problems. HCV patients have increased risk cardiovascular ailments such as carotid plaques, insulin resistance, diabetes and hypertension (Petta et al., 2012; Younossi et al., 2013).

HCV also hurts patients through less tangible reductions to quality of life. When compared to uninfected and HBV-infected controls, HCV patients reported a significantly more fatigue, low energy, and body pain (Foster et al., 1998). Fatigue and cognitive impairment are common in people with hepatitis C (Cacoub et al., 2002; Weissenborn et al., 2004). Though sickness can itself be a cause of depression, when compared to other people with liver disease, hepatitis C patients had worse quality of life and more depressive feelings, even after viral clearance (Tillmann et al., 2011).

The Staging and Progression of Hepatitis C

The progression of HCV infection is closely linked to the severity of fibrosis. Liver biopsy is considered the standard way to assess fibrosis, but the procedure has many limitations. Only a small sliver of liver tissue is drawn in biopsy. A specimen that accounts for only about $1/50{,}000^{th}$ of the organ may not be representative of the liver as a whole. Even experienced pathologists can disagree on the stage of a sample; inter- and intra-observer variability of 10 to 20 percent is not unusual (Bravo et al., 2001). The specialists needed to draw and read the specimen drives up the cost of the procedure, which can also be painful, and carries a risk of bleeding and drop in blood pressure that can require hospitalization in 1 to 3 percent of patients (Bravo et al., 2001). For these reasons, less invasive methods are needed to stage fibrosis. Certain panels of serum markers and non-invasive imaging techniques such as transient elastography and magnetic resonance elastography can also be used to assess fibrosis, and have promise for describing the disease burden in the growing population of hepatitis C patients (Poynard et al., 2007; Vallet-Pichard et al., 2007; Venkatesh et al., 2013; Wai et al., 2003).

Twenty to 40 percent of chronic hepatitis C patients will develop cirrhosis; the median duration of time from infection to cirrhosis is around 30 years (Poynard et al., 1997). Age, sex, and lifestyle appear to influence disease progression: Men infected after age 40 progress about

13 years faster than the median, while non-drinking women infected before age 40 might be expected to live 42 years before the onset of cirrhosis (Poynard et al., 1997). Estimating any patient's risk of fibrosis is complicated, however, because of often unidentifiable interactions between the virus and the host. Among strains of HCV, genotype 3 appears more virulent; infection with HBV or HIV speeds the progression of fibrosis in HCV patients, though interestingly, neither viral load nor means of infection consistently appear to have an effect on the progression of the disease (AASLD-IDSA, 2015c; Poynard et al., 2001). Other predictors of disease progression include fibrosis stage, inflammation grade, male sex, past organ transplantation, and age at time of HCV infection.

Fibrosis does not generally progress in a predictable or linear way, however. After 20 years of HCV infection the overall risk of cirrhosis is about 16 percent, after 30 years, 41 percent (Thein et al., 2008). Age at the time of exposure and duration of infection are established risk factors for development of advanced fibrosis and cirrhosis. The process does accelerate at the patient ages, however; fibrosis progresses most quickly after age 50 (Poynard et al., 2001). Therefore, both the patient's age and the duration of his or her infection should be taken into account when identifying those at high risk of illness or death from advanced fibrosis and cirrhosis.

Still, certain patient characteristics seem to predict faster progression of fibrosis, some of these are within the patient's ability to control. Alcohol consumption, for example, increases the HCV-infected person's odds of developing cirrhosis four fold, and appears to speed the path to cirrhosis (Harris et al., 2001; Thomas et al., 2000a). HCV patients who drink alcohol are hospitalized and die younger than those who abstain (Kim et al., 2001). Given these risks, abstinence from alcohol is the safest strategy for preventing cirrhosis in HCV-infected people, and support for alcohol cessation in heavy drinkers might influence the success of an elimination program.

The co-morbidities of obesity aggravate the natural course of HCV. Dyslipidemia and type 2 diabetes can develop as both cause and an effect of a non-alcoholic fatty liver disease, a condition of fatty infiltration in the liver found in about 20 percent of American adults (Chalasani et al., 2012; Vernon et al., 2011). When HCV patients also have fatty liver disease, they appear more likely to develop advanced fibrosis (Sanyal et al., 2003). Fatty liver and other obesity-related metabolic conditions are common in the United States; they could influence the speed at which HCV patients develop complications.

Co-infection with HIV, though found in less than 20 percent of people with HCV, can do the same (AASLD-IDSA, 2015b; Rotman and Liang, 2009). Infection with both HIV and HCV causes more aggressive progression to fibrosis, and speeds the onset of cirrhosis by 12 to 16 years (Di Martino et al., 2001; Rockstroh and Spengler, 2004). A prospective study comparing HCV patients with and without HIV found higher rates of hepatic decompensation in the patients with both infections (hazard ratio accounting for competing risks, 1.56 [95% confidence interval (CI), 1.31-1.86]). Even when the patient's HIV was well-controlled, the risk of hepatic decompensation persisted (Lo Re et al., 2014). Given the particularly aggressive course of liver disease in people infected with both HIV and HCV, their treatment with direct-acting antivirals for HCV should be a priority. Curing infection in this group could prevent the complications of advanced liver disease (Naggie et al., 2015).

Prevention of Cirrhosis and Hepatocellular Carcinoma Through Treatment

The curative treatments available for HCV make it different from other chronic viral infections. The new drugs have made cure or sustained virologic response possible in more than 95 percent of patients with relatively short courses of treatment with few or mild side effects (Afdhal et al., 2014; Feld et al., 2014). Sustained virological response is usually described as durable, meaning that it persists for years after cure. In follow up studies over 5 years and longer, patients with sustained virologic response have undetectable HCV RNA; relapse is rare and associated with pre-treatment cirrhosis (George et al., 2009; Maylin et al., 2009)

Eradicating the virus before the patient starts progression to advanced fibrosis can also largely eliminate the risk of hepatic complications. HCV treatment can also improve liver histology. In a pooled analysis of 3,010 treatment-naïve patients who underwent liver biopsy before and after interferon based therapy, patients who achieved sustained virologic response had a significant improvement in disease activity (Poynard et al., 2002). Another study on paired biopsies on 49 patients who achieved sustained virologic response, 82 percent had a decrease in fibrosis score and 20 percent had normal or near normal histology after 5 years (George et al., 2009). The clinical and histologic evidence that disease progression stops in patients with early stage fibrosis who are cured of HCV infection informed the current American Association for the Study of Liver Disease (AASLD) and Infectious Disease Society of America (IDSA) recommendation that no further monitoring of these patients is warranted after cure (AASLD-IDSA, 2015a). In short, curing HCV before the disease progresses to advanced fibrosis is the most efficient way to prevent the complications of the infection.

Prevention of Complications in Patients with Advanced Fibrosis

HCV patients who already have cirrhosis are at risk of decompensated liver disease, hepatocellular carcinoma, and death. In those with compensated cirrhosis, portal pressures remain relatively low; despite histologic evidence of cirrhosis, clinical presentations are largely asymptomatic. The compensated cirrhosis of chronic HCV infection can progress to decompensated cirrhosis, marked by increase in portal pressure, which causes ascites, portal hypertensive gastrointestinal bleeding, hepatic encephalopathy, and jaundice. Portal hypertensive complications significantly increase risk of death. For example, 1-year mortality risk in a patient with non-bleeding esophageal varices and without ascites is 3.4 percent, but with bleeding esophageal varices, the 1-year mortality jumps to 57 percent (D'Amico et al., 2006). One-year survival in patients with decompensated cirrhosis is approximately 82 percent, and 5-year survival was near 51 percent (Planas et al., 2004).

Direct-acting antiviral therapy has been shown to be safe and highly effective in achieving sustained virologic response among cirrhotic patients (Afdhal et al., 2014; Charlton et al., 2015). Patients with compensated cirrhosis who undergo curative therapy are unlikely to progress to a decompensated state. In patients with cirrhosis or advanced fibrosis, sustained virologic response has been associated with improvement in histology as well as decreased liver-related death, incidence of liver failure, development of hepatocellular carcinoma and all-cause mortality rates (Backus et al., 2011; Veldt et al., 2007). Antiviral treatment has also recently been shown to restore liver function in decompensated cirrhosis. HCV patients with Child[4] B and C cirrhosis not only had high response rates to direct-acting antiviral therapy, with 86 to 89 percent

[4] Officially, Child-Pugh or Child-Turcotte-Pugh score, a classification used to assess the prognosis of chronic liver disease. Child class B and C have 3-year survival rate of 59 and 46 percent, respectively (Angermayr et al., 2003).

showing sustained virologic response, but also had improvements in Childs score, MELD score,[5] albumin and bilirubin levels (Charlton et al., 2015). In some ways, cirrhotics have the most to gain from curative HCV treatment, as the nature of their disease puts them at the most immediate risk of death.

When cirrhosis is advanced, viral eradication alone may not restore synthetic dysfunction and portal pressures. Today, these patients require liver transplantation. Transplantation is an expensive procedure. The scarcity of donor organs motivates requirements that candidates be otherwise healthy and have strong social support. In the future, transplant might be avoided with the use of anti-fibrotic and portal pressure lowering therapies now in development (Friedman, 2015). In the meantime, antiviral therapy is an effective means to prevent progression to severely decompensated cirrhosis.

In patients with chronic hepatitis C, risk of hepatocellular carcinoma is closely linked to development of fibrosis (Yoshida et al., 1999). Because hepatocellular carcinoma in the absence of advanced fibrosis is rare, halting progression of fibrosis though therapy will be an effective means of cancer prevention. For those who already have advanced fibrosis, sustained virologic response is still an effective means to reducing cancer risk. A recently published meta-analysis showed that among 2,649 patients with advanced fibrosis only 4.2 percent of patients who achieved sustained virologic response developed hepatocellular carcinoma, compared to 17.8 percent of patients who did not respond to therapy (Morgan et al., 2013).

Need for Further Research

Preventing complications of advanced liver disease in people with HCV requires reliable predictive models for disease progression. Although risk factors such as HIV and alcohol use have been well described, most of the factors influencing disease progression are not understood well, making it difficult to predict any patient's likely outcome. More research into host and viral genomics might help advance such understanding, as would better predictive models for progression of fibrosis (Harouaka et al., 2016). Ultimately, such tools would help clinical teams identify patients who should be the first priority for therapy.

Clinical management of HCV patients would also benefit from better therapy to avoid the complications of portal hypertension among cirrhotic patients. Anti-fibrotic therapies and better pharmacologic treatment for portal hypertension are possibilities currently under investigation (Friedman, 2015). Although successful HCV therapy allows for regression of disease in most patients, these treatments will be necessary for those who still progress or continue to have significant amount of fibrosis after treatment with direct-acting antivirals.

[5] The Model for End-Stage Liver Disease, or MELD score, rates the severity of chronic liver disease on a scale of 1 to 40 with higher scores indicating higher 3-month mortality (Cholongitas et al., 2005).

Key Findings and Conclusions

- Chronic hepatitis C virus (HCV) infection greatly increases risk of death, especially among people with cirrhosis. HCV-related cirrhosis is the leading indication for liver transplantation in the United States.
- Twenty to 40 percent of people with chronic HCV infection will develop cirrhosis. Age, sex, and factors such as alcohol use, obesity, diabetes, HIV infection, influence its onset.
- Curing hepatitis C in patients with decompensated cirrhosis can avoid the need for transplantation entirely or prolong graft survival after transplantation.
- HCV-infected people often report fatigue, depression, and cognitive impairment. Even when compared to other liver disease patients, hepatitis C patients report lower quality of life.
- Curing HCV before it progress to cirrhosis is the most efficient way to prevent fibrosis, hepatocellular carcinoma, and death from hepatitis C.

CROSSCUTTING BARRIERS TO HEPATITIS C ELIMINATION

Any progress toward reducing transmission of HCV, toward eliminating chronic infection, or to reducing the morbidity and mortality attributable to chronic infection could be impeded by certain systemic barriers. Problems with disease surveillance, enrolling and managing patients in care, the cost of the curative treatment necessary to eliminate chronic infection, stigma, and motivation to eliminate the disease could also pose serious impediments to progress against the infection.

Surveillance

Chapter 2 describes problems with viral hepatitis surveillance in the United States. A 2010 Institute of Medicine (IOM) report on hepatitis and liver cancer recommended improving national surveillance for these viruses, but to date the CDC funds such programs in only seven jurisdictions (HHS, 2015a; IOM, 2010).

Surveillance for viral hepatitis could improve understanding of the true burden of disease across the care cascade. Identifying acute cases is essential to identifying an outbreak and instituting control measures, especially for nosocomial outbreaks or ones connected to medical care (Apostolou et al., 2015). Follow-up on acute cases can also help identify changes in the pattern of the HCV epidemic. If, for example, the public health officer sees a spike in infections among young people who inject drugs or among HIV+ men who have sex with men then they can adapt preventative measures accordingly (Breskin et al., 2015; Onofrey et al., 2011).

Challenges to conducting acute surveillance for HCV abound, however. First of all, the unsafe injection of drugs drives most transmission in the United States (Alter, 1997). People who inject drugs are less likely to receive medical care, and are therefore less commonly reported to the health department. Identifying acute HCV cases is also an imprecise process. The Massachusetts health department recently found that of 183 patients clinically diagnosed with HCV over ten years, only one would have met the case definition required for inclusion in national statistics (Onofrey et al., 2015). (See Box 3-2 for case definitions.) As the CDC bases its estimates of HCV incidence on reported acute cases, overly restrictive definitions and inconsistencies in clinical or laboratory reporting could lead to an amplified underestimate of

true disease burden (Onofrey et al., 2015). Without a simple test for acute cases this problem will likely persist, as will the challenge of identifying asymptomatic cases.

Identifying spikes in acute infection is important, and a reasonable expectation for a surveillance system. But a good understanding of chronic hepatitis C prevalence in an area is essential for allocating resources for prevention and treatment. Estimates of national prevalence are derived from the NHANES, Aside from the sampling limitations of the NHANES discussed earlier, the survey does not distinguish between differences in disease burden among different jurisdictions (Edlin et al., 2015). A more accurate response to the epidemic would require better local data, which could give a more accurate picture of the full, local care cascade, not just the acute infections.

BOX 3-2
Council of State and Territorial Epidemiologists
Definitions for Case Classification of Hepatitis C Infection

The case definition for *hepatitis C* requires:

- *Clinical evidence:* An illness with discrete onset of any sign or symptom consistent with acute viral hepatitis (e.g., fever, headache, malaise, anorexia, nausea, vomiting, diarrhea, and abdominal pain), AND jaundice OR a peak elevated serum alanine aminotransferase (ALT) level >200 IU/L during the period of acute illness
- *Laboratory criteria:* A positive test for antibodies to hepatitis C virus (anti-HCV+), HCV RNA+ (including qualitative, quantitative or genotype testing)
- *Case classification:* A *confirmed, acute case* meets clinical criteria and has HCV RNA+ OR a documented anti HCV–, HCV core Ag–, or HCV RNA– test followed within 12 months by a positive result on any of these tests (called test conversion)
  A *probable acute case* meets clinical criteria and has an anti-HCV+ test, but no reports of an HCV RNA+ AND does not have test conversion within 12 months or has no report of test conversion
  A *chronic, confirmed case* does not meet clinical criteria or has no report of clinical criteria AND does not have test conversion within 12 months or has no report of test conversion AND has positive HCV RNA
  A *chronic, probable case* does not meet clinical criteria or has no report of clinical criteria AND does not have test conversion within 12 months or has no report of test conversion AND has an anti-HCV+ test, but no report of a HCV RNA+

SOURCE: (DeMaria, 2015)

Surveillance for HCV requires a strong public health infrastructure; chronically infected people often need multiple assays every year for years. The volume of testing needs to move through the system promptly to allow for real-time follow-up on potential outbreaks. A proper understanding of HCV burden would also attempt to capture the consequences of chronic infection, linking surveillance to health insurance claims, electronic health records, and birth, death, and cancer registries. There is also a need for deliberate attention to those populations at high risk for the disease: people who inject drugs, the homeless, and incarcerated. A system that can promptly identify seroconversion in these groups has the chance to react to new outbreaks

and spot trends in how the disease is transmitted. Contact tracing, a common practice in outbreaks of sexually transmitted disease such as syphilis and HIV, may be a useful practice for HCV as well.

Screening

Even the best disease surveillance cannot change the fact that about half the chronically infected people in the United States are undiagnosed (Smith et al., 2012). In 2012 the CDC expanded HCV screening guidelines; later the US Preventive Services Task Force recommended testing everyone born between 1945 and 1965 (often called the Baby Boomers) (Smith et al., 2012; USPSTF, 2013). Baby Boomers account for about three-quarters of the country's chronic hepatitis C (Ward, 2013). When screening this birth cohort became the default at the University of Alabama Hospital emergency room (meaning that anyone born in these years was tested unless he or she declined testing), they identified chronic infection in one out of every nine people screened (Feld et al., 2015). This prevalence is considerably higher than what would be expected, even among Baby Boomers, possibly because poor and uninsured people are both more likely to seek care at emergency departments and more likely to have hepatitis C (Galbraith et al., 2015). The greatest incidence of HCV is in younger age groups, driven largely by drug injection among whites in rural areas and small towns (Suryaprasad et al., 2014). This changing pattern of disease complicates the protocol for screening. There might be transferable lessons from HIV screening, which has established methods of linking HIV+ patients to treatment and social support, and some overlapping target populations. There is also room to make better use of screening opportunities in prisons and in drug treatment and harm reduction programs. Research in sexually transmitted disease clinics found that HCV counselling, testing, and referral for people who inject drugs cost about $25 per patient tested (Honeycutt et al., 2007)[6]. About 45 percent of participants who inject drugs returned to the clinic for their results, a far better rate of return that found among the non drug-using patients of whom less than 13 percent returned (Honeycutt et al., 2007).

About half of the chronically HCV-infected people in the United States are unaware of their condition (Denniston et al., 2014; Holmberg et al., 2013). The first steps to preventing deaths in these people is diagnosing and retaining them in care. Most hepatitis C screenings are done in clinical settings, which can ease the patient's referral to care and provide better assurance that the test result will be documented (CDC, 2013). But those at highest risk for HCV, including people who inject drugs, the homeless, and the incarcerated, can remain outside the reach of clinical screenings (Larney et al., 2014). Community screening might be a way to reach more patients, provided there is a strong referral system in place (Trooskin et al., 2015). Correctional facilities pose a similar opportunity. Maintaining contact with patients met through community screening is challenging, however. A team working in New Jersey and New York City found that screening at community organizations allowed for diagnosis of new patients, most of whom had no traditional risk factor for HCV, but 36 percent of these newly diagnosed people were lost to follow-up and never evaluated for treatment (Perumalswami et al., 2013). The method of screening might contribute to the attrition. Research in mobile clinics in New Haven found that HCV-infected patients diagnosed with point-of-care tests were significantly more likely to link to care and get treatment then those tested with traditional and slower phlebotomy tests (Morano et al., 2014).

[6] In 2006 dollars.

Enrolling and Retaining Patients in Hepatitis C Care

Once patients are referred to care, the challenge of managing them over time remains. HCV might be particularly difficult to manage because of the demands it puts on primary care. A 2014 survey found that about half of primary care physicians were already at full capacity, about a third reported being over-extended and over-worked (The Physicians Foundation, 2014). In general these providers are obliged to give more attention to acute and urgent problems than to the management of chronic disease (Bodenheimer et al., 2002). This burden on the health system could impede progress toward the elimination of hepatitis C.

A concern with redesigning the health system to meet the needs of the chronically ill is the essence of Edward Wagner's chronic care model described in Box 3-3 (Glasgow et al., 2001; Wagner et al., 2001). These principles have been shown to be useful in clinical practice. A 2009 review found that the chronic care model improved patient outcomes or the care process; when diabetic care conformed to the model, for example, HbA1c score and risk of heart disease decreased (Coleman et al., 2009; Parchman et al., 2007). Granted, research on the chronic care model often has many component interventions. It can be difficult to separate the benefits directly due to the chronic care model from those due to an observer bias, but the research suggests that the model has promise to greatly improve outcomes for patients with chronic disease (Coleman et al., 2009; Landon et al., 2004).

BOX 3-3
Wagner's Chronic Care Model

Much of the medical system was designed to respond to acute health crises, but nowadays the more common health problem are chronic ones. The Chronic Care Model was developed in response to this observation and aims to improve care of patients with chronic illness by encouraging informed, motivated patients and prepared, responsive practice teams. It had six components, validated in a national project involving 104 health providing organizations in the United States. There components are:

1. **Health Care Organization,** specifically, the support of institution leaders and their commitment to quality improvement for chronic care
2. **Community Resources,** increasing access to programs and services through negotiated relationships with the community, a cost-effective way to improve and expand access
3. **Self-Management Support,** shifting away from lecturing patients to interventions that emphasize support, encouragement, and build the patient's confidence to manage his or her condition, this kind of support can be individual or group.
4. **Delivery System Design,** involving case managers to help change behavior, adjust their medications, adhere to treatment, and follow-up with their providers improves outcomes and makes more efficient use of resources.
5. **Decision Support,** the full integration of current treatment guidelines in care
6. **Clinical Information System,** the use of a registry to organize patient records and create reports.

SOURCE: (Wagner et al., 2001)

It is also possible that patient navigators, lay health workers who can help patients overcome barriers in the health system, can help HCV-infected people stay in care. The patient navigator model has been shown effective in managing chronic conditions such as HIV and cancer (Vargas and Cunningham, 2006; Wells et al., 2008). The strategy has not yet been fully evaluated for HCV, though. Recent work in Philadelphia found that patient navigators can greatly facilitate diagnosis and retention in care of patients identified through community screening (Trooskin et al., 2015). Another Philadelphia group demonstrated that routine HCV testing and referral could be successfully integrated with ambulatory care for poor and homeless people (Coyle et al., 2015). Medical assistants helped relieve the burden on clinicians and other health center staff by guiding patients through their appointments and follow up. They also used reflex HCV testing technology to ensure that anti-HCV-positive patients received HCV RNA testing; the reflex technology also has the advantage of providing HCV antibody and RNA test results in one visit. Intensive services carried out by a patient navigator further increased the number of HCV-infected patients who received their results and were referred and seen by a specialist (Coyle et al., 2015).

Cost

An emphasis on diagnosis and bringing patients to care will do much to reduce the burden of disease from HCV, but the most promising tool to eliminate chronic disease is the direct-acting antiviral drugs that elicit sustained virologic response in more than 95 percent of patients (Kohli et al., 2015). These response rates are similar across genotypes, with the exception of genotype 3, and for treatment-naïve patients as well as those who failed prior treatments.

Although effective treatment is now a reality, access to treatment remains poor. Estimates that pre-date the development of curative HCV drugs suggested that about a third of people aware of their chronic HCV infection were on treatment (Kanwal et al., 2010; Moorman et al., 2013). No recent population-based studies have examined the fraction of people with HCV infection on direct acting agents, but some inferences may be drawn from sales data of pharmaceutical firms selling these agents. In 2014, US sales of Harvoni®[7] and Sovaldi®[8]—the two blockbuster direct acting agents marketed by Gilead— totaled $10.5 billion, and an estimated 140,000 patients initiated HCV treatment using one of these two drugs (Gilead Sciences, 2015a; Pollack, 2015). So the revenue per patient initiating therapy was about $75,000.[9] In the first three-quarters of 2015, US sales of these drugs totaled $10.1 billion, the latest sales data available at the time of this report, and another ~200,000 patients initiated treatment with Harvoni® or Sovaldi® (Gilead Sciences, 2015b,c,d). So the revenue per patient initiating therapy in 2015 was $52,000. The decline in revenue per patient or discounted price might reflect competition from new HCV therapies such as AbbVie's Viekira®[10] approved in December 2014. AbbVie reported US sales of Viekira® of roughly $600 million in the first three

[7] The US proprietary name of 90 mg of the viral NS5A inhibitor ledipasvir and 400 mg of sofosbuvir, a nucleotide inhibitor of the viral RNA polymerase.
[8] The US proprietary name of sofosbuvir.
[9] Revenue per patient is simply the $10.5 billion in revenue divided by the 140,000 patients initiating therapy. Revenue per patient is a good approximation of the discounted price for a full course of treatment received by the manufacturer from health plans and other payers. It is lower than the list price for these drugs as it includes the discounts offered by the manufacturer to payers.
[10] The US proprietary name of ombitasvir, paritaprevir, and ritonavir tablets co-packaged with dasabuvir tablets.

quarters of 2015 (Abbvie, 2015). Assuming that revenue per patient initiating therapy was $50,000, it follows that roughly 12,000 patients initiated treatment with Viekira® in 2015. Taken together these estimates imply that roughly 350,000 patients have initiated treatment with direct acting agents since their introduction in late 2013. Given the estimated HCV prevalence in the United States, one can assume between seven and fourteen percent of people with HCV infection have initiated treatment with direct acting agents (Edlin et al., 2015).

So despite the impressive effectiveness of direct acting agents only about 1 in 10 chronically infected people is given curative treatment. Admittedly, part of the problem is the asymptomatic nature of HCV, leaving about half of chronically infected people unaware of their condition. The high prevalence of HCV among marginalized and difficult to reach people also complicates the problem. Still, the price of direct acting agents is a major barrier to eliminating the disease. The first direct acting agent introduced in the market (Gilead's Sovaldi®) was launched at a price of $1,000 per pill or about $84,000 for a 12-week course of treatment (Sanger-Katz, 2014). Subsequent introductions of similar drugs were priced between $54,000 and $168,000 per course of treatment (Bickerstaff, 2015; Loria, 2016). Treating all diagnosed HCV infections in the United States with these drugs would cost about $175 billion up front, and would be unmanageable in other ways; treating millions of hepatitis C patients would exceed the capacity of available providers (Van Nuys et al., 2015a,b). Even treating only 5 percent of known infections would cost about $25 billion up front (Van Nuys et al., 2015a).

These prices have met widespread criticism for being too high (Hoofnagle and Sherker, 2014; Pollack, 2015). The Senate Finance Committee's 18-month investigation into the pricing of Sovaldi® and Harvoni® concluded that Gilead priced the drug to maximize profits without consideration of affordable access (US Senate Committee on Finance, 2015). The committee also recognized that Gilead's pricing analyses had not accounted for the restrictions Medicaid and insurance companies would place on access (US Senate Committee on Finance, 2015).

There are two primary arguments to support the claim that the prices of direct-acting agents are too high. First, is that the high prices are unaffordable—not only for the uninsured patient, but also for insured patients and their health plans. Roughly one-third of the people with HCV infection lack insurance coverage (Ditah et al., 2015; Stepanova et al., 2011). Lack of insurance coverage is highly predictive of not receiving follow-up care or treatment after diagnosis with HCV infection(Ditah et al., 2015). And even if the uninsured were all to enroll in care, the financial burden of paying for treatment would be tremendous. Insurers have responded to the drugs' prices by imposing clinical restrictions on access. As the previous section mentions, most Medicaid programs restrict access to direct-acting antivirals by limiting eligibility for treatment to those with advanced fibrosis or cirrhosis or by limiting coverage to prescriptions from specialist (Barua et al., 2015; Canary et al., 2015). The drug and alcohol testing described earlier in this chapter pose further barriers. Finally, for people co-infected with HIV and HCV, some states' Medicaid programs limit access to individuals receiving antiretroviral therapy for HIV or to those who have suppressed HIV RNA levels (Barua et al., 2015). Three-quarters of states' Medicaid programs limit access to persons with advanced liver disease, two-thirds of states have restrictions based on prescriber type, and half require a period of abstinence (Barua et al., 2015). These restrictions in access to direct-acting agents are not just limited to Medicaid, several private insurers, including Aetna, BlueCross, and United Healthcare, have instituted similar controls (Aetna, 2015; BlueCross BlueShield of Mississippi, 2015; United Health Care, 2015). No clinical evidence or treatment guidelines support the restrictions; they appear to be

motivated only by concerns about cost (Harvard Law School, 2013). A national analysis of prescription drug spending found that expenditures on prescription drugs increased by 12.2 percent in 2014—a sharp acceleration from growth of 0.2 percent in 2012 and 2.4 percent in 2013 (Martin et al., 2015). The introduction of direct-acting antivirals drove most of this acceleration and accounted for one-third of the 2014 spending increase (Martin et al., 2015). Another recent analysis found that unrestricted coverage of direct-acting agents would increase California's Medicaid budget by about 5 percent per member per month (Institute for Clinical and Economic Review, 2015). Such dramatic budget increases to cover just one therapy are not common, making insurers reluctant to provide unrestricted coverage for these drugs.

At the same time, not everyone agrees that the prices of direct-acting agents are too high or unsustainable. There are three arguments that support their case. First, despite the high prices, direct acting-agents are cost-effective for treating patients with genotype 1 HCV, the most prevalent genotype (Bickerstaff, 2015; Chhatwal et al., 2015; Najafzadeh et al., 2015; Younossi et al., 2015). That is, even at the high prices, the benefits from treatment outweigh the costs (Van Nuys et al., 2015a). For example, Chhatwal and colleagues (2015) found that for treatment naïve patients with genotype 1 HCV, the incremental cost effectiveness ratio[11] for sofosbuvir-based therapies compared to older interferon therapies ranged from $31,452 to $9,703 per quality-adjusted life year.

It is difficult to say how much society is willing to pay for one quality-adjusted life year; $100,000 is a common, if conservative, threshold (Hirth et al., 2000; Neumann et al., 2014). By this measure, sofosbuvir-based therapies are highly cost-effective. The incremental cost-effectiveness for patients with genotype 1 who had already tried other treatments were higher (ranging from $35,853 to $79,238), but well below the $100,000 threshold (Giovanni et al., 2016). Sofosbuvir-ledipasvir treatments show similar cost-effectiveness for patients with genotype 1 HCV (Najafzadeh et al., 2015; Younossi et al., 2015). But there are some patients for whom sofosbuvir-based treatments might not be cost effective, such as people with genotype 2 or 3 HCV who had failed earlier treatment genotype 2 or genotype 3 HCV (Chhatwal et al., 2015). Treating 1.6 million cases of chronic hepatitis C with direct acting agents would cost about $49 billion ($65 billion in direct costs, less $16 billion in offsets) (Chhatwal et al., 2015). Assuming society is willing to pay $100,000 for a quality-adjusted year of life, the benefits of treatment are $88 billion, exceeding the costs by $39 billion (Chhatwal et al., 2015).

Second, proponents of the current pricing model maintain that high prices are needed to encourage innovation. Most economists agree that there is a trade-off in lowering prices; such action will improve access to existing treatments but reduce the pace of innovation or access to future treatments (Lakdawalla and Sood, 2012). This is why most developed countries have patent regimes, to encourage innovation by allowing the patent holders to charge higher prices and increase revenues from new products for the length of the patent. Research on the effects of patent length on innovation is scant, but several studies show that pharmaceutical research and development are responsive to revenues or market size (Acemoglu and Linn, 2004; Blume-Kohout and Sood, 2013). By some estimates, a 10 percent change in market size leads to about a 30 percent change in innovation measured as new drug approvals (Blume-Kohout and Sood,

[11] The incremental cost-effectiveness ratio is the cost of adding one quality-adjusted life year due to an intervention. When the incremental cost-effectiveness ration is $50,000, for example, it can be interpreted as costing society $50,000 to gain one quality-adjusted life year.

2013). Third, the initial high prices on the drug are temporary; ultimately, such prices are thought to encourage competition. For example, as new therapies have come on the market, discounted prices or revenue per patient initiating therapy with Sovaldi® and Harvoni® has fallen from $75,000 in 2014 to $52,000 in 2015 (Gilead Sciences, 2015a,d).

Eliminating HCV infection would require near universal access to treatment, something that appears infeasible given the current pricing and policy environment. The committee believes, however, that there is room for creative solutions that promote universal access to treatment while maintaining incentives for innovation. Potential solutions might include licensing deals where insurers provide universal access and pharmaceutical firms offer volume discounts or rebates to offset some of the costs. Or, as in the Vaccines for Children program, the federal government could serve as the negotiator of a discounted price for poor patients. There might also be need for regulations to correct for market failures in private insurance markets. For example, private insurers might be reluctant to cover new treatments due to fear of adverse selection: HCV-infected clients dropping coverage from stricter plans and enrolling in more generous ones. Before the Affordable Care Act, exclusions on insurance coverage for pre-existing conditions made such moves impossible; now insurers have reason to fear them.

It might also be possible to expand insurance coverage and safety net programs for uninsured HCV patients as the Ryan White Program and AIDS Drug Assistance Program did for poor HIV patients (HRSA, 2016). The parallels between response to HIV and HCV should not be overstated, however. HCV is more than twice as common in the United States as HIV (Edlin et al., 2015). As of 2007, it also causes more annual deaths (Ly et al., 2012). But far fewer resources are allocated to HCV prevention, testing, treatment, and research efforts than to HIV. Unless the disease is a public priority, as HIV was from the 1990s on, it will be difficult to marshal funds for any elimination program.

Stigma, Injection Drug Use, and Corrections

HIV was not always the global priority it is today. Like HCV, HIV disproportionately affects marginalized people whose circumstances carry a stigma that isolates them. For HIV in the United States the group most affected was men who have sex with men; for HCV it is people who inject drugs. The HIV epidemic encouraged men who have sex with men to overcome stigma and advocate for people with the disease, improving worldwide access to treatment and services (Sengupta et al., 2011). The same transition is unlikely for HCV. People imprisoned or injecting drugs are, almost by definition, not in good position to rally public support for their health problems.

The social stigma that accompanies HCV can impair the HCV-infected person's mental health and sense of well-being (Marinho and Barreira, 2013). These feelings in turn can contribute to poor treatment uptake and retention in care (Grebely and Dore, 2014; Zeremski et al., 2013). Providers might also be driving the stigma that keeps HCV-infected people from care (Ahern et al., 2007; Paterson et al., 2007; Valdiserri, 2002). Doctors may feel uncomfortable or uncertain when treating people who inject drugs, something often interpreted as intentional mistreatment (Merrill et al., 2002) Stigmatized people tend to internalize perceived judgments, developing a self-image of incompetence and dangerousness; perceptions of stigma can lead the HCV infected person to avoid medical care entirely (Link and Phelan, 2006; Miller et al., 2012). So stigma could undermine the best hepatitis C elimination program by keeping the population at greatest risk for transmitting the virus away from treatment (Treloar et al., 2013).

About 60 percent of prevalent hepatitis C cases in the United States are associated with injection drug use (McGowan and Fried, 2012). Drug abuse, in turn, can be both a cause and an effect of mental health problems. Prior illicit drug use in HCV patients has been linked to lower levels of social support and increased self-report of depression and anxiety (Blasiole et al., 2006). Almost 30 percent of chronic hepatitis C patients in a cohort study met the criteria for depression, though sustained virologic response post-treatment was found to improve these symptoms (Boscarino et al., 2015). Good-quality, non-judgmental medical care can have benefits beyond improvement in markers of HCV. Such treatment can improve social and mental stability and decrease high-risk behaviors in people who inject drugs (Newman et al., 2013).

The Opportunity to Treat HCV in Corrections

Injection drug use is also a strong predictor of lifetime likelihood of incarceration (DeBeck et al., 2009; Milloy et al., 2008). By a conservative reckoning, between 24 and 36 percent of people addicted to heroin pass through the American prison system each year (Boutwell et al., 2007). Drug users are frequently and repeatedly incarcerated. The number of people incarcerated grew by 33 percent in the decade ending in 2006, but the proportion of prisoners with a drug problem grew by 10 percentage points more (Dolan et al., 2015; Walmsley, 2014) Sixty-five percent of inmates in the United States meet diagnostic criteria for substance abuse disorder; though incarceration does not appear to reduce drug use (DeBeck et al., 2009; The National Center on Addiction and Substance Abuse at Columbia University, 2010). Only 11.2 percent of inmates with addiction receive treatment for their condition while incarcerated (The National Center on Addiction and Substance Abuse at Columbia University, 2010).

Of the roughly 6.9 million adults[12] estimated to be involved in the correction system, over a third are in state or federal prisons or county jails; the rest are in community corrections including probation and parole (Glaze and Kaeble, 2014). Prisons are generally larger than jails and sentence inmates for extended periods of time, though some large jails (including Rikers, Cook and Los Angeles County facilities) hold 10,000 people or more (NY DOC, 2016). Jails have rapid population turnover with an average length of stay around 23 days (Subramanian et al., 2015). Though prisons are managed by state governments, jails are usually in domain of county and municipal authorities, though six states[13] have unified management of all corrections in one system (Krauth, 1997).

Prisoners are legally entitled to medical care while incarcerated, though there are concerns about the quality of the care provided (*Estelle v. Gamble*, 1976; Wilper et al., 2009). As state and local taxes support the prison system, there is also a wide variability in what different prisons can afford to provide. Medicaid and federal matching funds are not generally available for inmates unless they are admitted to community hospital for more than 24 hours. Still, prisons present an excellent venue for HCV elimination and control programs. Prison inmates account for between 28.5 and 32.8 percent of the national burden of hepatitis C (Varan et al., 2014). Prevalence in different prisons systems tends to vary between 9.6 and 41.1 percent, with the average national prison prevalence between ten and 20 percent (American Correctional Association, 2015; Larney et al., 2014; Varan et al., 2014).

[12] 2013 estimate.
[13] Alaska, Connecticut, Delaware, Hawaii, Rhode Island, and Vermont .

Prison health systems could be instrumental in hepatitis C elimination, as the prison health authorities have access to an otherwise difficult to reach patient population. Prisons are obligated to provide care, and if scheduled properly, the prison system would allow for treatment with very little loss to follow-up and few missed doses. On the other hand, treating hepatitis C is expensive. Prison health systems are not generally large enough to negotiate a substantial discount on direct-acting agents. As the director of the Rhode Island Department of Corrections explained in an interview with National Public Radio, treating HCV can be assumed to cost roughly $150,000 per patient and hundreds of Rhode Island inmates have chronic hepatitis C, but the maximum drug budget for the whole system is $19 million (Gourlay, 2014).

Direct acting agents have also cause prisons to confront various patient management challenges. Older hepatitis C treatments, which needed to be given with certain foods and several times a day, were logistically incompatible with the prison timetable, but simpler direct acting regimens are changing that (Hepatitis C Online, 2016). Furthermore, pegylated interferon therapy took about 48 weeks to complete, but a full course of direct acting agents can be finished in 8 or 12 weeks, making treatment in jails as well as prisons in option (Hepatitis C Online, 2016). Unplanned transfers and releases can disrupt treatment, however (Liu et al., 2014).

Prisons may also be a good venue for drug and alcohol treatment programs. In the first 2 weeks after release former, inmates have more than 12.7 times greater risk of death then other people (95 percent CI 9.2 to 17.4); their risk of death from drug use is 129 times greater (95% CI: 89-186) (Binswanger et al., 2007). Opioid replacement therapy is not typically offered in corrections, despite being the UN and WHO recommended standard of care for all populations (Kastelic et al., 2008; Pecoraro and Woody, 2011).

Prisoners account for almost a third of all hepatitis C cases in the United States (Varan et al., 2014). Treating this population is essential to the success of any elimination program; treating substance use disorder in the same patients could help reduce their risk of reinfection after release. Nevertheless, treating HCV would require more staff and budget that prison health systems can allocate to any one problem.

The questions of logistics and competing priorities that make hepatitis C a challenge for the prison system are found in other parts of society as well. Eliminating the public health problem of HCV in the United States will require attention to the medical management of the disease and the distribution of infection in the population, as well the social factors that put people at risk for infection and those that keep them care. These are important barriers, and the strategy to overcome them will be discussed in the phase two report.

Key Findings and Conclusions

- Injection drug use drives most hepatitis C virus (HCV) transmission in the United States, and people who inject drugs are less likely to be tested for HCV or captured in disease surveillance data.
- Deliberate attention to the populations most at risk for HCV infection is essential for tracking progression against elimination.
- Half of people with chronic HCV infection are undiagnosed. The first step to preventing the progression of their disease is diagnosing and bringing them to care.
- Hepatitis C puts demands on overworked primary care providers.
- Some insurers have responded to the high price of HCV drugs by restricting access. Only about one in ten people with chronic HCV infection receives curative treatment.
- The introduction of direct-acting antivirals for hepatitis C drove most of the acceleration in prescription drug spending between 2013 and 2014.
- Even at the current prices, these drugs are cost-effective. The benefits of treatment outweigh the costs.
- Eliminating Hepatitis C would require near universal access to treatment, something that appears unfeasible given the current pricing and policy environment.
- Though HCV is more than twice as common as HIV and causes more deaths, it is less of a public priority, far fewer resources are allocated to its prevention, testing, treatment, and research.
- HCV infection carries a stigma that could undermine the elimination effort.
- Almost a third of the United States' chronic hepatitis C cases are found in prisons, but managing the infection is not usually within the capacity of a prison health system.

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4

Conclusion

Hepatitis B and C kill about 20,000 people every year in the United States, and more than 1 million worldwide (CDC, 2013; WHO, 2016). Hepatitis B virus (HBV) and hepatitis C virus (HCV) together account for most viral hepatitis, which kills more people every year than road traffic injuries, HIV and AIDS, and diabetes (WHO, 2016). While the deaths from other common killers (i.e., malaria, tuberculosis, and HIV) have decreased since the early 2000s, deaths attributable to viral hepatitis continue to rise (IHME, 2016).

These deaths can be averted. Three doses of HBV vaccine convey 95 percent immunity (WHO, 2015). Though HBV infection cannot be cured, proper treatment can reduce viral load to an undetectable level (EASL, 2012). While there is no vaccine for HCV, new curative treatments can eliminate the infection in over 95 percent of patients (Afdhal et al., 2014; Charlton et al., 2015; Feld et al., 2014). Improved prevention and expanded access to viral hepatitis treatments could greatly reduce the burden of these infections. The World Health Organization (WHO) estimates that reducing the incidence of chronic hepatitis B and C by 90 percent and reducing mortality by 65 percent would save 7.1 million lives by 2030 (WHO, 2016).

The United States has an opportunity and a responsibility to be part of the global action against hepatitis B and C. Already the Department of Health and Human Services' viral hepatitis action plan lays out ambitious goals for improving prevention and care, and expanding hepatitis surveillance (HHS, 2014). In the near term, the committee finds control of both diseases to be imminently possible. This committee also believes that a more ambitious goal is within our reach: Elimination of HBV and HCV as public health problems in the United States. Although an elimination goal is entirely feasible, it is not necessarily likely without considerable attention to the barriers discussed in this report. First of all, disease reductions programs require an accurate understanding of the true burden of disease in a population. There is wide uncertainty in all estimates of HBV and HCV incidence and prevalence. Limited surveillance contributes to the uncertainty, as does the often asymptomatic course of the infections. Wider screening could help identify more chronically infected people, but screening for both infections is complicated.

Expanding screening for chronic HBV and HCV infections would surely identify new cases, but some would be among people with no access to care. Diagnosis with a chronic disease requires follow-up in primary care. Diagnosis of chronic hepatitis B carries with it the opportunity for treatment and monitoring to reduce the long-term risk of liver cancer and cirrhosis. It also offers the opportunity to vaccinate the patient's uninfected contacts. Such follow-up is not an option for people who are uninsured and ineligible for Medicaid.

Hepatitis B and C care require a health workforce knowledgeable about long-term management of viral hepatitis. Much of the burden falls on primary care providers, who are already overworked, and extends indefinitely. There is no cure for hepatitis B, and infected individuals require management for the rest of their lives. Hepatitis C, in contrast, can be cured in 8 to 12 weeks, thanks to new direct-acting antiviral drugs. These drugs are expensive in the United States. The first of these treatments to gain Food and Drug Administration approval cost $1,000 per pill in 2014 (Sanger-Katz, 2014). Competition from other products has brought the price down, but curing a chronically infected HCV patient in the United States still costs between

$54,000 and $168,000 (Bickerstaff, 2015; Loria, 2016). Even at such prices, curing hepatitis C is cost-effective (Bickerstaff, 2015; Chhatwal et al., 2015; Najafzadeh et al., 2015; Younossi et al., 2015). The tension between the expense and cost-effectiveness of treating HCV puts Medicaid and insurance companies in a difficult position. They have responded by restricting access to treatment to only the sickest HCV patients. Even so, HCV treatments alone accounted for about a third of the sharp acceleration in drug spending between 2013 and 2014 (Martin et al., 2015). It is currently not financially possible to treat all the estimated 2.7 to 4.7 million people thought to have chronic HCV infection given the current prices (Edlin et al., 2015; Ward and Mermin, 2015).

The high price of treatment creates a tension in determining which patients' treatment should be a priority. Those at most immediate risk of death are not necessarily those transmitting the virus, so the goals of ending HCV transmission and ending deaths from hepatitis C are somewhat at odds with each other.

There are creative strategies to mitigate this and other barriers to eliminating hepatitis B and C. Five years ago curing HCV infection with short-term, tolerable therapy seemed impossible. Similar breakthroughs in the treatment and management of hepatitis B are possible, as is the development of a prophylactic vaccine for HCV. This report has identified no shortage of research questions for basic scientists, pharmaceutical companies, and health services researchers. None of these questions is especially new, however. The challenge of directing more research interest to viral hepatitis remains.

It is also possible that limitations in disease surveillance, screening, treatment, vaccination, and research are all consequences of a more basic problem. Viral hepatitis is not a public priority in the United States. This too could change; attitudes toward disease can shift rapidly. Education and successful elimination of HBV among Alaskan Natives accompanied changes in local attitudes toward the disease. Liver disease often carries a stigma, perhaps because of its association with drug and alcohol use and sex; HBV and HCV can cause particular shame and distress in patients. Stigma, in turn, encourages silence and inaction among infected people, which is antithetical to any elimination program.

In making its conclusion regarding the feasibility of hepatitis B and C elimination, the committee acknowledges that considerable barriers must be overcome to meet these goals. For example, as elimination policies gain traction, the risk of infection should fall. Some people may respond by reducing efforts to protect themselves from infection. Public health campaigns highlighting the importance of elimination and the need to prevent individual infection might mitigate such behavior. A discussion of this and other solutions to the problems discussed in this report is not within the scope of the project. A second report, to be released in 2017, will outline a national strategy to eliminate hepatitis B and C. This report will discuss ways to address the critical factors and reduce the barriers to elimination set out in this document. The second phase of this project will also explore specific national targets for the elimination effort.

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A

Committee Meeting 1 Agenda

COMMITTEE ON A NATIONAL STRATEGY FOR THE ELIMINATION OF HEPATITIS B AND C

The Keck Center, 500 Fifth Street NW
Washington, DC 20001

NOVEMBER 30, 2015
ROOM 105

THE CHARGE TO THE COMMITTEE AND PHASE 1 REPORT

10:45-11:30	The Charge to the Committee **John Ward,** *Director, Office of Viral Hepatitis*, Centers for Disease Control and Prevention **Nadine Gracia,** *Deputy Assistant Secretary for Minority Health and Director, Office of Minority Health*, Department of Health and Human Services
11:30-12:00	Study Timeline **Brian Strom**, *Committee Chair*
12:00-1:00	Lunch

OVERVIEW OF HBV AND LOGISTICAL AND SOCIAL ASPECTS OF ELIMINATION

1:00-1:30	Overview of Epidemiology and Natural History of Hepatitis B **Jules Dienstag,** *Carl W. Walter Professor Medicine*, Massachusetts General Hospital
1:30-2:00	Gaps in Hepatitis B Monitoring and Screening **Mandana Khalili,** *Professor of Clinical Medicine*, University of California, San Francisco
2:00-2:30	The Costs and Logistics of Community HBV Screening Programs **Chari Cohen,** *Director of Public Health*, Hepatitis B Foundation
2:30-2:45	Break
2:45-3:15	The Health Systems Obstacles to Hepatitis B Elimination

Robert Gish, *Principal*, Robert Gish Consultants, LLC

3:15-3:45 Management of the Chronic Hepatitis B Patient in Alaska
Brian McMahon, *Medical and Research Director*, Alaska Native Tribal Health Consortium (by video)

3:45-5:00 Panel Discussion Social and Logistical Feasibility of Eliminating HBV
Art Reingold, *Moderator*

- **Chari Cohen,** *Director of Public Health*, Hepatitis B Foundation
- **Jules Dienstag,** *Carl W. Walter Professor Medicine*, Massachusetts General Hospital
- **Adrian DiBesceglie**, *Co-Director*, Saint Louis University Liver Center (by phone)
- **Robert Gish,** *Principal*, Robert Gish Consultants, LLC
- **Brian McMahon,** *Medical and Research Director*, Alaska Native Tribal Health Consortium (by video)

5:15 Adjourn

DECEMBER 1, 2015
ROOM 100

SCIENTIFIC AND MEDICAL ASPECTS OF ELIMINATION

9:00-9:15 Welcome and Meeting Overview
Brian Strom, *Committee Chair*

9:15-9:45 Medical Management of Hepatitis B
Anna Lok, *Alice Lohrman Andrews Research Professor*, University of Michigan Health System

9:45-10:15 Hepatitis B Reactivation
Rohit Loomba, *Professor of Medicine*, University of California, San Diego

10:15-10:30 Break

10:30-11:00 Immunology of Hepatitis B
Kyong-Mi Chang, *Associate Chief of Staff for Research and Development*, Corporal Michael J. Crescenz Veterans Affairs Medical Center

11:00-11:30 Virology of Hepatitis B
T. Jake Liang, *Chief of Liver Diseases Branch, Deputy Director of Translational Research*, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health

11:30-12:30	Panel Discussion Scientific and Clinical Feasibility of Eliminating HBV **Randy Mayer,** *Moderator* • **Kyong-Mi Chang,** *Associate Chief of Staff for Research and Development*, Corporal Michael J. Crescenz Veterans Affairs Medical Center • **T. Jake Liang,** *Chief of Liver Diseases Branch, Deputy Director of Translational Research*, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health • **Anna Lok,** *Alice Lohrman Andrews Research Professor*, University of Michigan Health System • **Rohit Loomba,** *Professor of Medicine*, University of California, San Diego
12:30	Adjourn

B

Committee Meeting 2 Agenda

COMMITTEE ON A NATIONAL STRATEGY FOR THE ELIMINATION OF HEPATITIS B AND C

The Keck Center, 500 Fifth Street NW
Washington, DC 20001

DECEMBER 16, 2015
ROOM 105

SESSION 1 - OPEN
THE SCIENTIFIC AND CLINICAL FEASIBILITY OF ELIMINATING HCV

8:45-9:00	Welcome and Introductions **Brian Strom,** *Committee Chair*
9:00-9:30	The Epidemiology and Natural History of Hepatitis C Virus **David Thomas,** *Professor of Medicine and Director of Infectious Diseases*, Johns Hopkins University School of Medicine
9:30-10:00	Screening and Clinical Management of Hepatitis C **Marc Ghany,** *Staff Clinician, Liver Diseases Branch*, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health
10:00-10:30	Treatment of Hepatitis C **Jay Hoofnagle,** *Director*, Liver Disease Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health
10:30-10:45	Break
10:45-11:15	Prevalence of HCV and a Framework for Understanding Cost-Effectiveness **Arthur Kim,** *Director Viral Hepatitis Clinic*, Massachusetts General Hospital
11:15-12:30	Panel Discussion on the Scientific and Clinical Feasibility of Eliminating HCV **Stuart Ray,** *Moderator*

- **David Thomas,** *Professor of Medicine and Director of Infectious Diseases*, Johns Hopkins University School of Medicine
- **Marc Ghany,** *Staff Clinician, Liver Diseases Branch*, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health
- **Jay Hoofnagle,** *Deputy Director*, Liver Disease Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health
- **Arthur Kim,** *Director Viral Hepatitis Clinic*, Massachusetts General Hospital

SESSION 2 - OPEN
THE LOGISTICAL AND SOCIAL FEASIBILITY OF ELIMINATING HCV

1:30-2:00	Price and Access to Hepatitis C Drugs **Camilla Graham,** *Assistant Professor of Medicine*, Beth Israel Deaconess Medical Center
2:00-2:30	The National Infrastructure for Hepatitis C: Is There Anyone Home? **Daniel O'Connell,** *Director*, New York State Department of Health AIDS Institute
2:30-2:45	Break
2:45-3:15	The Feasibility of Eliminating Hepatitis C among Injection Drug Users **Brian Edlin,** *Senior Principal Investigator*, Institute for Infectious Disease Research National Development and Research Institutes
3:15-3:45	The Logistics of Reaching the Hepatitis C Patient in Corrections **Lara Strick,** *Infectious Disease Specialist*, Washington State Department of Corrections (by video)
3:45-5:00	Panel Discussion on the Logistical and Social Feasibility of Eliminating HCV **Paul Kuehnert,** Moderator • **Camille Graham,** *Assistant Professor of Medicine*, Beth Israel Deaconess Medical Center • **Brian Edlin,** *Senior Principal Investigator*, Institute for Infectious Disease Research National Development and Research Institutes • **Daniel O'Connell,** *Director*, New York State Department of Health AIDS Institute

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Committee Biographies

Brian L. Strom, M.D., M.P.H. (*Chair*), is the inaugural chancellor of Rutgers Biomedical and Health Sciences (RBHS) and the executive vice president for Health Affairs at Rutgers University. RBHS is comprised of eight schools and five centers/institutes, and includes academic, patient care, and research facilities. These are most of the units of the former University of Medicine and Dentistry of New Jersey (UMDNJ), now dissolved, several Rutgers University units with health-related missions, and two research units historically co-managed by Rutgers and UMDNJ. The integration of these entities is designed to create a single organization that will lead to new models for clinical care and community service, educate the next generation of health care providers utilizing health care team approaches, and conduct research. Dr. Strom was formerly the executive vice dean of Institutional Affairs, founding chair of the Department of Biostatistics and Epidemiology, founding director of the Center for Clinical Epidemiology and Biostatistics, and founding director of the graduate program in epidemiology and biostatistics, all at the Perelman School of Medicine of the University of Pennsylvania (Penn).

Dr. Strom earned a B.S. in molecular biophysics and biochemistry from Yale University in 1971, and then an M.D. from the Johns Hopkins University School of Medicine in 1975. From 1975 to 1978 he was an intern and resident in internal medicine and from 1978–1980 he was an NIH fellow in clinical pharmacology at the University of California, San Francisco. He simultaneously earned an M.P.H. degree in epidemiology at the University of California, Berkeley. He has been on the faculty of the University of Pennsylvania School of Medicine since 1980. The Center for Clinical Epidemiology and Biostatistics (CCEB) that he created at Penn includes more than 550 faculty, research and support staff, and trainees. At the time Dr. Strom stepped down, CCEB research received nearly $49 million per year in extramural support. Its total budget was approximately $67 million.

Although Dr. Strom's interests span many areas of clinical epidemiology, his major research interest is in the field of pharmacoepidemiology, i.e., the application of epidemiologic methods to the study of drug use and effects. He is recognized as a founder of this field and for his pioneer work in using large automated databases for research. He is editor of the field's major text (now in its fifth edition) and editor-in-chief for *Pharmacoepidemiology and Drug Safety*, the official journal of the International Society for Pharmacoepidemiology. As one of many specific contributions, his research was pivotal in prompting the American Heart Association and American Dental Association to reverse 50 years of guidelines, and recommend against use of antibiotics to prevent infective endocarditis, instead of recommending for this widespread practice. In addition to writing more than 600 papers, and 11 books, he has been principal investigator for more than 275 grants, including more than $115 million in direct costs alone. Dr. Strom has been invited to give more than 400 talks outside his local area, including presentations as the keynote speaker for numerous international meetings. He has been a consultant to the National Institutes of Health (NIH), Food and Drug Administration (FDA),

Centers for Disease Control and Prevention, US Pharmacopeial Convention (USP), Association of American Medical Colleges (AAMC), Joint Commission on Accredition of Healthcare Organizations (JCAHO), foreign governments, most major pharmaceutical manufacturers, and many law firms.

Dr. Strom is also a nationally recognized leader in clinical research training. At the Perelman School of Medicine, Dr. Strom developed graduate training programs in epidemiology and biostatistics. More than 625 clinicians have been trained or are in training through the largest of these training programs, which leads to a Master of Science in clinical epidemiology degree. All but approximately 65 former trainees in this program have appointments in academic or other research institutions. Dr. Strom was principal investigator (PI) or Co-PI of 11 different NIH-funded training grants (T32, D43, K12, and K30), each of which supported clinical epidemiology trainees in different specialties and subspecialties, and has been the primary mentor for more than 40 former and current clinical research trainees and numerous junior faculty members. Internationally, Dr. Strom was a key contributor to the conceptualization and planning that led to the development of the International Clinical Epidemiology Network (INCLEN), created in 1979 with support provided by The Rockefeller Foundation to provide clinical research training to clinicians from selected developing country sites. Penn was an INCLEN founding member and one of five training centers. INCLEN phase I, from 1979 through 1995, resulted in the establishment of 26 clinical epidemiology units in Africa, India, Latin America, India, and Southeast Asia. The Penn training program alone, led by Dr. Strom, trained 63 INCLEN trainees.

Dr. Strom was a member of the Board of Regents of the American College of Physicians, the Board of Directors of the American Society for Clinical Pharmacology and Therapeutics, and the Board of Directors for the American College of Epidemiology, and is currently a member of the Board of Directors for the Association for Patient-Oriented Research. He was previously president of the International Society for Pharmacoepidemiology and the Association for Clinical Research Training. Dr. Strom was on the Drug Utilization Review Committee and the Gerontology Committee of the US Pharmacopoeia, served on the Drug Safety and Risk Management Advisory Committee for the FDA, chaired the Institute of Medicine (IOM) Committee to Assess the Safety and Efficacy of the Anthrax Vaccine, chaired the IOM Committee on Smallpox Vaccine Program Implementation, chaired the IOM Committee to Review NIOSH's Traumatic Injury Program, chaired the IOM Committee on the Consequences of Reducing Sodium in the Population, was a member of the IOM Committee to Review the CDC Anthrax Vaccine Safety and Efficacy Research Program, and was a member of the IOM Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. He is currently a member of the National Academies of Sciences, Engineering, and Medicine's Forum on Drug Discovery, Development, and Translation.

Dr. Strom is a member of the American Epidemiology Society, and is one of a handful of clinical epidemiologists ever elected to the American Society of Clinical Investigation and American Association of Physicians. He has also been an elected member of the National Academy of Medicine since 2001. Dr. Strom received the 2003 Rawls-Palmer Progress in Medicine Award from the American Society for Clinical Pharmacology & Therapeutics, the Naomi M. Kanof Clinical Investigator Award of the Society for Investigative Dermatology, the George S. Pepper Professorship of Public Health and Preventive Medicine, and in 2006 he received the Sustained Scientific Excellence Award from the International Society for Pharmacoepidemiology. In addition, Dr. Strom was named the 2008 recipient of the John Phillips Memorial Award for Outstanding Work in Clinical Medicine. This award is from the

American College of Physicians and is considered to be one of the highest awards in internal medicine. Dr. Strom also received the 2013 Association for Clinical and Translational Science/American Federation for Medical Research National Award for Career Achievement and Contribution to Clinical and Translational Science for translation from clinical use into public benefit and policy. Penn awards that Dr. Strom received include the class of 1992 Class Teaching Award and the Samuel Martin Health Evaluation Sciences Research Award. Dr. Strom received the 2004 Christian R. and Mary F. Lindback Award, the university's most prestigious teaching award, in recognition of the contribution he has made in his career to clinical research teaching.

Jon Kim Andrus, M.D., joined the Sabin Vaccine Institute in October 2014 where he serves as executive vice president and director of the Vaccine Advocacy and Education (VAE) program. VAE works to reduce the suffering caused by vaccine preventable diseases by bringing together key stakeholders to foster collaboration, share best practices, and develop improved vaccine policy and access. Previously, Dr. Andrus served as deputy director of the Pan American Health Organization (PAHO). Prior to that, he was the lead technical advisor for PAHO's immunization program, providing oversight and guidance for technical cooperation to member countries.

Dr. Andrus holds faculty appointments at the University of California, San Francisco, and the Johns Hopkins Bloomberg School of Public Health. He began his global health career as a Peace Corps volunteer, serving as a district medical officer in Malawi and has since held positions in the Centers for Disease Control and Prevention's (CDC's) Global Immunization Division, as head of the, Vaccinology and Immunization Program at the Institute for Global Health at the Universities of California at San Francisco and Berkeley, and as director of the Global Health MPH Program at George Washington University.

Dr. Andrus has received numerous other awards for his leadership in the eradication of polio, measles, rubella, and congenital rubella syndrome, as well as the introduction of new vaccines in developing countries. In 2013, Dr. Andrus received the Transformational Leadership Award of the University of California. In 2011, he received the Global Leadership Award of the Pneumococcal Awareness Committee of Experts. In 2007, he received the Philip R. Horne Award for global leadership in immunization. In 2000, he received the Distinguished Service Medal, the highest award of the US Public Health Service, for his leadership in working to eradicate polio in Southeast Asia. Dr. Andrus holds a Bachelor of Science degree from Stanford University, obtained his medical degree from the University of California, Davis, and completed his residencies in family medicine at the University of California, San Francisco, School of Medicine, and preventive medicine at the CDC. He has published more than 100 scientific peer-reviewed papers on disease eradication, the introduction of new vaccines, and primary care.

Andrew Aronsohn, M.D., is an associate professor of medicine in the Center for Liver Diseases at the University of Chicago Medical Center. Dr. Aronsohn is also a faculty member at the MacLean Center for Clinical Medical Ethics at the University of Chicago. Dr. Aronsohn is the co-principal investigator of HepCCATT, an initiative to diagnose, link to care and treat hepatitis C virus (HCV) in the Chicago area. This project utilizes telehealth technology to expand HCV management into the primary care setting. Dr. Aronsohn is a member of the (Asmerican Association for the Study of Liver Disease/Infectious Disease Society of America (AASLD/IDSA) HCV guidance writing committee and has a busy clinical practice which includes both general and transplant hepatology.

Daniel R. Church, M.P.H., is the viral hepatitis prevention coordinator and an epidemiologist in the Bureau of Infectious Disease at the Massachusetts Department of Public Health. In this role he has helped to develop and implement the statewide viral hepatitis program, including disease surveillance, medical management services, counseling and testing programs, adult vaccination programs, educational campaigns for providers, patients and communities, and evaluation of projects. He was a member of the Institute of Medicine committee that authored the report *Hepatitis and Liver Cancer: A National Strategy for Prevention and Control of Hepatitis B and C*. Mr. Church received his M.P.H. in epidemiology and biostatistics from the Boston University School of Public Health.

Seymour S. Cohen, Ph.D., has worked on bacterial viruses since 1945, offering the first systematic exploration of the biochemistry of virus-infected cells and of how viruses multiply. His subsequent research included delineating the phenomenon of thymineless death, developing derivatives of ara-A compound, working on RNA synthesis, studying the effects of polyamines on metabolic systems, and studying plant viruses (including viral cations). Much of his research has contributed to the chemical treatment of cancer and viral infections.

Alison A. Evans, Sc.D., is an associate professor in the Department of Epidemiology and Biostatistics at the Drexel University Dornsife School of Public Health. She is also adjunct research faculty in the Public Health Program of the Hepatitis B Foundation, Doylestown, Pennsylvania. Prior to joining Drexel, she was an associate member at the Fox Chase Cancer Center. Her research interests include the epidemiology and natural history of the hepatitis B virus and other chronic viral infections, the association of chronic viral infections with cancer, and public health interventions to decrease the burden of HBV infection globally. She received her Sc.D. in epidemiology from the Harvard School of Public Health.

Paul Kuehnert, D.N.P., R.N., is a nurse and public health expert who currently oversees the Robert Wood Johnson Foundation's work in building bridges among the health care system, public health, and other community services and agencies to improve overall population health. As a former county health officer in Illinois and former deputy state health officer in Maine, he brings extensive public health experience to the group. He has an acute awareness of the strengths of local and state public health agencies in combatting conditions such as hepatitis B and C as well as the challenges they face. He is extremely familiar with the topics of surveillance, implementation of disease control programs, screening, epidemiology, and community based program implementation (see in particular his prior work in HIV/AIDS).

Vincent Lo Re III, M.D., M.S.C.E., earned his medical degree from the University of Pennsylvania, completed an internship and residency in internal medicine and completed a fellowship in infectious diseases at the Hospital of the University of Pennsylvania (Penn). He also earned a Master of Science in clinical epidemiology degree from Penn. Dr. Lo Re has a nationally recognized clinical research program in viral hepatitis epidemiology. He joined the Penn faculty in 2008 and is currently an assistant professor of medicine in the Division of Infectious Diseases and assistant professor of epidemiology in the Department of Biostatistics and Epidemiology at Penn. He is also co-director of the HIV/Viral Hepatitis Scientific Working Group within the Penn Center for AIDS Research and a senior scholar in the Penn Center for Clinical Epidemiology and Biostatistics. Additionally, he is co-chair of the Liver Core of the

Veterans Aging Cohort Study. He has been invited to speak on topics related to chronic viral hepatitis infection, HIV/viral hepatitis coinfection, and pharmacoepidemiology at ID Week, the Interscience Conference on Antimicrobial Agents and Chemotherapy, Conference on Retroviruses and Opportunistic Infections, the Food and Drug Administration (FDA), and the International Society for Pharmacoepidemiology. He has been a standing member of the FDA's Antiviral Drug (now Anti-Infective) Advisory Committee since 2014. He also served as a member of the National Institute of Allergy and Infectious Diseases study section reviewing the Centers of Excellence for Influenza Research and Surveillance.

Kathleen Maurer, M.D., M.P.H., M.B.A., is the Connecticut Department of Correction's director of health and addiction services and medical director. Before assuming her current post in 2011, she was assistant medical director at Correctional Managed Health Care, a division of the University of Connecticut Health Center, which contracts with the state corrections department for offender medical care. During her career, Dr. Maurer has provided hands-on clinical care and medical program management in the private sector. In the realm of correctional care, she is particularly interested in the quality of patient care, in the role of correctional healthcare in the broader scope of public health such as in the treatment of hepatitis C virus in our offender-patients, and in facilitating re-entry programs through integration of community and correctional healthcare. Several of her recent and ongoing initiatives include working to expand Medicaid access to halfway house residents and to integrate Medicaid utilization management with the correctional system. She is also developing a system-wide medication assisted therapy program for the Connecticut Department of Corrections. Dr. Maurer is the primary author of the monograph titled "Hepatitis C in Correctional Settings: Challenges and Opportunities," published by the American Correctional Association. Dr. Maurer earned her M.D. from the Yale University School of Medicine. She also earned an M.P.H. from Yale. She holds an M.B.A. from the University of Connecticut and is board-certified in internal medicine, occupational and environmental medicine, and addiction medicine.

Randall R. Mayer, M.P.H., M.S., serves as interim director of the Division of Behavioral Health at the Iowa Department of Public Health. While working with the Iowa Department of Public Health, Mr. Mayer served as the chief of the Bureau of HIV, STD, and Hepatitis, HIV surveillance coordinator and the HIV and Hepatitis program manager. He received his M.P.H. in epidemiology from the University of Minnesota and his M.S. in plant cell physiology from Purdue University.

Shruti Mehta, Ph.D., M.P.H., is a professor in the Johns Hopkins Bloomberg School of Public Health. Her primary research interests include working with hard-to-reach populations to understand the epidemiology, natural and treated history of HIV, hepatitis C virus (HCV) and HIV/HCV co-infection; populations of interest include injection drug users and men who have sex with men as well as their sexual partners in both Baltimore and international settings, particularly India; special interest in identifying and overcoming barriers to care and treatment of HIV and hepatitis C virus among such populations.

Stuart C. Ray, M.D., serves as vice chair of medicine for Data Integrity and Analytics, associate fellowship program director and professor in the Division of Infectious Diseases within the Department of Medicine, with secondary appointments in Viral Oncology and Health Sciences

Informatics, at the Johns Hopkins University School of Medicine. He directs the virology laboratory and is a clinical investigator in the Center for Viral Hepatitis Research in the Division of Infectious Diseases. He is a faculty member of the graduate immunology program, the graduate pharmacology program, and of the Janeway Firm of the Osler Medical Service. Dr. Ray received his M.D. from the Vanderbilt University School of Medicine in 1990. After an internship and residency at Johns Hopkins Hospital, he continued there as an assistant chief of service and fellow in infectious diseases. During his fellowship, he studied the immunology and sequence variation of HIV in the laboratory of Dr. Robert Bollinger. During that time, he developed an interest in HIV sequence variation during antiretroviral therapy in a productive collaboration with Dr. Robert Siliciano that continues to the present.

In 1997, Dr. Ray joined the Johns Hopkins faculty, and under the mentorship of Dr. David Thomas shifted his primary research focus to hepatitis C virus (HCV). His laboratory work has focused on the sequence variation of HCV during acute and chronic infection, developing and applying computational and molecular biology tools to underlying mechanisms including stochastic variation, immune selection, and viral fitness. He continues to care for inpatients and outpatients with HIV, HCV, and other infectious diseases.

Arthur L. Reingold, M.D., is Edward Penhoet Distinguished Professor of Global Health and Infectious Diseases at the School of Public Health, University of California, Berkeley (UCB). He is also professor of epidemiology and biostatistics and clinical professor of medicine at the University of California, San Francisco (UCSF). His research interests include emerging and reemerging infections and vaccine-preventable diseases in the United States and developing countries. Dr. Reingold serves on the World Health Organization's Strategic Advisory Group of Experts on vaccines and vaccine policy as vice-chair. He is also director of the California Emerging Infections Program, and of the National Institutes of Health Fogarty AIDS International Training and Research Program at UCB/UCSF. His recent publications include articles on the impact of the introduction of pneumococcal conjugate vaccine in the United States and related topics. Before joining the faculty at UCB, Dr. Reingold worked for 8 years at the Centers for Disease Control and Prevention. He is a member of the National Academy of Medicine.

Samuel So, M.B., is a professor of surgery and the Lui Hac Minh Professor at Stanford University. He is also the director of the Asian Liver Center and director of the Multidisciplinary Liver Cancer Program at the same institution. He has published numerous studies on solid organ transplantation, gastric and liver cancers. Dr. So is well known for his work on hepatitis B and liver cancer education and prevention programs. Through his research, Dr. So has identified the need for a public health approach to liver cancer prevention among recent Asian immigrants and first and second generation Asians living in the United States. These populations have not been the typical focus of US screening and prevention programs. Dr. So is listed among the Best Doctors in America published by Woodward/White Inc. For his work in education and prevention, he received the 2005 National Leadership Award from the New York University Center for the Study of Asian American Health, and the 2008 American Liver Foundation Salute to Excellence Award. He is a member of the National Academies of Sciences, Engineering, and Medicine's Board on Population Health and Public Health Practice. Dr. So received his M.B. and B.S. in medicine and surgery from the University of Hong Kong and did postdoctoral and clinical fellowships at the University of Minnesota.

Neeraj Sood, Ph.D., is the vice dean for research at the University of Southern California (USC) Price School of Public Policy. In addition, he currently serves as the director of research at the Leonard D. Schaeffer Center for Health Policy and Economics and is an associate professor at the Price School and the School of Pharmacy's Department of Pharmaceutical and Health Economics. His prior work has focused on the economics of innovation, HIV/AIDS, health care financing, and global health.

His research has been published in several peer-reviewed journals and books including leading journals in economics, medicine and health policy. He has testified frequently on health policy issues before state legislators and his work has also been featured in several media outlets including *The New York Times*, *The Washington Post*, *U.S. News & World Report*, and *Scientific American*. Dr. Sood was the finalist for the 16th and 21st Annual National Institute for Health Care Management Foundation (NIHCM) Health Care Research Award, recognizing outstanding research in health policy. He was also the 2009 recipient of the Eugene Garfield Economic Impact Prize, recognizing outstanding research demonstrating how medical research impacts the economy.

Dr. Sood is on the editorial boards of Health Services Research and Forum for Health Economics and Policy and is a research associate at the National Bureau of Economic Research. Prior to joining USC, Dr. Sood was a senior economist at RAND and professor at the Pardee RAND Graduate School.

Grace Wang, M.D., M.P.H., is a board certified family physician for International Community Health Services in Seattle, Washington. Dr. Wang graduated from the University of Michigan with a degree in early childhood education. She received her medical training at Cornell University Medical College in New York City and has a master's in public health also from the University of Michigan. Dr. Wang has worked in primary care and public health in New York City and Seattle. She is currently a member of the Executive Committee for the National Association of Community Health Centers board of directors and also serves on the boards for Project Access Northwest and Kin On.

Lucy E. Wilson, M.D., Sc.M., is a medical epidemiologist and infectious disease physician at the Maryland Department of Health and Mental Hygiene, where she serves as the chief of the Center for Surveillance, Infection Prevention and Outbreak Response. At the state of Maryland, Dr. Wilson implements surveillance and prevention of reportable infectious diseases (including hepatitis B and C infections), consults on infection control issues across the healthcare continuum and in the general community, and oversees Maryland's outbreak responses, including food-related outbreaks, novel influenza pandemic response, and Ebola virus disease response. Dr. Wilson is the principal investigator of the Healthcare Associated Infections (HAI) branch of the Centers for Disease Control and Prevention (CDC)/Maryland Emerging Infections Program, conducting HAI surveillance and prevention research and is the medical advisor for the CDC grant "Community-based Programs to Test and Cure Hepatitis C" in Maryland. Dr. Wilson is an adjunct assistant professor at the Johns Hopkins University School of Medicine, where she previously was on the Johns Hopkins School of Medicine Division of Infectious Diseases faculty as the medical director of the Johns Hopkins HIV County Program, and where her research focused on the natural history of hepatitis C in injection drug users and HIV clinical outcomes research.

D

Glossary

95% immunity – 95% of people that are immunized become immune. For most of the millions of people who get immunized every year, a protective effect occurs; however, in a small percentage of people, this is not the case. Ineffective immunization results when an individual's immune system does not respond appropriately. While unlikely to occur in the United States, vaccines can also be ineffective if not manufactured properly or not stored and handled properly.

acetaminophen – A crystalline compound used in chemical synthesis and in medicine to relieve pain and reduce fevers.

adherence – The extent to which the patient continues the agreed-upon mode of treatment under limited supervision when faced with conflicting demands, as distinguished from compliance or maintenance.

Affordable Care Act – Legislation passed by Congress and then signed into law by the president on March 23, 2010. On June 28, 2012, the Supreme Court rendered a final decision to uphold the health care law. The Affordable Care Act refers to two separate pieces of legislation—the Patient Protection and Affordable Care Act (P.L. 111-148) and the Health Care and Education Reconciliation Act of 2010 (P.L. 111-152)—that together expanded Medicaid coverage to millions of low-income Americans.

AIDS Drug Assistance Program – The program was authorized under the Ryan White Comprehensive AIDS Resources Emergency (CARE) Act and provides HIV-related prescription drugs to underinsured and uninsured individuals living with HIV/AIDS.

anamnestic response – A rapid increase in production of antibodies in response to an immunogenic substance after serum antibodies from the first response can no longer be detected in the blood.

anti-HBc immunoglobulin M (IgM) – Anti-HBc indicates precious or ongoing infection with hepatitis B virus in an undefined time frame. IgM is an antibody to the HBV core antigen that appears during acute infection, with levels typically decreasing within 6 months despite persistence of infection.

antibody – A protein produced by the body’s immune system when it detects harmful substances, called antigens.

antigen – A harmful substance that is capable of stimulating an immune response, specifically activating lymphocytes. An antigen may be a substance from the environment, such as chemicals, bacteria, viruses, or pollen. An antigen may also form inside the body.

ascites – The accumulation of fluid in the peritoneal cavity, causing abdominal swelling.

B cell non-Hodgkin's lymphoma – A cancer the presents itself when B cells grow and multiply uncontrollably and then travel to many parts of the body and form tumors. Hodgkin's lymphoma is marked by the presence of Reed-Sternberg cells, which are mature B cells that have become malignant, are unusually large, and carry more than one nucleus. Non-Hodgkin's lymphoma, by contrast, can be derived from B cells or T cells and can arise in the lymph nodes as well as other organs.

B cell response – B cells are a type of lymphocyte that differentiates into plasma cells in the presence of a specific antigen. The plasma cells produce antibodies that attack or neutralize the antigen in what is called the humoral immune response.

carcinoma – An invasive malignant tumor derived from epithelial tissue of the skin or the lining of the internal organs that tends to metastasize to other areas of the body.

carotid plaque – Carotid artery disease occurs when fatty deposits (plaques) clog the blood vessels that deliver blood to the brain and head (carotid arteries). The blockage increases the risk of stroke.

case management – A collaborative process of assessment, planning, facilitation, care coordination, evaluation, and advocacy for options and services to meet an individual's and family's comprehensive health needs through communication and available resources to promote quality, cost-effective outcomes.

cell surface – Cell surface receptors (membrane receptors, transmembrane receptors) are receptors at the surface of a cell (built into its cell membrane) that act in cell signaling by binding to extracellular molecules.

cellular response – The immune response produced when sensitized T cells attack foreign antigens and secrete lymphokines that initiate the body's humoral immune response.

Child-Pugh or Child-Turcotte-Pugh score – A classification used to assess the prognosis of chronic liver disease.

chronic hepatitis B – Hepatitis B is a serious liver infection caused by the hepatitis B virus (HBV). HBV is transmitted in infected blood, causing fever, debility, and jaundice. Hepatitis B becomes chronic when it lasts more than 6 months.

chronic hepatitis C – Hepatitis C is a serious liver infection caused by the hepatitis C virus (HCV). HCV is transmitted in infected blood. Most people infected with HCV have no symptoms. Hepatitis C becomes chronic when it lasts more than 6 months.

cirrhosis – A chronic disease of the liver characterized by the replacement of normal tissue with fibrous tissue and the loss of functional liver cells. It can result from alcohol abuse, nutritional deprivation, or infection especially by the hepatitis viruses.

control – Reduction of disease incidence, prevalence, morbidity, or mortality to a locally acceptable level as a result of deliberate efforts; continued intervention measures are required to maintain the reduction.

cost-effective – Economical in terms of tangible benefits produced by money spent.

covalently closed circular DNA (cccDNA) – A double-stranded DNA that originates in a linear form that is ligated by means of DNA ligase to a covalently closed ring. In HBV cccDNA persists within the nuclei of infected liver cells, produces viral RNA transcripts, and is difficult to eradicate. cccDNA is thought to be the form of the virus responsible for both chronic HBV infection and persistent viral infection after antiviral treatment.

cryoglobulinemia – A medical condition that occurs when cryoglobulin proteins become insoluble at reduced temperatures, causing inflammation and blocking blood vessels throughout the body. This may lead to problems ranging from skin rashes to kidney failure.

cutaneous vasculitis – A group of disorders in which there are inflamed blood vessels in the skin. These may include capillaries, venules, arterioles, and lymphatics.

cytoplasm – The cell substance between the cell membrane and the nucleus, containing the cytosol, organelles, cytoskeleton, and various particles.

decompensated cirrhosis – Development of clinically evident complications of portal hypertension (ascites, variceal hemorrhage, hepatic encephalopathy) or jaundice. Survival is poor in patients with decompensated cirrhosis and they should be considered for liver transplantation.

diabetes – Any of several metabolic diseases in which the body's inability to produce any or enough insulin causes elevated levels of glucose in the blood. Diabetes is marked by excessive discharge of urine and persistent thirst.

dyslipidemia – Elevated total or low-density lipoprotein cholesterol levels, or low levels of high-density lipoprotein cholesterol. Dyslipidemia is an important risk factor for coronary heart disease and stroke.

effectiveness – The degree to which something is successful in producing a desired result; success.

efficacy – The ability to produce a desired or an intended result.

electronic health record – an electronic version of a patient's medical history, that is maintained by the provider over time, and may include all of the key administrative clinical data relevant to that persons care under a particular provider, including demographics, progress notes, problems, medications, vital signs, past medical history, immunizations, laboratory data, and radiology reports.

electronic medical record – A digital version of the traditional paper-based medical record for an individual. The electronic medical record represents a medical record within a single facility, such as a doctor's office or a clinic.

elimination of disease – Reduction to zero of the incidence of a specified disease in a defined geographic area as a result of deliberate efforts; continued intervention measures are required to maintain the reduction.

elimination of infection – Reduction to zero of the incidence of infection caused by a specific agent in a defined geographic area as a result of deliberate efforts; continued measures to prevent reestablishment of transmission are required.

endemic – Regularly found among particular people or in a certain area.

eradication – Permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts; intervention measures are no longer needed.

esophageal varices – Abnormal, enlarged veins in the lower part of the esophagus—the tube that connects the throat and stomach. Esophageal varices occur most often in people with serious liver diseases when normal blood flow to the liver is obstructed by scar tissue in the liver or a clot. Seeking a way around the blockages, blood flows into smaller blood vessels that are not designed to carry large volumes of blood. The vessels may leak blood or even rupture, causing life-threatening bleeding.

fatty liver disease – A reversible condition wherein large vacuoles of triglyceride fat accumulate in liver cells due to abnormal retention of lipids within the cells. Fatty liver disease occurs when more than 5 to 10 percent of the liver weight is fat. Hepatitis C virus, alcohol, and obesity are common causes of fatty liver disease.

fibrosis – The thickening and scarring of connective tissue as a reparative or reactive process.

fulminant hepatitis – A rare and frequently fatal form of acute hepatitis B in which the patient's condition rapidly deteriorates, with hepatic encephalopathy, necrosis of the hepatic parenchyma, coagulopathy, renal failure, and coma.

genotype – The genetic constitution of an organism or a group of organisms.

glomerulonephritis – Renal disease marked by bilateral inflammatory changes in the glomeruli (the filters in the kidneys) that are not the result of kidney infection.

graft survival – The success of an organ transplant.

harm reduction – A set of practical strategies and ideas aimed at reducing negative consequences associated with drug use. Harm reduction is also a movement for social justice built on a belief in, and respect for, the rights of people who use drugs.

harm-reduction services – Strategies aimed at reducing negative consequences associated with drug use such as needle and syringe exchange programs, opioid substitution therapy, training, and education.

Harvoni® – A drug used to treat hepatitis C virus; the US proprietary name of 90 mg of the viral NS5A inhibitor ledipasvir and 400 mg of sofosbuvir, a nucleotide inhibitor of the viral RNA polymerase. Harvoni® provides cure rates of 94 to 99 percent in people infected with genotype 1 but the average cost of treatment in the United States is more than $90,000. The drug became available in October 2014.

HBV core antibody – Anti-HBc appears at the onset of symptoms in acute hepatitis B and persists for life. The presence of hepatitis B virus core antibodies indicates previous or ongoing infection with hepatitis B in an undefined time frame.

HBV e antibody – Anti-HBe is produced by the immune system temporarily during acute hepatitis B infection or consistently during or after a burst in viral replication. Spontaneous conversion from e antigen to e antibody (a change known as seroconversion) is a predictor of long-term clearance of hepatitis B virus (HBV) in patients undergoing antiviral therapy and indicates lower levels of HBV.

HBV e antigen – A secreted product of the nucleocapsid gene of hepatitis B virus (HBV) that is found in serum during acute and chronic hepatitis B. Its presence indicates that the virus is replicating and the infected person has high levels of HBV.

HBV surface antibody – The presence of hepatitis B virus (HBV) surface antibodies is generally interpreted as indicating recovery and immunity from HBV infection. HBV surface antibodies also develop in a person who has been successfully vaccinated.

HBV surface antigen – A protein on the surface of hepatitis B virus (HBV); it can be detected in high levels in serum during acute or chronic HBV infection. The presence of HBV surface antigens indicates that the person is infectious. The body normally produces antibodies to HBV surface antigens as part of the normal immune response to infection. The antigen is also used to make the HBV vaccine.

health disparity – The inequalities that occur in the provision of health care and access to health care across different racial, ethnic, and socioeconomic groups.

hepatic encephalopathy – A decline in brain function that occurs as a result of severe liver disease. In this condition, the liver cannot adequately remove toxins from the blood. This causes a buildup of toxins in the bloodstream, which can lead to brain damage.

hepatitis – An inflammation of the liver. The condition can be self-limiting or can progress to fibrosis (scarring), cirrhosis or liver cancer. Hepatitis viruses are the most common cause of hepatitis in the world but other infections, toxic substances (e.g., alcohol, certain drugs), and autoimmune diseases can also cause hepatitis. There are five main hepatitis viruses, referred to as types A, B, C, D and E. Types B and C lead to chronic disease in hundreds of millions of people and, together, are the most common cause of liver cirrhosis and cancer.

hepatitis B immune globulin – A substance that is used as an injection to prevent hepatitis B virus (HBV) from occurring again in HBV surface antigen positive liver transplant patients after surgery. This injection also reduces the chance of the development of HBV after exposure to the virus.

hepatocellular carcinoma – A cancer derived from parenchymal cells of the liver. Hepatocellular carcinoma most commonly occurs in people with liver disease, particularly in people with chronic hepatitis B and hepatitis C. Symptoms often do not appear in the early stages of the cancer. Later, symptoms include weight loss, upper abdominal pain, or jaundice.

histology – The science concerned with the minute structure of tissues and organs in relation to their function.

humoral response – The immune response involving the transformation of B cells into plasma cells that produce and secrete antibodies to a specific antigen.

hypertension – Persistent high blood pressure.

immune clearance (or immune active) – The accelerated removal of an antigen from the bloodstream that follows the initiation of an antibody response by the immune system. This leads to the formation of antigen-antibody complexes, which are ingested by macrophages and other phagocytic cells.

immune tolerance – A state of unresponsiveness to a specific antigen or group of antigens to which a person is normally responsive. Immune tolerance is achieved under conditions that suppress the immune reaction and is not just the absence of an immune response.

immunity – Inherited, acquired, or induced resistance to infection by a specific pathogen.

incidence – The extent or rate of occurrence, especially the number of new cases of a disease in a population over a period of time.

insulin resistance – A state of diminished effectiveness of insulin in lowering the levels of blood sugar, usually resulting from insulin binding by antibodies, and associated with such conditions as obesity, ketoacidosis, and infection.

inter-observer variability – The variability between observers of the same phenomenon; the amount observers vary from one another when reporting on the same material.

interoperability – The ability of different information technology systems and software applications to communicate, exchange data, and use the information that has been exchanged.

intra-observer variability– The variability within observers of the same phenomenon; the amount one observer varies between observations when reporting more than once on the same material.

jail – A building designated or regularly used for the confinement of individuals who are sentenced for minor crimes or who are unable to gain release on bail and are in custody awaiting trial.

latent cellular reservoir – The cells of the body where an infection is able to hide (or "persist") even in the face of optimal antiviral therapy. These cellular reservoirs are located throughout the body.

LDL receptor – Low-density lipoprotein (LDL) is a complex of lipids and proteins that functions as a transporter of cholesterol in the blood, and which, in high concentrations is associated with an increased risk of atherosclerosis and coronary heart disease. The LDL receptors are on the outer surface of many types of cells, where they bind to LDLs circulating in the bloodstream and transport them into the cell.

lipo-viro-particle – Triglycerid-rich lipoprotein-like particle containing viral RNA and proteins. Lipo-viro-particles are a constant feature of chronic hepatitis C.

lipoprotein – Any of a group of conjugated proteins having at least one lipid component; they are the principal means by which lipids are transported in the blood.

liver aminotransferase level – Liver enzymes include aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (ALT or SGPT). These enzymes are normally predominantly contained within liver cells and to a lesser degree in muscle cells. If the liver is injured or damaged, the liver cells spill these enzymes into the blood, raising the AST and ALT enzyme blood levels and signaling liver disease.

longitudinal study – An observational research method in which data is gathered for the same subjects repeatedly over a period of time. Longitudinal research projects can extend over years or even decades.

low replicative (or inactive) HBV carrier – A phase of chronic hepatitis B distinguished by loss of hepatitis B virus (HBV) e antigen (if present) and development of HBV e-antibody with suppression of HBV DNA and normalization of liver aminotransferase levels.

magnetic resonance elastography – A non-invasive magnetic resonance imaging–based technique for quantitatively assessing the mechanical properties of tissues in vivo. Magnetic resonance elastography is performed by using a vibration source to generate low frequency mechanical waves in tissue. Specially developed mathematical algorithms are used to analyze the wave images and to generate quantitative images depicting the stiffness and other mechanical properties of tissue. Magnetic resonance elastography is a useful imaging tool with the capability to: (1) noninvasively "palpate by imaging" regions of the body that are beyond the reach of the physician's hand, (2) delineate tumors and other abnormalities before they are severe enough to detect by touch, (3) provide greater sensitivity for assessing changes in tissue mechanical properties, and (4) provide useful new quantitative imaging biomarkers for characterizing tissue properties.

marginalization – Comprises those processes by which individuals and groups are ignored or relegated to the sideline of political debate, social negotiation, and economic bargaining—and kept there. Homelessness, age, language, employment status, skill, race, and religion are some criteria historically used to marginalize. Marginalized groups tend to overlap and groups marginalized in the past have the greatest chance of being marginalized in the future.

Medicaid – A joint federal and state program that helps low-income individuals or families pay for the costs associated with long-term medical and custodial care. Although largely funded by the federal government, Medicaid is run by states where coverage may vary.

Model for End-Stage Liver Disease – A reliable measure of mortality risk in patients with end-stage liver disease. The model is used as a disease severity index to help prioritize allocation of organs for transplant.

morbidity – How often a disease occurs in a specific area; also used to describe a focus on death.

mortality – The number of deaths in a given time or place; also used to describe the quality or state of being mortal.

nosocomial – Acquired or occurring in a hospital.

NS3/NS4A protease – An enzyme associated with hepatitis C virus (HCV) that mediates four specific cleavages of the viral polyprotein. Its activity is considered essential for the biogenesis of the HCV replication machinery.

NS5A phosphoprotein – A zinc-binding and proline-rich hydrophilic phosphoprotein that plays a key role in hepatitis C virus RNA replication.

NS5B RNA polymerase – NS5B is a protein found in hepatitis C virus. It has the key function of replicating the hepatitis C viral RNA by using the viral positive RNA strand as its template and catalyzes the polymerization of ribonucleoside triphosphates during RNA replication.

nucleocapsid – The basic structure of a virus, consisting of a core of nucleic acid enclosed in a protein coat.

nucleos(t)ide analogue therapy – Lamivudine, adefovir dipivoxil, entecavir, telbivudine, and tenofovir disoproxilfumarate are nucleos(t)ide analogues registered for the treatment of chronic hepatitis B. All nucleos(t)ide analogues are given once daily per oral at a fixed dosage and have been shown to dramatically improve the clinical outcome of patients with chronic hepatitis B. The nucleos(t)ide analogues are potent inhibitors of hepatitis B virus (HBV) polymerase/reverse transcriptase activity and are highly effective in the suppression of HBV replication, but rarely eliminate the virus. Long-term therapy is usually required to achieve sustained hepatitis B e antigen seroconversion, HBV DNA suppression, alanine aminotransferase normalization and fibrosis reversal.

obesity-related metabolic conditions – Obesity is excess body weight, defined as a body mass index (BMI) of $\geq$30 kg/m^2. Complications include cardiovascular disorders (particularly in people with excess abdominal fat), diabetes mellitus, certain cancers, cholelithiasis, fatty liver, cirrhosis, osteoarthritis, reproductive disorders in men and women, psychologic disorders, and, for people with BMI $\geq$35, premature death.

observer bias – A form of reactivity in which a researcher's cognitive bias causes them to subconsciously influence the participants of an experiment.

occult HBV infection – Defined as hepatitis B virus (HBV) DNA detection in serum or in the liver in HBV surface antigen negative patients with or without serologic markers of previous viral exposure. Occult HBV infection seems to be higher among subjects at high risk for HBV infection and with liver disease.

opportunity cost – The loss of potential gain from other alternatives when one alternative is chosen.

pegylated interferon – Interferons are a group of signaling proteins made and released by host cells in response to the presence of pathogens. Pegylated interferon, usually called peginterferon, is a chemically modified form of the standard interferon. The difference between interferon and peginterferon is a molecule called polyethylene glycol. By attaching to the interferon the polyethylene glycol allows it to stay in the blood much longer. Peginterferon alfa-2a and peginterferon alfa-2b have been approved for the treatment of chronic hepatitis C virus (and sometimes hepatitis B virus) infection in adults who have compensated liver disease and have not been previously treated with interferon alfa.

phylogenetic analysis – Phylogenetics is the study of evolutionary relationships. Phylogenetic analysis is the means of inferring or estimating these relationships. The evolutionary history inferred from phylogenetic analysis is usually depicted as branching, treelike diagrams that represent an estimated pedigree of the inherited relationships among molecules ("gene trees"), organisms, or both.

prison – A secure facility that houses people who have been convicted of a felony criminal offense and are serving a sentence of (typically) 1 year or more.

proprietary name – The name of a product or service registered by its owner as a trademark and not usable by others without permission.

public health problem – A disease that by virtue of transmission or morbidity or mortality commands attention as a major threat to the health of the community.

reactivation – To make activate again. In hepatitis B virus (HBV) reactivation is an increase in HBV viral replication in patients with chronic or past HBV infection. The chance of HBV reactivation is closely linked to the serological profile of the infected patient.

reservoir of infection – Any person, animal, plant, soil, or substance in which an infectious agent normally lives and multiplies. The reservoir typically harbors the infectious agent without injury to itself and serves as a source from which other individuals can be infected.

resolved HBV infection – Occurs when chronic hepatitis B virus (HBV)-infected patients become HBV surface antigen-negative.

reverse transcription – A process in which a sequence of nucleotides is copied from an RNA template during the synthesis of a molecule of DNA.

ribavirin – An antiviral drug that is used orally in combination with interferon for the treatment of chronic hepatitis C. Although the exact mechanism of its action is unknown, ribavirin is thought to interfere with the production and/or action of viral DNA and RNA which are critical to the survival and multiplication of the virus. Ribavirin was approved by the Food and Drug Administration in December 1998.

ribosome – A minute round cytoplasmic particle composed of RNA and protein that is the site of protein synthesis as directed by mRNA.

Ryan White Program – Named after a teenager who was expelled from his middle school because he had HIV, the Ryan White Program is the largest federal program designed specifically for people with HIV/AIDS in the United States. The program works with cities, states, and local community-based organizations to provide services to an estimated 536,000 people each year who do not have sufficient health care coverage or financial resources to cope with HIV disease.

seroconversion – Development of antibodies in blood serum as a result of infection or immunization.

serum – An amber-colored, protein-rich liquid that separates out when blood coagulates.

Sovaldi® – The US proprietary name of sofosbuvir, a prescription medicine used with other antiviral medicines to treat chronic hepatitis C virus (HCV) infection in adults. Sofosbuvir inhibits the RNA polymerase HCV uses to replicate its RNA. Compared to previous treatments, sofosbuvir-based regimens provide a higher cure rate, fewer side effects, and a two- to four-fold reduced duration of therapy. The drug has been on the market since 2013.

stigma – A mark of disgrace associated with a particular circumstance, quality, or person.

surveillance – The ongoing systematic collection and analysis of data and the provision of information which leads to action being taken to prevent and control a disease, usually one of an infectious nature.

sustained virological response – The most widely used efficacy endpoint of hepatitis C virus (HCV), and represents the eradication of HCV from the body. Sustained virological response is defined as aviremia 24 weeks after completion of antiviral therapy. The incidence of relapse after sustained virological response is less than one percent.

T-cell response – T cells are a type of lymphocyte that play a central role in cell-mediated immunity. T helper cells assist other white blood cells in immunologic processes, including maturation of B cells into plasma cells and memory B cells, and activation of cytotoxic T cells and macrophages. Helper T cells become activated when they are presented with peptide antigens by MHC class II molecules, which are expressed on the surface of antigen-presenting cells. Once activated, they divide rapidly and secrete small proteins called cytokines that regulate or assist in the active immune response. These cells can differentiate into one of several subtypes which secrete different cytokines to facilitate different types of immune responses.

titer – The strength of a solution or the concentration of a substance in solution. Titer is determined by a technique where a solution of known concentration is used to determine the concentration of an unknown solution. Typically, the titrant (the know solution) is added from a buret to a known quantity of the analyte (the unknown solution) until the reaction is complete.

TORCH titer – A blood test used in infants that measures the presence of antibodies and their level of concentration. The TORCH titer tests for toxoplasmosis and other pathogens including hepatitis B virus.

transient elastography – Known by the brandname FibroScan, transient elastography is a technique used to assess liver stiffness (measured in kPa correlated to fibrosis) without invasive investigation. The device uses probes to measure wave velocity as they pass through the body. Exam results help to anticipate various complications, as well as to monitor and assess the damage caused by conditions such as cirrhosis.

treatment as prevention – A virus prevention method that use antiviral treatment to decrease the risk of transmission. Antiviral treatment reduces the viral load to very low levels, reducing an individual's risk of onwards transmission. Treatment as preventions has been shown to be a successful tool in preventing the spread of HIV, which has led researchers to consider using it as a tool to decrease the spread of hepatitis C virus.

variceal hemorrhage – Varices are dilated submucosal veins, most commonly detected in the distal esophagus or proximal stomach and are associated with portal hypertension. Varices occur when normal blood flow to the liver is obstructed by scar tissue in the liver or a clot. Seeking a way around the blockages, blood flows into smaller blood vessels that are not designed to carry large volumes of blood. This can sometimes cause hemorrhaging and may be fatal.

vertical transmission – An infection caused by bacteria, viruses, or in rare cases, parasites transmitted directly from the mother to an embryo, fetus, or baby during pregnancy or childbirth. Transmission might occur across the placenta, in the breast milk, or through direct contact during or after birth.

Viekira® – The US proprietary name of ombitasvir, paritaprevir and ritonavir tablets co-packaged with dasabuvir tablets. Viekira® is an oral, interferon-free prescription medicine used with or without ribavirin to treat adults with genotype 1 chronic hepatitis C virus infection. Viekira® provides cure rates of 95 percent in people infected with genotype 1 but the average cost of treatment in the United States is more than $80,000. The drug was approved for public use in December 2014.

viral envelope protein – Virus particles contain their viral genome packaged in a protein coat called the capsid. For some viruses, the capsid is surrounded by a lipid bilayer that contains viral proteins. This lipid and protein structure is called the virus envelope, and is derived from the host cell membranes. The capsid and envelope play many roles in viral infection, including virus attachment to cells, entry into cells, release of the capsid contents into the cells, and packaging of newly formed viral particles.

viral hepatitis – Liver inflammation due to a viral infection. It may present in acute or chronic forms.

viral load – A measurement of the amount of a virus in an organism, typically in the bloodstream, usually stated in virus particles per milliliter.

viral suppression – When antiviral therapy reduces a person's viral load to an undetectable level. Viral suppression does not mean a person is cured.

viremic – The presence of a virus in the blood.

virion – A complete viral particle, consisting of RNA or DNA surrounded by a protein shell.

virulent – Extremely infectious, malignant, or poisonous. Used of a disease or a toxin.

visceral vasculitis – The visceral arteries supply blood to the intestines, spleen, and liver. Visceral vasculitis occurs when there is inflammation of these blood vessel walls.