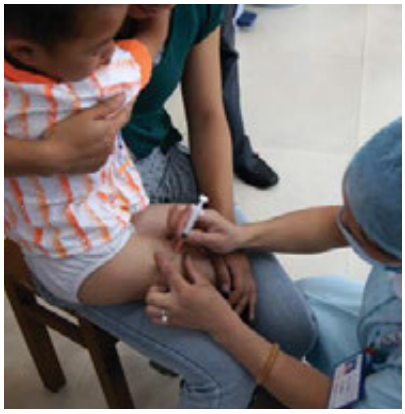
World Health Organization

GLOBAL HEPATITIS REPORT, 2017

PREVENT



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TREAT

World Health Organization

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Global hepatitis report 2017

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CONTENTS

FOREWORD

The global response to viral hepatitis entered a new phase in 2015, when the UN General Assembly adopted the 2030 Agenda for Sustainable Development, which called on the international community to combat hepatitis. The following year, the World Health Assembly adopted WHO's first "Global Health Sector Strategy on viral hepatitis", with elimination as its overarching vision.

The *Global hepatitis report, 2017* provides a baseline for the drive towards elimination. It sets out global statistics on viral hepatitis B and C, the rate of new infections, the prevalence of chronic infections and mortality caused by these two high-burden hepatitis viruses, as well as coverage levels of key interventions, as at the end of 2015.

As these statistics reveal, viral hepatitis is a major public health challenge that requires an urgent response. The disease caused 1.34 million deaths in 2015, a number comparable to annual deaths caused by tuberculosis and higher than those caused by HIV. While mortality from HIV, tuberculosis, and malaria is now declining, mortality caused by viral hepatitis is on the rise. The report provides guidance on how to reverse this alarming trend, describing a number of high-impact interventions and opportunities for their scaled-up implementation.

We have good evidence that eliminating viral hepatitis is technically feasible. Many countries have achieved outstanding coverage with the hepatitis B vaccine, scoring an early win for prevention. The recent development of highly effective direct-acting antivirals, with cure rates exceeding 95%, has revolutionized the treatment of chronic hepatitis C infections. Most countries have also made good progress in keeping blood supply safe and improving injection safety in health-care settings, substantially reducing the risk of both hepatitis B and C virus infections.

However, a large number of people – about 325 million worldwide in 2015 – are carriers of hepatitis B or C virus infections, which can remain asymptomatic for decades. Each year, 1.75 million people newly acquire hepatitis C virus infection. These people are at risk of a slow progression to severe liver disease and death, unless they receive timely testing and treatment. Unfortunately, access to affordable care is disturbingly low, as highlighted in the report.

The world has only recently expressed its alarm about the burden of viral hepatitis. The response is still at an early phase in most countries, which limits the reliability and scope of available data. At the same time, some countries have taken groundbreaking actions to combat the epidemic, with results that bring encouragement everywhere.

I urge all countries to seize the opportunities set out in this report to eliminate viral hepatitis as a public health threat by 2030. Doing so will free the world from what we now know is a leading killer worldwide.

Dr Margaret Chan
WHO Director-General

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ABBREVIATIONS

CDA	Center for Disease Analysis
DAA	direct-acting antiviral
DALY	disability-adjusted life-year
DNDi	Drugs for Neglected Diseases initiative
EIA	enzyme immunoassay
EPI	Expanded Programme on Immunization
FIND	Foundation for Innovative New Diagnostics
GARPR	Global AIDS Response Progress Monitoring
GATHER	Guidelines for Accurate and Transparent Health Estimates Reporting
GAVI	the Vaccine Alliance (earlier Global Alliance for Vaccines and Immunization)
GBD	Global Burden of Disease (project/study)
GHP	Global Hepatitis Programme
GHSS	Global Health Sector Strategy on viral hepatitis
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
GPRM	Global Price Reporting Mechanism
HAV	hepatitis A virus
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDV	hepatitis D virus
HEV	hepatitis E virus
LSHTM	London School of Hygiene and Tropical Medicine
MSM	men who have sex with men
PMTCT	prevention of mother-to-child transmission
PROLIFICA	Prevention of Liver Fibrosis and Cancer in Africa
PWID	people who inject drugs
SARA	Service Availability and Readiness Assessment
SVR	sustained virological response
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNODC	United Nations Office on Drugs and Crime
USFDA	United States Food and Drug Administration
WHO	World Health Organization

EXECUTIVE SUMMARY

In May 2016, the World Health Assembly endorsed the *Global Health Sector Strategy (GHSS) on viral hepatitis 2016–2021*. The GHSS calls for the elimination of viral hepatitis as a public health threat by 2030 (reducing new infections by 90% and mortality by 65%).

This WHO *Global hepatitis report* describes, for the first time, the global and regional estimates on viral hepatitis in 2015, setting the baseline for tracking progress in implementing the new global strategy.

The report focuses on hepatitis B and C, which are responsible for 96% of all hepatitis mortality. It presents data along the five strategic directions (strategic information, interventions, equity, financing and innovation) – key pillars of the GHSS to facilitate monitoring of progress in countries, regions and globally, and to measure the impact of interventions on reducing new infections and saving lives between 2015 and 2030.

VIRAL HEPATITIS IS A MAJOR PUBLIC HEALTH PROBLEM IN NEED OF AN URGENT RESPONSE.

01

Viral hepatitis caused 1.34 million deaths in 2015, a number comparable to deaths caused by tuberculosis and higher than those caused by HIV. However, the number of deaths due to viral hepatitis is increasing over time, while mortality caused by tuberculosis and HIV is declining. Most viral hepatitis deaths in 2015 were due to chronic liver disease (720 000 deaths due to cirrhosis) and primary liver cancer (470 000 deaths due to hepatocellular carcinoma). Globally, in 2015, an estimated 257 million people were living with chronic HBV infection, and 71 million people with chronic HCV infection. The epidemic caused by HBV affects mostly the WHO African Region and the Western Pacific Region. The epidemic caused by HCV affects all regions, with major differences between and within countries. The WHO Eastern Mediterranean Region and the European Region have the highest reported prevalence of HCV.

VACCINATION DRAMATICALLY REDUCED NEW HBV INFECTIONS AMONG CHILDREN, BUT OTHER HBV AND HCV PREVENTION INTERVENTIONS HAVE NOT BEEN IMPLEMENTED SUFFICIENTLY.

02

An early win in the global response to viral hepatitis was achieved through the effective scaling up of hepatitis B vaccine. In 2015, global coverage with the three doses of hepatitis B vaccine in infancy reached 84%. This has substantially reduced HBV transmission in the first five years of life, as reflected by the reduction in HBV prevalence among children to 1.3%. However, coverage with the initial birth dose vaccination is still low at 39%. Other prevention interventions are available but insufficiently implemented. Although injection drug use is the major route of HCV transmission in some regions, the provision of effective harm reduction services has been inadequate. Globally, 5% of health-care-related injections remained unsafe. As a result, an estimated 1.75 million new HCV infections occurred worldwide in 2015.

A LARGE BURDEN OF CHRONIC INFECTIONS AMONG ADULTS CALLS FOR GREATER ACCESS TO TESTING AND TREATMENT.

03

Access to affordable hepatitis testing is limited. Few people with viral hepatitis have been diagnosed (9% of HBV-infected persons, 22 million, and 20% of HCV-infected persons, 14 million). Among those diagnosed, treatment has reached only a small fraction. In 2015, 8% of those diagnosed with HBV infection or 1.7 million persons were on treatment, while 7.4% of those diagnosed with HCV infection or 1.1 million persons had started treatment. While the cumulative number of persons treated for HCV reached 5.5 million in 2015, only about half a million of these persons had received the newer, more effective and better tolerated class of drugs called direct-acting antivirals (DAAs). There were more new HCV infections than patients who were started on treatment in 2015.

"EARLY ADOPTER" COUNTRIES ARE ON THE ROAD TO ELIMINATING VIRAL HEPATITIS.

04 Several "early adopter" countries are showing that rapid scale up of testing and treatment can be achieved through committed political leadership, and a reduction in the prices of essential medicines and diagnostics to expand testing and treatment services. First-line tests for the diagnosis of viral hepatitis are available for as little as US$ 0.5. The most effective hepatitis B treatment – tenofovir – is available for US$ 48 per year. Hepatitis C can be cured within 2–3 months with highly effective DAAs, and in some countries a full course of generic DAAs can be accessed for only US$ 200.

OPPORTUNITIES FOR IMMEDIATE ACTION EXIST: FOR EXAMPLE, THROUGH EXPANDED TREATMENT FOR PEOPLE WITH HIV WHO ARE COINFECTED WITH HBV OR HCV.

05 Among the 36.7 million persons living with HIV in 2015, an estimated 2.7 million had chronic HBV infection and 2.3 million had been infected with HCV. Liver diseases are a major cause of morbidity and mortality among those living with HIV and coinfected with viral hepatitis. These people should be diagnosed and provided with appropriate and effective treatment for both HIV and hepatitis as a priority.

THE ROAD TO ELIMINATION BY 2030 REQUIRES A COMPREHENSIVE PUBLIC HEALTH APPROACH TAKEN TO SCALE.

06 The information contained in this global report can guide countries and global partners on the road to elimination of viral hepatitis. First, a strategic information system based on surveillance and programme data is needed to direct policy change and implementation. Second, service coverage of testing and treatment needs to be rapidly scaled up. Third, hepatitis services need to be delivered through a public health approach to benefit all. Fourth, sustainable financing is required to enable universal health coverage, the overarching framework for health in the 2030 Agenda for Sustainable Development. Fifth, innovations are necessary; new diagnostics, treatments, cure and vaccines need to be developed, tested and delivered urgently to transform the hepatitis response and attain the elimination targets.

01

INTRODUCTION: SETTING THE BASELINE FOR ELIMINATION OF HEPATITIS

01 – Field investigations in Mongolia

Five viruses are responsible for most cases of viral hepatitis, which is an inflammation of the liver due to a viral infection. These are the hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV) and hepatitis E virus (HEV). All the hepatitis viruses can cause acute hepatitis. However, only HBV, HCV and HDV frequently cause chronic hepatitis, which can lead to progressive scarring of the liver (cirrhosis) and to primary liver cancer (hepatocellular carcinoma). Of these, HBV and HCV cause 96% of the mortality from viral hepatitis and are therefore the main focus of this report (although for some of the deaths from HBV infection, HDV may also be a cofactor).

Public health activities to control viral hepatitis have progressively increased over the past three decades. In the 1990s, the World Health Assembly first recommended the inclusion of hepatitis B vaccine in routine infant immunization schedules. Hepatitis B vaccine given shortly after birth prevents HBV infection that occurs early in life. HBV infection acquired during infancy carries a greater risk of death later in life from cirrhosis and hepatocellular carcinoma *(1)*. Coverage of immunization against HBV increased from the early 2000s with support from the Global Alliance for Vaccines and Immunization (GAVI, now known as the Vaccine Alliance) *(1)*, and optimized procurement in the American Region through the revolving fund.

From the 2000s, iterations of the Global Burden of Disease (GBD) project improved estimations of the real burden of mortality from viral hepatitis. It then became clear that cirrhosis and hepatocellular carcinoma accounted for the majority of the burden from viral hepatitis *(2)*. Prevention interventions progressed further, with initiatives on blood safety *(3)*, health-care injection safety *(4)*, infection control, and harm reduction for people who inject drugs. However, the early medications for the treatment of viral hepatitis B and C had limited effectiveness, and were poorly tolerated and expensive. This lack of treatment options meant that little or no progress was made in the management of people with chronic hepatitis infection.

By 2010, there was growing public awareness of the public health burden of viral hepatitis. However, there were major gaps in the response and mortality was increasing. In 2010, the World Health Assembly adopted the first resolution on viral hepatitis *(5)*, which led to the establishment of WHO's Global Hepatitis Programme in 2011. Research and development led to new revolutionary treatments for HCV infection, which improved treatment outcomes. A second resolution in 2014 *(6)* further underlined the public health importance of viral hepatitis, and raised the possibility of elimination of HBV and HCV.

In May 2016, the World Health Assembly adopted the Global Health Sector Strategy (GHSS) on viral hepatitis for 2016–2021. It has five strategic directions: (i) information for focused action; (ii) interventions for impact; (iii) delivering for equity; (iv) financing for sustainability; and (v) innovation for acceleration *(7)*.

The 194 Member States of WHO committed to eliminating viral hepatitis as a public health threat by 2030 (defined as a 65% reduction in mortality and a 90% reduction in incidence compared with the 2015 baseline) *(7)*. Elimination can be achieved through sufficient service coverage of five synergistic prevention and treatment interventions. These are (i) immunization against hepatitis B, (ii) prevention of mother-to-child transmission of HBV, (iii) blood and injection safety, (iv) prevention of transmission of HBV and HCV among persons who inject drugs through comprehensive harm reduction services, and (v) testing and treatment. WHO also developed a monitoring and evaluation framework for the GHSS on viral hepatitis *(8)*.

This report provides an update on the epidemiological situation and response to the HBV and HCV epidemics globally, and in each of WHO's six regions in 2015. It provides baseline data for monitoring the implementation and impact of the GHSS on viral hepatitis, and uses selected examples from countries. It highlights areas of uncertainty and calls for more evidence where information is lacking.

TIMELINE – TOWARDS THE ELIMINATION OF VIRAL HEPATITIS

PREVENTION BEGINS

1990

First ever Harm Reduction International Conference

1992

First WHO Resolution on hepatitis B vaccine

1999

Launch of WHO's Safe Injection Global Network (SIGN)

2000

Global Burden of Disease - mortality burden from viral hepatitis is first documented.

2001

The first HBV vaccines funded by GAVI

2004

First Strategic Advisory Group of Experts (SAGE) recommendation for timely birth dose

First World Blood Donor Day

2010

First World Health Assembly Resolution on viral hepatitis – World Hepatitis Day an official WHO day

PREVENTION IS STRENGTHENED AND TREATMENT IMPROVED

2011

Global Hepatitis Programme established at WHO following WHA resolution 63.18

2012

WHO publishes *Guidance on prevention of HBV and HCV infection among PWID.*

Civil society advocacy – World Hepatitis Alliance establishes official relations with WHO.

2013

A cure is developed – the first direct-acting antivirals revolutionize hepatitis C treatment.

2013

World Hepatitis Alliance and WHO launch the *Global policy report on the prevention and control of viral hepatitis.*

2014

WHA67.6 resolution asks countries to develop national plans and to include civil society and asks WHO "to examine the feasibility of elimination of HBV and HCV with a view to setting targets".

WHO publishes *Guidelines for the prevention, care and treatment of persons with chronic hepatitis C infection.*

2014

WHO Director-General forms first Hepatitis Scientific and Technical Advisory Committee (STAC).

WHO prequalifies the first enzyme immunoassay (EIA) for detection of HBsAg.

GLOBAL ACTION

JUNE 2015

WHO prequalifies the first EIA for detection of HCV antibodies.

SEPTEMBER 2015

Glasgow Declaration from the first World Hepatitis Summit

Plan of Action for the Prevention and Control of Viral Hepatitis 2016–2019 in the Region of the Americas approved by Member States

OCTOBER 2015

The Regional Action Plan for Viral Hepatitis in the Western Pacific 2016–2020 approved by Member States

APRIL 2016

Regional Action Plan for Hepatitis in the South-East Asia Region approved by Member States

Joint society statement for elimination of viral hepatitis – EASL, APASL, ALEH and AASLD

First update of hepatitis C treatment guidelines with first-ever preferred and alternative direct-acting antiviral (DAA)-based regimen recommended

UN General Assembly Special Session on Drugs

MAY 2016

Adoption of first global health sector strategy on viral hepatitis "Towards ending viral hepatitis", 2016–2021. Eliminate viral hepatitis as a major public health threat by 2030.

JULY 2016

NOhep launched on World Hepatitis Day

AUGUST 2016

A Framework for Action 2016–2020 for the prevention, care and treatment of viral hepatitis in the African Region approved by Member States

SEPTEMBER 2016

Regional Action Plan for Viral Hepatitis in the European Region approved by Member States

OCTOBER 2016

Regional Action Plan for the Implementation of the Global Strategy for Viral Hepatitis 2017–2021 for the Eastern Mediterranean Region approved by Member States

First-ever WHO *Global report on access to hepatitis C treatment* showed over 1 million persons treated with DAA-based regimens in low- and middle-income countries.

NOVEMBER 2016

WHO prequalifies the first HCV rapid test.

FEBRUARY 2017

First WHO *Guidelines on hepatitis B and C testing*

APRIL 2017

First global hepatitis report with WHO-validated estimates

02 – Transmission of HBV from mother to child most often leads to chronic liver disease.

BEYOND THE SCOPE OF THE REPORT: HEPATITIS A, D AND E

HEPATITIS A VIRUS – HAV

Hepatitis A causes only acute hepatitis. HAV is transmitted mostly through exposure to contaminated food or water, or through exposure to infected persons. A safe and effective vaccine is available. WHO estimates that worldwide, hepatitis A caused approximately 11 000 deaths in 2015 (accounting for 0.8% of the mortality from viral hepatitis) *(9)*.

HEPATITIS D VIRUS – HDV

Hepatitis D is caused by an incomplete virus, HDV. It is transmitted mostly through the percutaneous route (exposure to blood). HDV infects only those persons who already have HBV infection. Infection of an HBV-infected person with HDV (a phenomenon referred to as "superinfection") worsens the outcome of HBV infection. Hence, HDV is a cofactor of chronic liver disease. Most experts estimate that 5% of HBV-infected persons are also coinfected with HDV *(10)*. However, there is substantial uncertainty, as in many countries, HBV-infected patients are not tested for HDV infection. In addition, in selected countries, such as Mongolia, up to 60% of HBV-infected persons may also have HDV infection *(11)*. Prevention of HBV infection through vaccination also prevents HDV infection. However, the treatment of HBV–HDV-coinfected patients differs from the treatment of persons with HBV infection alone. Newer antinucleos(t)ides that are highly effective against HBV infection do not work well in HBV–HDV coinfection. Only older, interferon-based treatments can be used, with suboptimal results. WHO does not have estimates of the proportion of deaths due to HBV in which HDV may be a cofactor *(12)*. The distribution of HDV infection varies around the world.

HEPATITIS E VIRUS – HEV

HEV causes mostly acute hepatitis. It is transmitted via the faecal–oral route, principally via contaminated water. Every year, there are an estimated 20 million HEV infections worldwide, leading to an estimated 3.3 million symptomatic cases of acute hepatitis E *(13)*. WHO estimates that hepatitis E caused approximately 44 000 deaths in 2015 (accounting for 3.3% of the mortality due to viral hepatitis). Hepatitis E is a usually self-limiting illness, but some patients may progress to acute liver failure. Hepatitis E has a higher case fatality in pregnant women. This leads to maternal mortality that is particularly devastating. Infection with HEV is reported worldwide, but it is most common in East and South Asia. A vaccine to prevent HEV infection has been developed and is licensed in China, but is not yet available in most other countries *(14)*.

02

EPIDEMIOLOGICAL UPDATE: INCREASING MORTALITY CALLS FOR ACTION

03 – Intensive care unit for patients with liver disease, India.

KEY FINDINGS

HBV

NEW INFECTIONS IN 2015

- The widespread use of hepatitis B vaccine in infants has considerably reduced the incidence of new chronic HBV infections. Between the pre-vaccine era (which, according to the year of introduction can range from the 1980s to the early 2000s) and 2015, the proportion of children under 5 years of age who became chronically infected fell from 4.7% to 1.3%. The remaining infections mostly occur from the mother at birth or through contact with other infected young children.[a]

CHRONIC INFECTIONS IN 2015

- WHO estimates that in 2015, 257 million persons, or 3.5% of the population, were living with chronic HBV infection in the world. The African and Western Pacific regions accounted for 68% of those infected.
- 2.7 million persons were coinfected with HBV and HIV.
- Most of the people currently living with HBV infection are persons born before hepatitis B vaccine was widely available and used in infancy.

HCV

NEW INFECTIONS IN 2015

- Unsafe health-care procedures and injection drug use were the leading causes of new HCV infections, accounting for most of the 1.75 million new infections in 2015.

CHRONIC INFECTIONS IN 2015

- WHO estimates that in 2015, 71 million persons were living with HCV infection in the world, accounting for 1% of the population.
- 2.3 million persons living with HIV also had HCV infection.
- HCV infection is unevenly distributed in the world. The European and Eastern Mediterranean regions are more affected, but there are variations in prevalence across and within countries.

MORTALITY IN 2015

- WHO estimates that in 2015, viral hepatitis was responsible for 1.34 million deaths. This number was comparable with the number of deaths from tuberculosis, but higher than the number of deaths from HIV.
- Left untreated, HBV and HCV infection can lead to cirrhosis (720 000 deaths) and hepatocellular carcinoma (470 000 deaths). These long-term complications are life-threatening and accounted for 96% of the deaths due to viral hepatitis.
- Mortality from viral hepatitis has increased by 22% since 2000. Unless people with HBV and HCV infection are diagnosed and treated, the number of deaths due to viral hepatitis will continue to increase.

[a] The WHO monitoring and evaluation framework for viral hepatitis B and C recommends monitoring the cumulative incidence of chronic HBV infections in children 5 years of age, as most persons infected later in life do not develop life-threatening complications of HBV infection.

UNDERSTANDING THE VIRAL HEPATITIS EPIDEMIC: THE FIRST STEP TOWARDS ELIMINATION

A LATENT PERIOD BETWEEN INFECTION AND DEATH

Persons infected with HBV or HCV are usually unaware of their infection, as they do not have well-defined symptoms before complications emerge. The natural history of HBV and HCV infection progresses through three stages.

01 **New infections.** After infection with HBV or HCV, a small subset of people may develop acute hepatitis. However, in most persons, this new infection goes unnoticed as it produces no symptoms. These new infections may then evolve into chronic infections. **Incidence** can be defined as the rate of occurrence of new infections. It is reported as the number of new infections in the population over a given period of time. Incidence measures the risk of contracting the infection and reflects transmission.

02 **Chronic infection.** Some new infections can evolve into chronic infections while others evolve towards spontaneous clearance of the virus. The risk of developing chronic infection with HBV is highest among children, whereas infection with HCV becomes chronic in most infected persons.[a] A person may be infected with HBV or HCV for as long as 30 years or more before they develop any clinical symptoms of disease. Unless persons are tested and diagnosed, they are not aware of their disease. However, hidden inflammation progresses in the liver. **Prevalence** is the proportion of a population infected at a given time.

03 **Mortality.** Untreated chronic viral hepatitis can progress to life-threatening complications. Depending on life expectancy, 20% or more of those with chronic infection develop end-stage chronic liver disease, such as cirrhosis or hepatocellular carcinoma. Cofactors (e.g. alcohol, HIV infection) can accelerate progression towards end-stage liver disease. Cirrhosis and hepatocellular carcinoma are life-threatening conditions.

[a] HCV not only affects the liver; it can also cause chronic fatigue, autoimmune conditions, renal diseases and lymphomas.

ELIMINATING VIRAL HEPATITIS AS A PUBLIC HEALTH THREAT

The burden of viral hepatitis constitutes a public health threat in many areas of the world. In 2016, the World Health Assembly approved a global strategy to achieve elimination of this public health threat by 2030. To do this, and starting from the 2015 baseline, countries and regions need to reduce new infections (incidence) by 90%[a] and reduce deaths (mortality) by 65% by 2030.

STATUS OF HEPATITIS B

FIRST FIVE YEARS OF LIFE – A CRITICAL TIME TO PREVENT HBV INFECTION

Most of the burden of disease from HBV infection comes from infections acquired before the age of 5 years *(15)*. Therefore, prevention of HBV infection focuses on children under 5 years of age. The United Nations selected the cumulative incidence of chronic HBV infection at 5 years of age as an indicator of the Sustainable Development Goal target for "combating hepatitis" *(16)*. This indicator is measured indirectly through the proportion of children 5 years of age who have developed chronic HBV infection (i.e. the proportion that tests positive for a marker of infection called hepatitis B surface antigen [HBsAg]).

Infants born to untreated HBV-infected mothers can acquire infection from the mother, mostly during birth. Infants born to mothers who are positive for both HBsAg and hepatitis B e antigen (HBeAg) are at a higher risk of acquiring infection (transmission risk for HBsAg-positive and HBeAg-positive mothers: 70–100% in Asia and 40% in Africa) than those born to HBsAg-positive mothers who have lost the HBeAg (5–30% in Asia and 5% in Africa) *(15, 17, 18)*. Early vaccination of the baby against hepatitis B with a first dose within 24 hours of birth (timely birth dose) contributes to the prevention of mother-to-child transmission. The efficacy of the vaccine decreases with the concentration of HBV in the blood of the mother. HBeAg-negative mothers have a near 0% risk of transmitting HBV to their offspring vaccinated at birth *(19)*, while HBeAg-positive mothers have a 20% risk of transmitting the virus despite vaccination at birth *(20)*. Treatment of pregnant mothers with antivirals, which is being introduced as a new intervention to prevent mother-to-child transmission of HBV, should further reduce the risks of transmission *(21)*.

Younger age cohorts have a lower incidence of chronic HBV infection compared to the pre-vaccination era

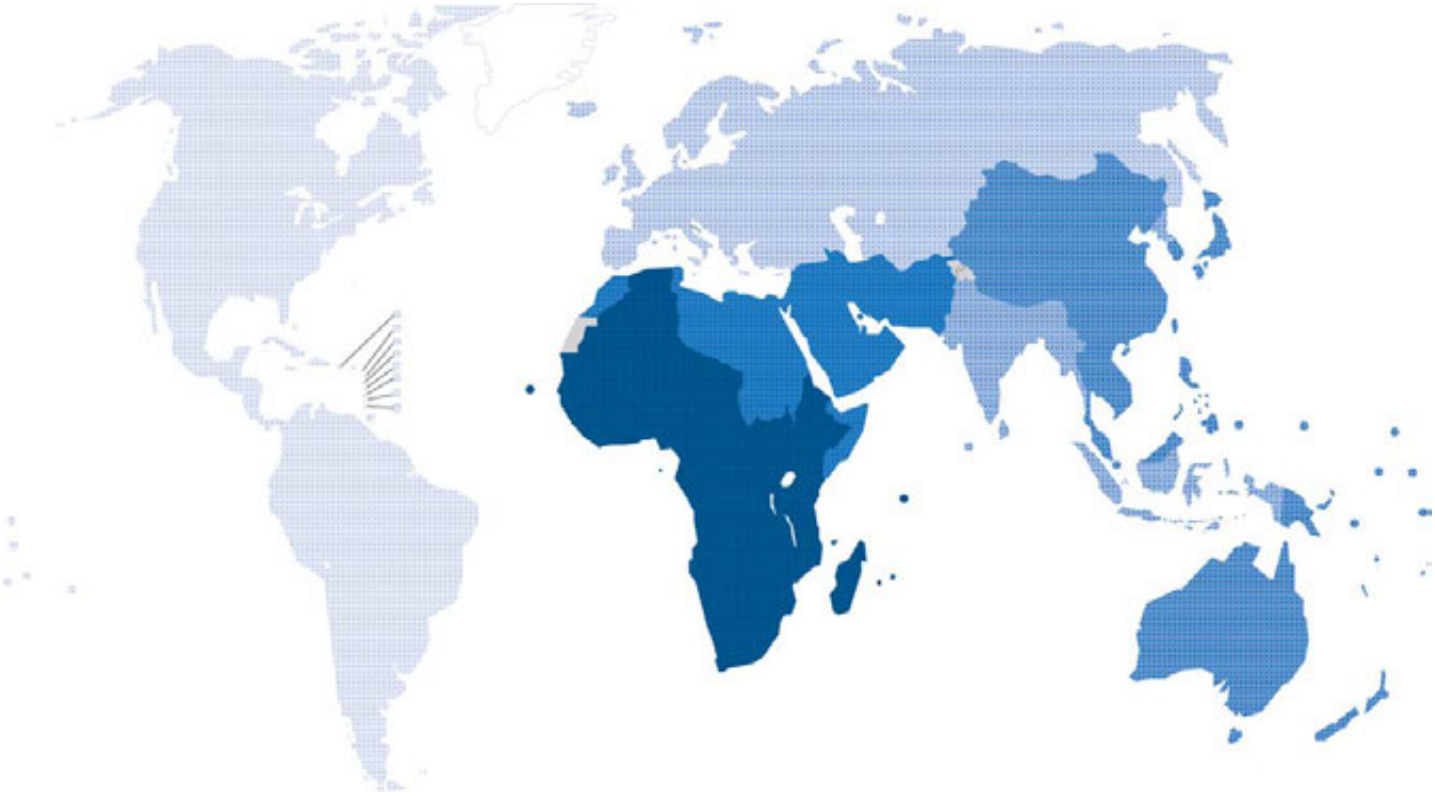
The low incidence of chronic HBV infection in children under 5 years of age at present can be attributed to the widespread use of hepatitis B vaccine. Worldwide, in 2015, the estimated prevalence of HBV infection in this age group was about 1.3% (Table 1), compared with about 4.7% in the pre-vaccination era (which, according to the year of introduction can range from the 1980s to the early 2000s).[b]

However, the prevalence was still 3% in the African Region. This fall in the incidence of chronic HBV infections among children means that in the long term, the global hepatitis B epidemic will decline. However, deaths among infected adults born before the era of vaccination will continue to increase if they are not diagnosed and treated.

[a] For HBV, a 90% reduction in incidence compared with the 2015 baseline would be equivalent to 0.1% prevalence of HBV infection in children five years of age in 2030.

[b] *Source:* WHO, work conducted by the London School of Hygiene & Tropical Medicine (LSHTM), data not shown.

Table 1 (with map). Cumulated incidence of chronic HBV infection, 2015 (prevalence of HBsAg in children under 5 years) after the use of the vaccine by WHO region: about 1.3% of under-5 children have developed chronic HBV infection



		Prevalence of HBsAg (%)		
			Uncertainty intervals	
WHO region	**Map key**	**Best**	**Lower**	**Higher**
African Region		3.0	2.0	4.7
Region of the Americas		0.2	0.1	0.5
Eastern Mediterranean Region		1.6	1.2	2.1
European Region		0.4	0.2	0.8
South-East Asia Region		0.7	0.5	1.6
Western Pacific Region		0.9	0.6	1.3
Total		**1.3**	**0.9**	**2.2**

Source: WHO, work conducted by the London School of Hygiene & Tropical Medicine (LSHTM). *See* Annex 2.

PREVALENCE OF CHRONIC HBV INFECTION: MAJOR EPIDEMICS IN THE AFRICAN AND WESTERN PACIFIC REGIONS

Prevalence of HBV infection

In 2015, the global prevalence of HBV infection in the general population was 3.5%. Among those born before the hepatitis B vaccine became available, the proportion of persons living with chronic HBV infection remains high. Prevalence was the highest in the African (6.1%) and Western Pacific regions (6.2%). Overall, about 257 million persons were living with HBV infection (Table 2). Assuming that women of reproductive age constitute 25.3% of the world's population (United Nations data), adults chronically infected may include 65 million women of childbearing age who can potentially transmit HBV to their babies. In addition, a proportion of these adults would benefit from long-term, if not lifelong, treatment, particularly those above 30 years of age, those who have cirrhosis, and those with HIV infection *(22)*. This proportion of patients who would benefit from treatment is not well known. In community-based studies, reports range from less than 5% *(23)* to about 10% *(24)*. In health-care facility-based studies, the proportion is higher *(25)*.

Prevalence of HBV–HIV coinfection

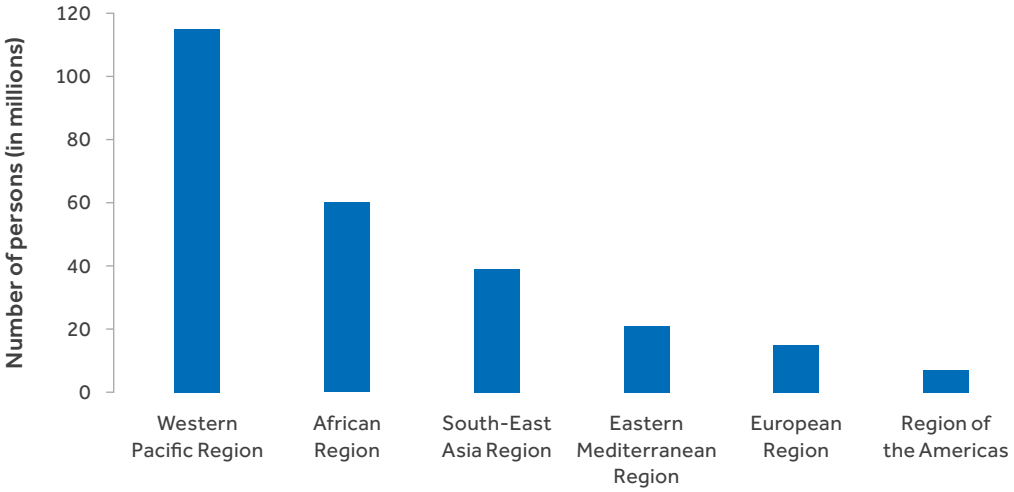
About 2.7 million (interquartile range: 1.8–3.9) of the 36.7 million living with HIV are also infected with HBV. The global prevalence of HBV infection in HIV-infected persons is 7.4%. The prevalence of HBV infection is similar across different groups of HIV-infected persons and, in particular, between persons without (6.6%) or with higher risk behaviours, such as persons who inject drugs (7.0%) and men who have sex with men (6.1%). Most HIV–HBV-coinfected persons live in sub-Saharan Africa (71%; 1.96 million) *(26)*. As HIV-infected persons continue to live longer due to increased uptake of antiretroviral therapy *(27)*, HBV coinfection is associated with accelerated progression of chronic hepatitis and higher liver-related mortality *(26, 28–30)*. Since 2015, WHO has recommended treatment for everyone diagnosed with HIV infection, regardless of the stage of disease *(31)*. However, by the end of 2016, only about 50% of people with HIV were receiving treatment *(32)*. WHO now recommends the use of tenofovir as part of first-line treatment for HIV and for the treatment of chronic HBV infection, including among pregnant HIV–HBV-coinfected women. Hence, expansion of tenofovir-based treatment for HIV will provide effective treatment for HBV infection for those who are coinfected with HIV and HBV, and will help prevent transmission of HBV from mother to child *(33)*. However, data are lacking on the actual coverage of tenofovir-based treatment for people who are coinfected with HIV and HBV.

04 – Population surveys provide reliable estimates of the proportion of the population living with HBV or HCV.

257

MILLION PERSONS WORLDWIDE ARE LIVING WITH HBV.

Table 2 (with graph). Prevalence of HBV infection (HBsAg) in the general population by WHO region, 2015: the WHO African and Western Pacific regions have the highest prevalence and the largest number of persons living with HBV



	Estimates of the prevalence of HBV infection (%)			Estimated number of persons living with HBV (millions)		
		Uncertainty interval (95%)			Uncertainty interval (95%)	
WHO region	**Best**	**Lower**	**Higher**	**Best**	**Lower**	**Higher**
African Region	6.1	4.6	8.5	60	45	84
Region of the Americas	0.7	0.4	1.6	7[a]	4	16
Eastern Mediterranean Region	3.3	2.6	4.3	21	17	28
European Region	1.6	1.2	2.6	15	11	23
South-East Asia Region	2.0	1.5	4.0	39	29	77
Western Pacific Region	6.2	5.1	7.6	115	93	140
Total	**3.5**	**2.7**	**5.0**	**257**	**199**	**368**

Source: WHO, work conducted by the London School of Hygiene & Tropical Medicine (LSHTM). *See* Annex 2.

STATUS OF HEPATITIS C

INCIDENCE OF HCV INFECTION: TRANSMISSION PERSISTS

Several studies suggest that the incidence of HCV infection has decreased since the second half of the 20th century. First, most countries have age-specific prevalence of serological evidence of past or present infection, suggesting lower incidence in recent years *(34–37)*. Second, countries that conduct surveillance for acute hepatitis C reported decreases in the rates *(38)*. Third, countries that conducted more than one biomarker survey, such as Egypt, reported an evolution over time that suggests a decrease in incidence *(39)*. Fourth, injection safety improved, which reduced the incidence of injection-associated HCV infection *(40)*. However, estimates obtained from modelling suggest that worldwide, in 2015, there were still 1.75 million new HCV infections (global incidence rate: 23.7 per 100 000).

Unsafe health-care practices (including unsafe health-care injections) and injection drug use remain the leading modes of transmission. Areas with high rates of infection are located in the Eastern Mediterranean Region (62.5 per 100 000) and the European Region (61.8 per 100 000). In the Eastern Mediterranean Region, the most common cause of transmission of infection is unsafe health-care injections *(41, 42)*. In the European Region, injection drug use accounts for a substantial proportion of new infections (Table 3) *(43)*.

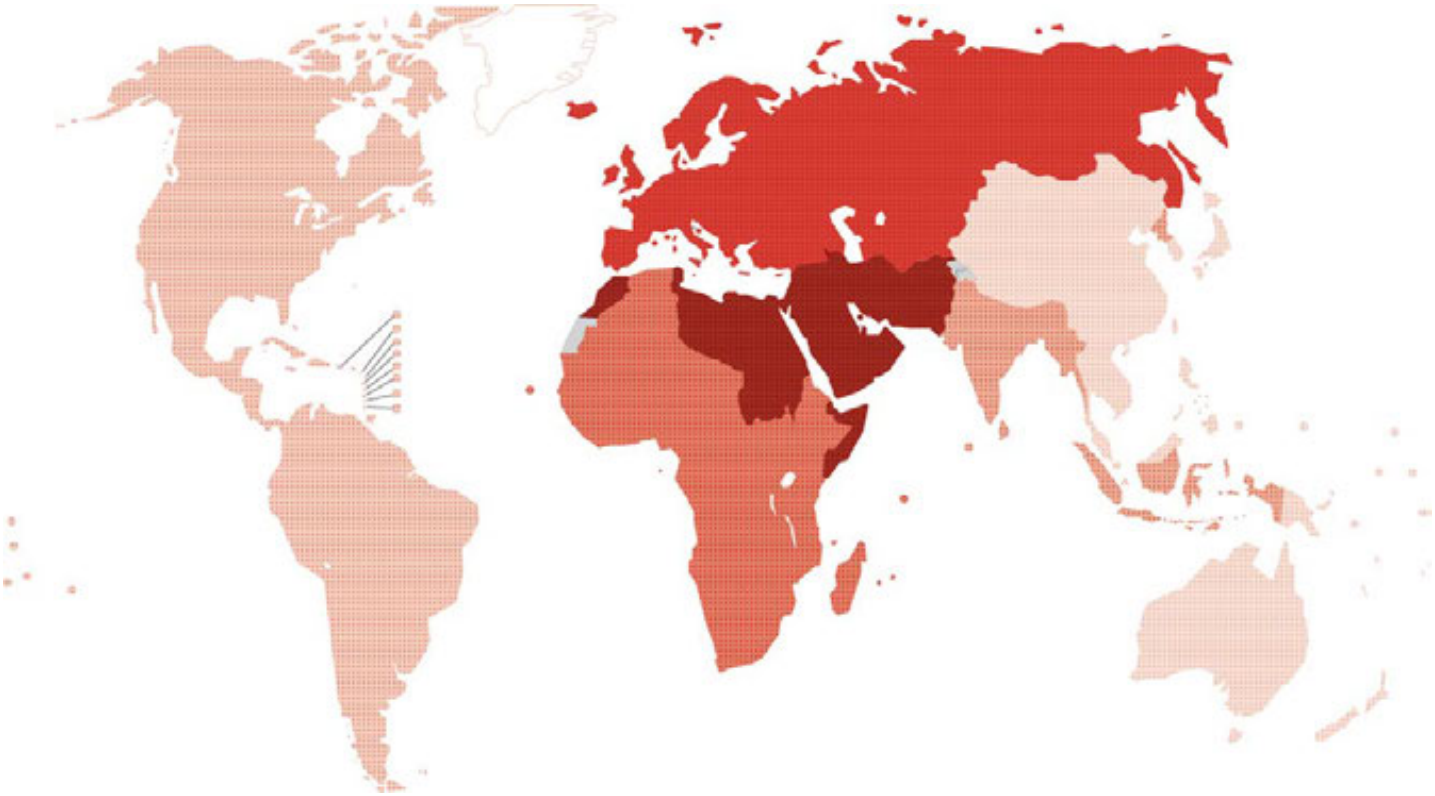
Even in areas of the world where the incidence was low in 2015, an increase in transmission may occur at any time, and through various modes of transmission. In the United States of America, for instance, after many years of decrease, the incidence of HCV infection doubled between 2010 and 2014 *(44)*. The number of reported cases of acute hepatitis C among persons reporting

[a] Modelled estimate: 6.6 million, rounded. The WHO Regional Office for the Americas has worked with its Member States to generate estimates through country consultations and modelling. These national estimates were consolidated in 2016 into a regional estimate of 2.8 million people living with chronic HBV infection. The difference between these estimates is consistent with the different methods used. In addition, low-prevalence settings may lead to lower precision and greater uncertainty. WHO headquarters and regional offices will continue to engage in comparative modelling to further understand the source of these differences. Such analyses should allow more precise consensus estimates in the future. *See* Annex 2, and *(123)*.

injection drug use increased, particularly in rural areas *(45, 46)*. Injection drug use among young persons results in rapid dissemination of HIV and HCV *(47)*, as well as some transmission of HBV *(48)*. Transmission of HCV has also been reported in Europe, Australia and the USA among men who have sex with men (MSM) infected with HIV *(49)*. Reinfection has been reported even among HIV-infected MSM who were successfully cured with treatment for hepatitis C *(50)*. No estimates are available to quantify how much this emerging issue contributes to the overall transmission of HCV *(51, 52)*.

To determine whether the number of infected persons is likely to increase or decrease, the number of new HCV infections needs to be compared with the number of persons who die and those who are cured. In 2015, as the estimated number of persons newly infected (*N*=1.75 million) exceeded the estimated number of persons dying from end-stage HCV infection (*N*=399 000)[a] and being cured (*N*=843 000), the global epidemic may continue to expand in magnitude in the absence of scaled-up interventions.

Table 3 (with map). Incidence of HCV infection in the general population, by WHO region, 2015: 1.75 million new infections in 2015



		Incidence of HCV infection			
		Incidence rate (per 100 000)		Total number (000)	
WHO region	Map key	Best estimate	Uncertainty interval	Best estimate	Uncertainty interval
African Region		31.0	22.5–54.4	309	222–544
Region of the Americas		6.4	5.9–7.0	63	59–69
Eastern Mediterranean Region		62.5	55.6–65.2	409	363–426
European Region		61.8	50.3–66.0	565	460–603
South-East Asia Region		14.8	12.5–26.9	287	243–524
Western Pacific Region		6.0	5.6–6.6	111	104–124
Global		**23.7**	**21.3–28.7**	**1 751**	**1 572–2 120**

Source: WHO, work conducted by the Center for Disease Analysis. *See* Annex 2.

[a] These deaths exclude those from the extrahepatic complications of HCV infection and background mortality from other causes among HCV-infected patients.

PREVALENCE OF CHRONIC HCV INFECTION: UNEVEN GLOBAL EPIDEMIC, WITH DIFFERENCES ACROSS AND WITHIN COUNTRIES

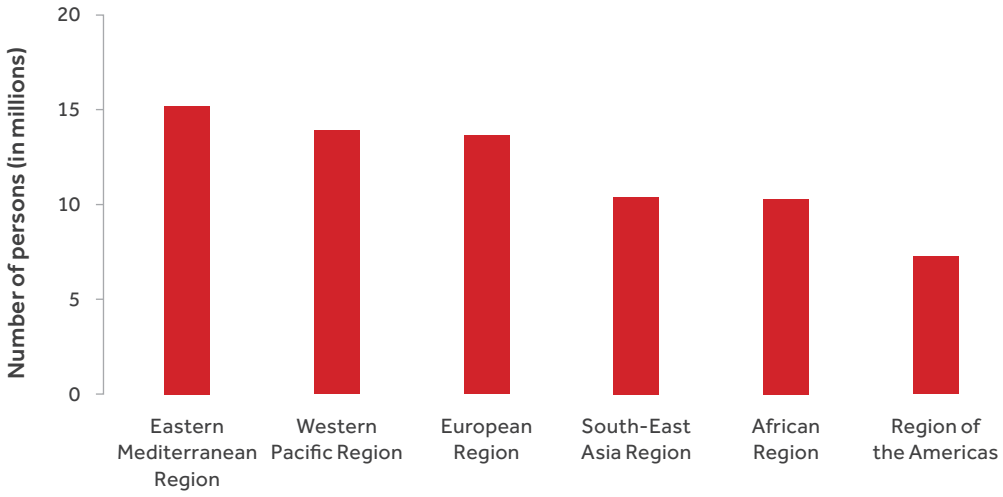
Prevalence of HCV infection

In 2015, 71 million persons were living with chronic HCV infection. Compared with HBV, the prevalence of HCV infection is lower, but more heterogeneously distributed, with differences across and within WHO regions and countries. Spread through breaks in infection control practices or injection drug use may explain this pattern. Overall, in 2015, the global prevalence of HCV infection was 1.0%. The Eastern Mediterranean Region had the highest prevalence (2.3%) followed by the European Region (1.5%) (Table 4).

71

MILLION PERSONS WORLDWIDE ARE LIVING WITH HCV.

Table 4 (with graph). Prevalence of HCV infection (HCV RNA positive) in the general population, by WHO region, with uncertainty intervals, 2015: 71 million persons living with HCV worldwide



	Estimates of the prevalence of HCV infection (%)			Estimated number of persons living with HCV (millions)		
		Uncertainty interval			Uncertainty interval	
WHO region	**Best**	**Lower**	**Higher**	**Best**	**Lower**	**Higher**
African Region	1.0	0.7	1.6	11	7	16
Region of the Americas	0.7	0.6	0.8	7	6	8
Eastern Mediterranean Region	2.3	1.9	2.4	15	13	15
European Region	1.5	1.2	1.5	14	11	14
South-East Asia Region	0.5	0.4	0.9	10	8	18
Western Pacific Region	0.7	0.6	0.8	14	10	15
Total	**1.0**	**0.8**	**1.1**	**71**	**62**	**79**

Source: WHO, work conducted by the Center for Disease Analysis. *See* Annex 2.

05 – Rapid diagnostic tests can be used in a broad range of health-care facilities.

The proportion of the population living with HCV infection often increases with age, in a way that exceeds what could be expected from the cumulative risk of infection year after year *(53)*. This is often referred to as a "cohort effect" and occurs in populations that were infected due to factors such as unsafe health-care-related injections, which contributed to the transmission of HCV on a larger scale earlier *(34–36)*. Of the 71 million persons infected with HCV, 5.6 million (8%) currently inject drugs. The proportion of current injectors among infected persons needs to be taken into account in order to provide adapted prevention, care and treatment services in an environment free from stigma and discrimination. A larger, ill-defined proportion of those living with HCV are former drug injectors or persons who were infected through unsafe health-care-related procedures. Such persons access health-care services more easily than persons who currently inject drugs *(54)*.

Prevalence of HIV–HCV coinfection

About 2.3 million people (interquartile range: 1.3-4.4) of the estimated 36.7 million living with HIV globally have serological evidence of past or present HCV infection (positive for antibodies to HCV, anti-HCV positive). Of these, 1.36 million are persons who currently inject drugs *(55)*. Conversely, among all HIV-infected persons, the prevalence of anti-HCV was 6.2%. Among HIV-infected persons, the prevalence of anti-HCV was highest in persons who inject drugs (82.4%), followed by men who have sex with men (6.4%), and was much lower in HIV-infected persons without higher risk behaviours (2.4%). Eastern Europe and central Asia account for the largest proportion of HIV-infected persons who have serological evidence of past or present HCV infection (27%), because of injection drug use. HIV coinfection doubles the risk of mother-to-child transmission of HCV *(56, 57)*, and is associated with less spontaneous HCV clearance, higher HCV viral loads, and more rapid progression of liver disease *(58–61)*. People living with HIV should be tested for HCV infection *(54, 62)*.

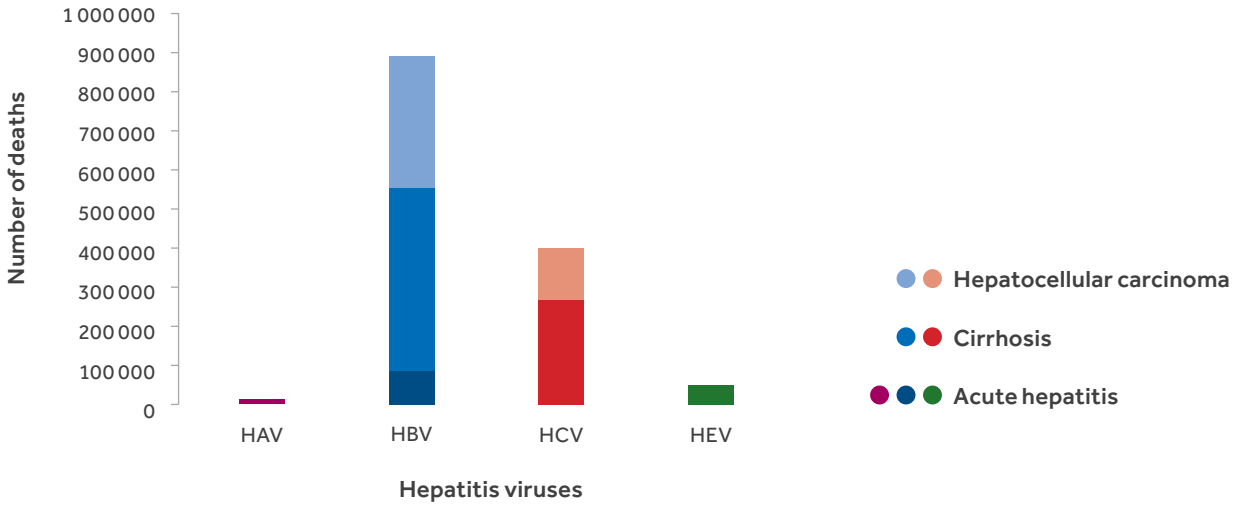
PERSONS WITH HIV AND HEPATITIS SHOULD BE PLACED ON EFFECTIVE TREATMENT FOR BOTH INFECTIONS.

MORTALITY: DEATHS ATTRIBUTABLE TO VIRAL HEPATITIS ARE AS COMMON AS THOSE DUE TO TUBERCULOSIS

1.34 MILLION DEATHS: 96% OF THESE ARE DUE TO THE SEQUELAE OF HBV AND HCV INFECTION

In 2015, viral hepatitis led to 1.34 million deaths, a death toll on a par with those due to tuberculosis (1.37 million deaths, without HIV-associated tuberculosis) and higher than those due to to HIV (1.06 million deaths) or to malaria (0.44 million deaths). Of these deaths, 96% were the result of complications of chronic HBV (66%) and HCV (30%) infections, while hepatitis A and hepatitis E accounted for 0.8% and 3.3% of deaths, respectively. A proportion of the deaths attributed to HBV infection may be explained by superinfection with HDV. Among the long-term complications of HBV and HCV infections, cirrhosis (720 000 deaths) accounts for more deaths than hepatocellular carcinoma (470 000 deaths, Fig. 1). In many patients with end-stage HBV or HCV liver disease, the viral infection is not mentioned on the death certificate when death occurs from cirrhosis or hepatocellular carcinoma. In the absence of such a link, these deaths are considered as deaths from noncommunicable diseases, and the burden of disease from viral hepatitis remains underestimated.

Fig. 1. Deaths from viral hepatitis, by virus and type of sequelae, 2015: most viral hepatitis deaths are due to the late complications of HBV and HCV infection



HAV: hepatitis A virus; HBV: hepatitis B virus; HCV: hepatitis C virus; HEV: hepatitis E virus
Source: WHO global health estimates for 2015 published in 2016 (Global Health Estimates 2015: deaths by cause, age, sex, by country and by region, 2000–2015. Geneva: World Health Organization; 2016.)

DEATHS DUE TO VIRAL HEPATITIS ARE INCREASING AND WILL CONTINUE TO DO SO UNLESS TREATMENT IS SCALED UP

From 2000 to 2015, scaled-up interventions led to a decrease in mortality from HIV (from 1.46 to 1.06 million deaths between 2000 and 2015), tuberculosis (from 1.67 to 1.37 million deaths between 2000 and 2015), and malaria (from 0.86 to 0.44 million deaths between 2000 and 2015). In contrast, mortality due to viral hepatitis is increasing (Fig. 2). The number of deaths rose from 1.10 million deaths in 2000 to 1.34 million deaths in 2015 (an increase of 22%).

Mortality is expected to further increase. For HBV, the widespread use of hepatitis B vaccine started in the 1990s and 2000s. Therefore, those born before this period in countries where infection is common would not have been vaccinated as children. These unvaccinated birth cohorts that have endemicity levels comparable to the pre-vaccine era are in their twenties or thirties in Asia *(63)* or in their teenage years in Africa *(64)*. Those who were infected are living with HBV and are at risk for progression to end-stage liver disease and cancer *(1)*.

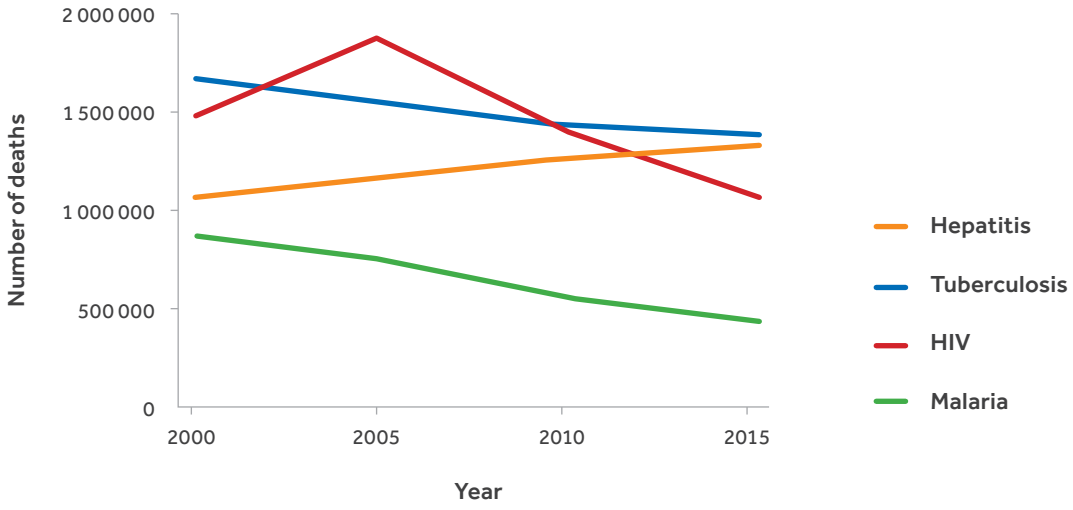
For HCV, the virus was transmitted on a large scale in many middle- and low-income countries at the end of the 20th century, largely due to unsafe health-care procedures and injection drug use *(65–67)*. In these countries,

mortality from the complications of chronic hepatitis C infection will continue to increase in the coming years if testing and subsequent treatment are not made available to those infected. In most high-income countries, transmission occurred earlier, just after the Second World War (e.g. Japan, Italy and France) *(68)*. Although mortality is decreasing the number of persons living with HCV today is too small to influence the global trend.

AFRICA AND ASIA FACE THE LARGEST BURDEN OF MORTALITY

The mortality rate from viral hepatitis (18.3 per 100 000 globally) is highest in the Western Pacific Region (24.1 deaths per 100 000), followed by the South-East Asia Region (21.2 per 100 000) and African Region (13.7 per 100 000), and lowest in the American Region (11.2 per 100 000). Worldwide, the Western Pacific, South-East Asia and African regions account for 446 000, 408 000 and 136 000 deaths, respectively (33%, 30% and 10% of the total deaths, respectively).

Fig. 2. Global annual mortality from hepatitis, HIV, tuberculosis and malaria, 2000–2015: unlike HIV, tuberculosis and malaria, the trend in mortality from viral hepatitis is increasing



Source: WHO global health estimates (Global Health Estimates 2015: deaths by cause, age, sex, by country and by region, 2000-2015. Geneva: World Health Organization; 2016.)

Sequelae of viral hepatitis kill mostly adults. Compared with those less than 30 years of age, persons 30 years of age and older have a higher mortality rate (34.3 per 100 000 versus 2.6 per 100 000) and account for a much larger proportion of deaths (93% versus 7%). Men have higher mortality rates (23.3 deaths per 100 000) than women (13.2 deaths per 100 000). Regionally, too, there is a difference, with deaths from HBV-associated hepatocellular carcinoma occurring at a younger age in sub-Saharan Africa (median: 38.9 years) than in the Western Pacific Region (median: 54.5 years) *(68)*.

This results in more years of life lost and greater economic loss among Africans. As the age-specific rate of incidence of hepatocellular carcinoma is not higher in Africa than in Asia, this difference in age at death may be explained, in part, by a different age pyramid in Africa and Asia, rather than by biological factors, such as aflatoxin exposure *(69)*. In 2015, as per the United Nations data, the population is younger in sub-Saharan Africa (median age: 18.3 years) than that in East Asia (median age: 37.9 years).

GLOBAL, REGIONAL AND NATIONAL RESPONSES TO THE GLOBAL EPIDEMIC OF VIRAL HEPATITIS

THE NUMBER OF COUNTRIES WITH NATIONAL POLICIES AND PLANS IS INCREASING

Globally, there is strong commitment to taking action, as reflected by World Health Assembly resolutions in 2010 *(5)* and 2014 *(6)*, and the World Hepatitis Summit in September 2015. This was followed in May 2016 with endorsement by the World Health Assembly of the Global Health Sector Strategy on viral hepatitis for 2016–2021 (GHSS) *(7)*. As of March 2017, 43 Member States had reported to WHO that they had formulated national viral hepatitis elimination plans and an additional 36 Member States reported that they were in the process of developing plans.

SURVEILLANCE GUIDES NATIONAL PLANS

Surveillance for viral hepatitis keeps track of the three components of the epidemic of HBV and HCV infection – acute hepatitis, chronic infections and mortality *(70)*. Of these, estimating the prevalence of chronic infection in the general population through a biomarker survey is key to an initial country assessment (Box 1).

BOX 1. CASE STUDY IN IMPROVING STRATEGIC INFORMATION: A BIOMARKER SURVEY TO EVALUATE PAST HEPATITIS B IMMUNIZATION EFFORTS AND PLAN TESTING AND TREATMENT, BHUTAN, 2016

Most people living with viral hepatitis in the population are asymptomatic. Since these chronic infections with HBV and HCV go unnoticed, surveys that collect and test blood specimens are required to estimate the number of infected persons. In 1997, Bhutan introduced hepatitis B vaccine in its Expanded Programme on Immunization (EPI), and in 2003, 95% coverage was attained. Almost 20 years later, in 2017, Bhutan is about to conduct a new national biomarker survey in the general population that will look back to evaluate the impact of hepatitis B vaccination on transmission in young children and look ahead to plan the future testing and treatment programme for HBV and HCV *(see photo)*. For efficient use of resources, this new biomarker survey will be integrated with a measles and rubella serological survey.

06 – Participants of a protocol-writing workshop for a hepatitis B and hepatitis C biomarker survey in the Kingdom of Bhutan, 2016.

WHAT SURVEILLANCE SYSTEMS ARE NEEDED TO GUIDE AND DOCUMENT ELIMINATION?

This report provides estimates of incidence, prevalence and mortality only at the regional level. In many countries, the surveillance systems in place do not fully capture the fact that the viral hepatitis epidemic is made up of individual infections that evolve through three phases. As key information is often missing, each country needs to consider three parts of viral hepatitis surveillance:

01 **Surveillance for acute hepatitis, which reflects new infections.** Syndromic surveillance (surveillance for clinically defined acute hepatitis) is often in place, but informs only about outbreaks of hepatitis A or hepatitis E. Enhanced case reporting (surveillance for laboratory-confirmed, type-specific viral hepatitis) is also needed to describe trends and identify risk factors for infection. Information on trends along with repeated estimates of prevalence may be used to estimate incidence through modelling.

02 **Biomarker surveys to estimate the prevalence of chronic infection.** In countries where the prevalence of HBV or HCV infection is unclear, biomarker surveys in the general population may provide baseline estimates among adults and evaluate the impact of national vaccination programmes among children.[a] Biomarker surveys among children who were vaccinated are used to evaluate impact.

03 **Reliable mortality monitoring.** Estimating mortality from HBV and HCV infection requires two pieces of information that come from different sources. First, national vital statistics and/or cancer registries measure the mortality from cirrhosis and hepatocellular carcinoma. Second, health-care facilities caring for patients with cirrhosis and hepatocellular carcinoma can estimate the proportion of patients with these sequelae who have HBV or HCV infection. This proportion can be used along with measures of association to calculate the fraction attributable to viral hepatitis. Applying the attributable fraction to the national estimates of mortality from cirrhosis and hepatocellular carcinoma leads to national estimates of mortality from viral hepatitis.

[a] As regions progress towards elimination of mother-to-child transmission of HBV, newer methods will be needed as the sample size needed for biomarker surveys will considerably increase as prevalence approaches 0.1%.

03

INTERVENTIONS FOR IMPACT: EXPANDING PREVENTION, TESTING AND TREATMENT

07 – Social mobilization for community-based testing for HBV infection in Africa.

KEY FINDINGS

PREVENTION

- In 2015, global coverage with the third dose of hepatitis B vaccine reached 84%, but the European, Eastern Mediterranean and African regions faced coverage gaps.
- In 2015, the global coverage with the birth dose of hepatitis B vaccine was 39%. The Region of the Americas and Western Pacific Region were the only regions that had wide coverage.
- Worldwide, in 2013, 97% of countries screened blood donations with quality assurance, but gaps persist.
- Unsafe injections decreased from 39% in 2000 to 5% in 2010 worldwide. However, in the Eastern Mediterranean and South-East Asia regions, needles and syringes were frequently reused without being sterilized.
- Harm reduction for persons who inject drugs falls short of the target of the GHSS on viral hepatitis, with on average globally only 27 syringe and needle sets distributed per person who injects drugs each year, as compared with a 2030 target of 300.

TESTING IN 2015

- Only a minority of those infected with HBV and HCV had been tested and knew their status: 9% of persons living with HBV (22 million) and 20% of persons living with HCV (14 million).

TREATMENT IN 2015

- Of those diagnosed with HBV infection, the proportion on treatment with WHO-recommended antivirals did not exceed 8% (1.7 million persons).
- Among people diagnosed with chronic HCV infection, 7% started treatment in 2015 (1.1 million persons). As of 2015, a cumulative total of 5.5 million people with chronic HCV had ever received treatment, but the majority of these treatments were older, less effective interferon-based regimens.

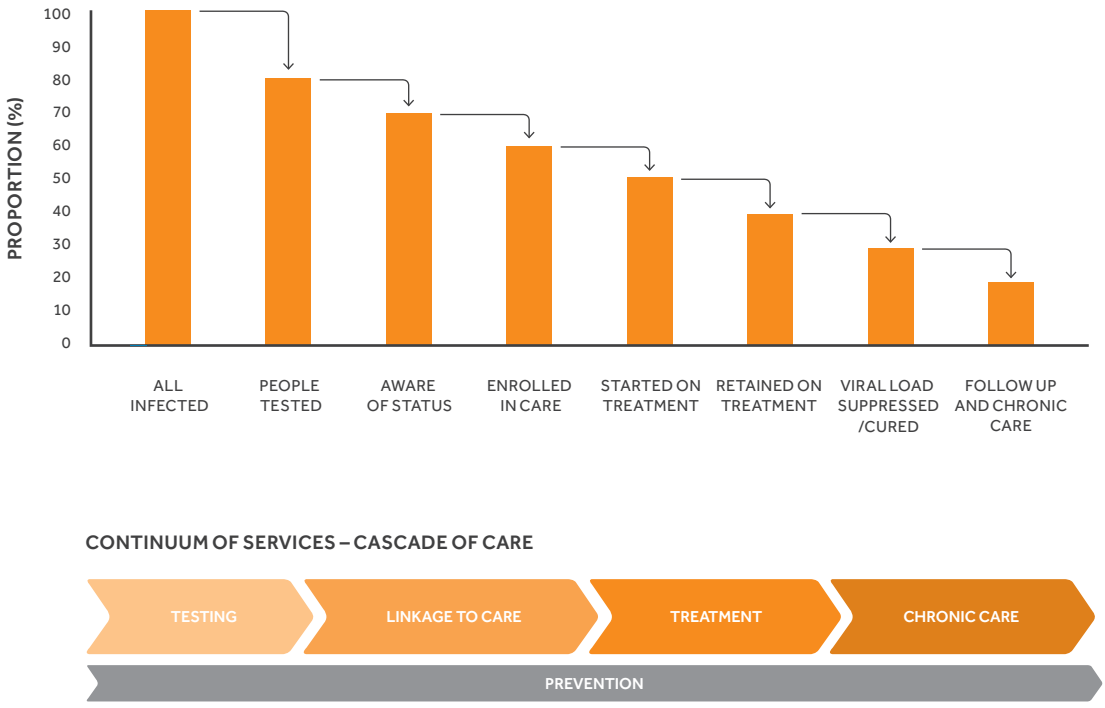
FIVE CORE INTERVENTIONS SHOULD BE SCALED UP TO REACH ELIMINATION

A comprehensive response to hepatitis requires the implementation of effective, high-impact interventions along the full continuum of hepatitis services, including interventions for prevention, testing, treatment and chronic care (Fig. 3).

INTERVENTIONS ALONG THE CONTINUUM OF HEPATITIS SERVICES

WHO commissioned a mathematical model, which suggests that hepatitis B and C could be eliminated as a public health threat by 2030 if the response to viral hepatitis reaches the service coverage targets for five core interventions *(71, 72)*. These synergistic interventions for prevention, testing and treatment are at the core of an effective hepatitis response and are promoted through the GHSS on viral hepatitis (Table 5). This report provides the best estimate of service coverage for these five interventions in 2015, the baseline, using standardized indicators.

Fig. 3. The continuum of viral hepatitis services and the retention cascade



PREVENTION INDICATORS (INTERVENTIONS 1–4, TABLE 5)

Within the public health system, interventions to prevent viral hepatitis are often led by different programmes (e.g. immunization, blood transfusion services and harm reduction). These programmes generate coverage estimates that can be used for monitoring and evaluation.

THE CASCADE OF CARE (INTERVENTION 5, TABLE 5)

At the population level, the "cascade of care" is a continuum of services that persons living with hepatitis should receive as they go through various stages, from diagnosis to treatment to chronic care and, for hepatitis C, to cure (*see* Fig. 3). The key indicators considered address diagnosis, treatment and viral suppression or the effectiveness of treatment.

- **Diagnosis.** The indicator is the proportion of infected persons who are diagnosed.
- **Treatment.** The indicator is the subset of those diagnosed who are on treatment. Once diagnosed, infected persons are placed on long-term, usually lifelong, treatment (for hepatitis B) or short-term curative treatment (for hepatitis C).
- **Treatment effectiveness.** This denotes the proportion of treated persons in whom the treatment is documented to be effective. For HBV, the indicator is the proportion of those on treatment who have viral suppression. For HCV, it is the proportion of those who have completed treatment and have a sustained virological response (viral load is measured 12–24 weeks after completion of treatment).

Table 5. Service coverage indicators for the core interventions of the Global Health Sector Strategy (GHSS) on viral hepatitis: 2015 baseline and targets

				Targets	
	Interventions	Indicator	2015 baseline	2020	2030
1	**Hepatitis B vaccination**	HEPB3 coverage	84%	90%	90%
2	**HBV PMTCT**[a]	HEP vaccine birth dose coverage	39%	50%	90%
3	**Blood safety**	Donations screened with quality assurance	97%	95%	100%
	Injection safety	Proportion of unsafe injections	5%	0%	0%
4	**Harm reduction**	Syringes & needles distributed/PWID/year	27	200	300
5	**Testing services**	% HBV-infected diagnosed	9%	30%	90%
		% HCV-infected diagnosed	20%	30%	90%
	Treatment	% diagnosed with HBV on treatment	8%[b]	–[c]	80%[d]
		% diagnosed with HCV started on treatment	7%[b]	–[c]	80%[d]

HEPB3: three doses of hepatitis B vaccine; PMTCT: prevention of mother-to-child transmission; PWID: person who injects drugs
Source: WHO, including commissioned work, United Nations, UNICEF and one published study *(73)*

a Interventions to prevent the mother-to-child transmission of HBV

b Less than 20% of persons living with HBV infection are eligible for treatment with antinucleos(t)ides available today.

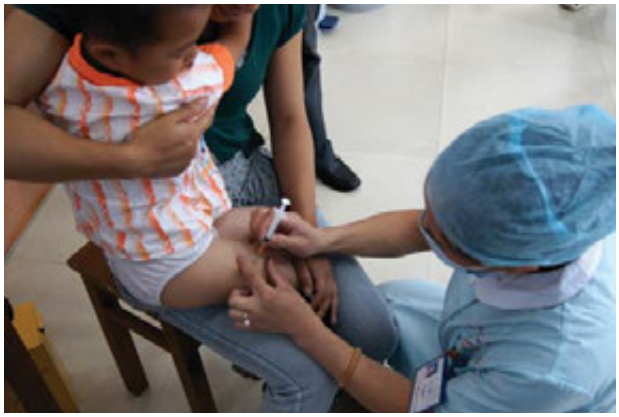
c 5 million treated for HBV and 3 million treated for HCV (cumulative targets)

d Of those eligible for treatment

SERVICE COVERAGE OF CORE INTERVENTIONS

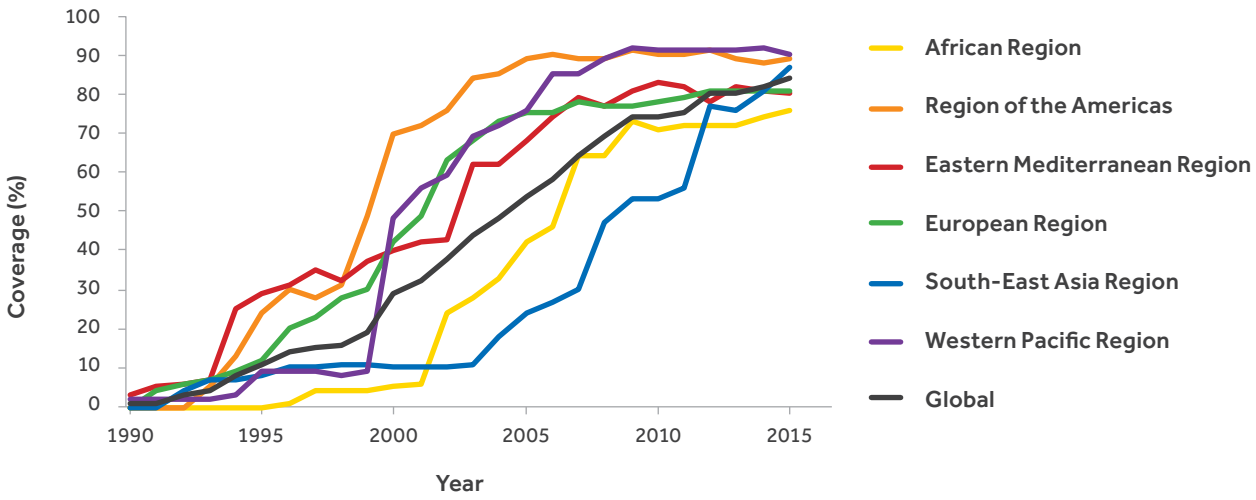
COVERAGE OF THIRD DOSE OF HEPATITIS B VACCINE HAS INCREASED, BUT NOT ENOUGH

In 2015, the global coverage with the third dose of hepatitis B vaccine reached 84%, which is not far from 90%, the 2020 target of the GHSS on viral hepatitis (Fig. 4). This high coverage explains the major reduction in the incidence of chronic HBV infection in children below the age of 5 years (*see* Chapter 2. Epidemiological update: increasing mortality calls for action). However, there are regional differences in coverage. The African, Eastern Mediterranean and European regions remain below the global average. Furthermore, national and subnational data often suggest that vaccination coverage varies between and within countries.



08 – Hepatitis B immunization in China.

Fig. 4. Three-dose hepatitis B vaccine coverage, by WHO region, 2000–2015: a major increase in coverage at the beginning of the 21st century



Source: Joint UNICEF–WHO reporting form

Progress has been made since 1992, when the World Health Assembly formulated a resolution recommending the inclusion of hepatitis B vaccine in the EPI by 1997 (WHA 45.17) *(1)*.This resolution paved the way for nations to incorporate hepatitis B vaccine into their national immunization programmes. In 2015, 185 of 194 WHO Member countries (95%) had included hepatitis B vaccine in the EPI. An additional nine countries used schedules that started later in life or that targeted high-risk populations. Between 1990 and 2015, hepatitis B vaccine coverage in infants increased from 1% to 84% (WHO–UNICEF joint reporting form data), in part due to the support of the Global Alliance for Vaccines and Immunization *(74)* and to facilitated procurement through the revolving fund of the Region of the Americas.

PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HBV REMAINS LOW IN FOUR REGIONS

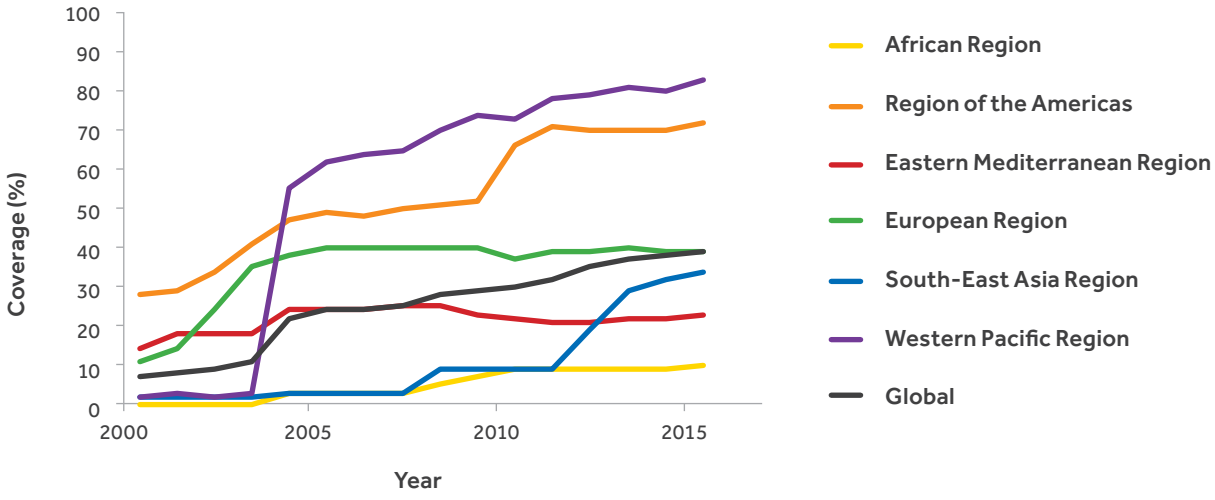
Following the progressive evolution in 2004 *(75)* and in 2009 *(1)* of the global WHO recommendation to start hepatitis B immunization at birth, coverage of the birth dose increased, reaching 39% globally in 2015 (Fig. 5). In 2015, the birth dose of hepatitis B vaccine remained the cornerstone of prevention of transmission of HBV from mother to child. Ideally, the birth dose should be given within 24 hours of birth. However, the exact timing of administration of the birth dose is not clear as it is not always readily reported. While a birth dose can still be partially effective against mother-to-child transmission

even if given more than 24 hours after birth, the effectiveness reduces with the passage of time *(76)*. In 2015, coverage with the birth dose exceeded 70% only in the Region of the Americas and the Western Pacific Region. In the African Region, a region highly endemic for HBV infection, the 2015 coverage was 10%. In some countries of sub-Saharan Africa, coverage with three doses is high but that with the birth dose remains low *(77)*. Prevention of mother-to-child transmission of HBV is particularly important in Asia, where the total number of women of childbearing age is large and many mothers have HBV infection with a high viral load. This high viral load is reflected by a specific marker of HBV infection called hepatitis B e antigen (HBeAg).

In the absence of the universal birth dose or other effective interventions, the risk of transmission from the mother to the child remains a major source of chronic liver disease when infected children become adults *(78)*. Efforts to deliver hepatitis B vaccine as soon as possible after birth, as well as increasing the number of births in health-care facilities and preventing mother-to-child transmission of other pathogens such as HIV and syphilis, should all be integrated. In the short term, administration of the birth dose needs to be scaled up worldwide, particularly in Africa. In the intermediate- and longer term, testing pregnant women for HBsAg and treating those HBV-infected before delivery will prevent transmission around birth *(21)*. The concept of "triple elimination" of mother-to-child transmission of HIV, syphilis and HBV *(79)* could then be considered as an incremental intervention for countries that have achieved high coverage of the timely birth dose.

09 – The first dose of hepatitis B vaccine needs to be given as soon as possible after birth, ideally within 24 hours.

Fig. 5. Hepatitis B birth dose coverage, by WHO region, 2000–2015: good progress in the Region of the Americas and Western Pacific Region



Source: Joint UNICEF–WHO reporting form

10 – Blood transfusion safety has improved since it was made a priority in 2000.

UNSAFE HEALTH CARE, INCLUDING BLOOD AND INJECTION SAFETY

Unsafe health care is an effective mode of HBV and HCV transmission. With respect to HBV, universal vaccination now protects most children in whom new infections could be a source of chronic liver disease, but health-care-associated infections remain a preventable source of acute hepatitis B in unvaccinated adults. With respect to HCV, health-care-associated infections add to the number of those chronically infected. Among all possible sources of health-care-associated transmission (e.g. dialysis, surgery, dental care), the GHSS includes blood and injection safety as a core intervention.

Unsafe blood transfusion is still a concern

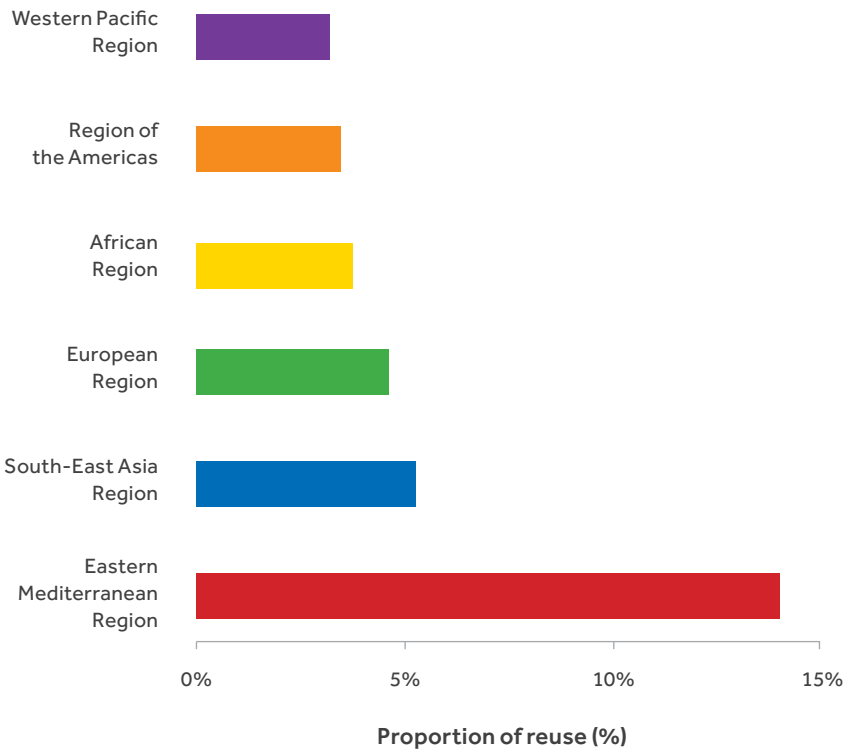
Since 2000, WHO has identified blood safety as a major public health priority *(3)*. The proportion of donations from voluntary non-remunerated donors increased from 54% in 2008 to 65% in 2013 *(80)*. In 2013, among the 137 countries that reported data on this indicator to the Global Database on Blood Safety, 97% were screening all blood donations using basic quality procedures, which included documented standard operating procedures and participation in an external quality assurance scheme. Among the low-income countries that reported data, 34% of blood donations were not screened using basic quality procedures *(80)*. Further, eight countries reported not being able to test 100% of the blood collected for HBV, and 12 countries reported not being able to test 100% of the blood collected for HCV *(80)*, often because of an irregular supply of test kits. In 2016, WHO published two guidance documents on haemovigilance *(81)* and external quality assessment programmes *(82)*. Unsafe transfusion is not a major source of HCV or HBV transmission at a population level *(66)*, because blood transfusions are an uncommon event in a person's life compared with other unsafe health-care exposures, such as dental treatment or injections *(83–85)*. However, unsafe blood transfusion is still a concern, especially in low- and middle-income countries, where the prevalence of transfusion-transmissible infections is high, and quality and coverage of blood screening are inadequate *(86, 87)*.

Unsafe health-care injections remain a driver of the epidemic

The Global Burden of Disease (GBD) 2000 study suggested that unsafe health-care injections were a major source of HCV infection. At that time, 30% of injections were given with injection equipment that had been reused without being sterilized. This accounted for about 30% of new HBV infections and 40% of new HCV infections *(83)*. Since 2000, substantial efforts have been made by the international community, under the leadership of the Safe Injection Global Network, to reduce the risks associated with unsafe injections. In 2010, worldwide, 5% of health-care injections were given with unsterilized, reused injection devices (Fig. 6) *(73)*, which caused 315 000 and 1 679 000 new HCV and HBV infections worldwide, respectively *(40)*. Progress in reducing unsafe health-care-associated injections was uneven across all WHO regions. According to 2010 data, health-care injections remained particularly unsafe in some countries of the Eastern Mediterranean Region, with 14% reuse still detected and a large number of unsafe injections per capita. The South-East Asia Region remains an area of concern with an average 5% reuse. In addition, the excessive use of injections to administer medications is a matter of concern *(40, 88)*. Coupled with poor injection practices, injection overuse accelerates transmission. This persisting driver of transmission needs to be addressed through safer health care, introduction of reuse-prevention devices *(89)* and a reduction in unnecessary health-care injections, particularly in the Eastern Mediterranean and South-East Asia regions. More recent data are also needed to monitor the evolution of injection safety since 2010.

11 – Prevention of injection-associated infections is about reducing injection overuse and making injections safe.

Fig. 6. Proportion of health-care injections given with equipment reused without sterilization, by WHO region, 2010: problems persist specifically in the Eastern Mediterranean and South-East Asia regions



Source: Pepin at al. *(40)*

HARM REDUCTION INTERVENTIONS AND SERVICES

WHO, UNODC, UNAIDS and the World Bank estimate *(90)* that in 2015, globally, there were 11.8 million persons who inject drugs (0.25% of the world population)*(91)*. Harm reduction includes, but is not limited to, distribution of sterile needle and syringes to people who inject drugs *(92)*. Implementation of harm reduction interventions for people who inject drugs is inadequate. The critical indicator of the number of syringes distributed annually per person who injects drugs falls short (27 syringes/person who injects drugs/year) of the 2020 target of 200 syringes/year/person who injects drugs. These data are from a review published in 2010 *(93)*, which is currently being updated. Ideally, the value should be at the 2030 target, which is 300 syringes/year/person who injects drugs (Table 6). However, only 26% of countries have the information that would allow them to monitor the situation. The substantial size of the population of people who inject drugs and their poor access to harm reduction services explains why injection drug use remains a key factor of HCV transmission in many countries. Overall, there is a need to scale up harm reduction services and implement policies that address stigma/discrimination *(94)*.

Table 6. Size of the population injecting drugs and harm reduction indicators, by region: major gaps towards targets of the global strategy

WHO region	Size of the population injecting drugs			Proportion of countries with needle and syringe programmes (%)[b]	Needle and syringe distribution[c] *(93)*	
	Number[a] (millions)	Prevalence (%) in the population 15–64 years	Proportion of countries reporting data on PWID (%)		% of countries with data[d]	Median # of syringes/ PWID/ year[e]
African Region	0.52	0.1	30	11	2	6
Region of the Americas	2.75	0.42	34	26	9	22
Eastern Mediterranean Region	0.92	0.23	43	38	14	25
European Region	3.97	0.66	92	91	58	59
South-East Asia Region	0.56	0.04	82	55	55	29
Western Pacific Region	3.03	0.23	33	33	26	57
World	11.75[f]	0.25	**53**	**36**	**26**	**27**

a UNODC. World Drug Report 2017 (forthcoming, to be released on 22 June 2017). (For countries not reporting data on people who inject drugs [PWID], the regional prevalence was used to extrapolate the PWID population size.)

b This refers to the proportion of countries in the region with at least one operational needle and syringe programme (NSP) (Reference: The global state of harm reduction 2016. Harm Reduction International. (https://www.hri.global/contents/1739).

c The data on needle–syringe distribution is poor and not recent – this review is currently being updated and will be published towards the end of 2017.

d Countries reporting NSP and reporting data on the number of needles–syringes distributed

e The median among those countries reporting NSPs and data on number of needles–syringes distributed

f This total excludes countries and territories not classified as full WHO Member States.

TESTING AND TREATMENT

Various approaches can be used in countries to test persons for infection with HBV or HCV. These range from testing in highly affected populations to testing in the general population, sometimes with a focus on persons in older age groups (a strategy referred to as "birth cohort" approach). In 2016, WHO published a policy brief on guidelines for testing persons for HBV and HCV infection *(62)*. This was followed by publication of the full guidelines in early 2017 *(95)*. These guidelines describe how to test, who to test and how to make sure that persons tested are referred to care. Interventions that should be considered to promote uptake of hepatitis testing and linkage to care include peer and lay health worker support in community-based settings, reminders to providers and provision of hepatitis testing as part of integrated services within mental health/substance use services *(96)*.

Cascade of care for HBV

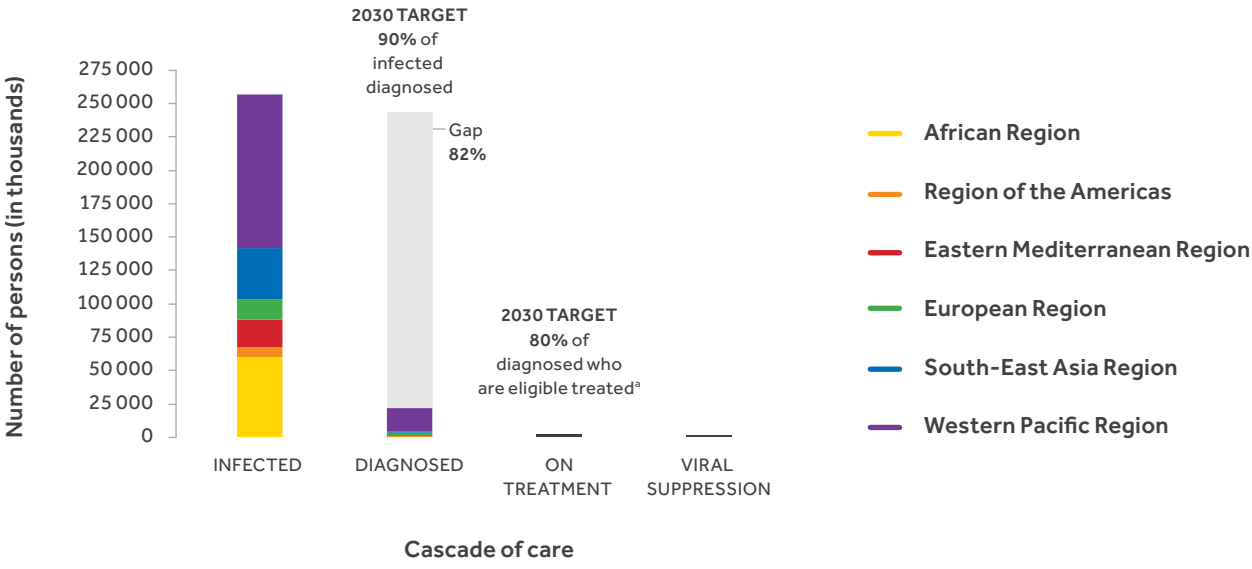
Since 1985, treatment for HBV infection became possible and progressively improved, first with interferon and, more recently, with the advent of newer medicines. Various antiviral agents are registered for the treatment of HBV in high-income countries. In 2015 *(22)*, WHO formulated a recommendation to include nucleos(t)ide analogues with a high barrier to resistance (i.e. tenofovir, entecavir). These are easier to administer (one pill a day), more effective, have less side-effects and induce less resistance. However, they seldom result in cure. Therefore, at present, long-term (potentially lifelong) therapy is required for the majority of patients. Following the formulation of the guidelines, WHO worked to disseminate these guidelines through regional workshops and translations.

In 2015, of the 257 million persons living with HBV infection, 9% (22 million) knew their diagnosis (Fig. 7). Of those diagnosed, the global treatment coverage was only 8% (1.7 million) in 2015. However, among the 22 million diagnosed, the proportion of persons eligible for treatment is unknown. Once on treatment, adherence to treatment influences the proportion of patients with viral suppression *(97)*.

12 – Diagnosis of hepatitis can be made with oral fluids, without a blood test.

13 – Most medicines for HBV or HCV infection can be administered orally.

Fig. 7. Cascade of care for HBV infection, by WHO region, 2015: effective treatment is underused in most regions



Source: WHO estimates, conducted by the Center for Disease Analysis. *See* Annex 2.

[a] As the proportion of persons eligible for treatment among those diagnosed is unknown, the treatment gap cannot be calculated.

BOX 2. PROLIFICA: A PILOT APPROACH TO TESTING AND TREATMENT FOR HBV INFECTION IN THE GAMBIA

The Gambia (West Africa) introduced hepatitis B vaccination in 1986, earlier than in many other countries. Despite this, chronic HBV infection remains common in the country: 9% of the adult general population is infected. The PROLIFICA (Prevention of Liver Fibrosis and Cancer in Africa) research study provided data on the feasibility and cost–effectiveness of population-level screening and treatment for HBV infection. As part of the PROLIFICA project, people have been tested and referred to care using two approaches *(23)*. First, during community-based testing activities, 69% of 8170 individuals who were approached accepted to be tested. Of those tested, 8.8% were infected with HBV. Of those infected, 81% were linked to care. Second, persons coming to donate blood were tested. Of the 6832 donors, 81% were tested, and 13% were infected with HBV. Forty-two per cent of infected persons were linked to care. Only less than 10% needed treatment *(98)*. After a year of treatment, 91.5% had viral suppression. Overall, in the Gambia, community screening was cost effective *(99)*. The project can now be considered for scaling up, although further negotiations are needed on the pricing of diagnostics and medicines, as well as improvements in the supply chain.

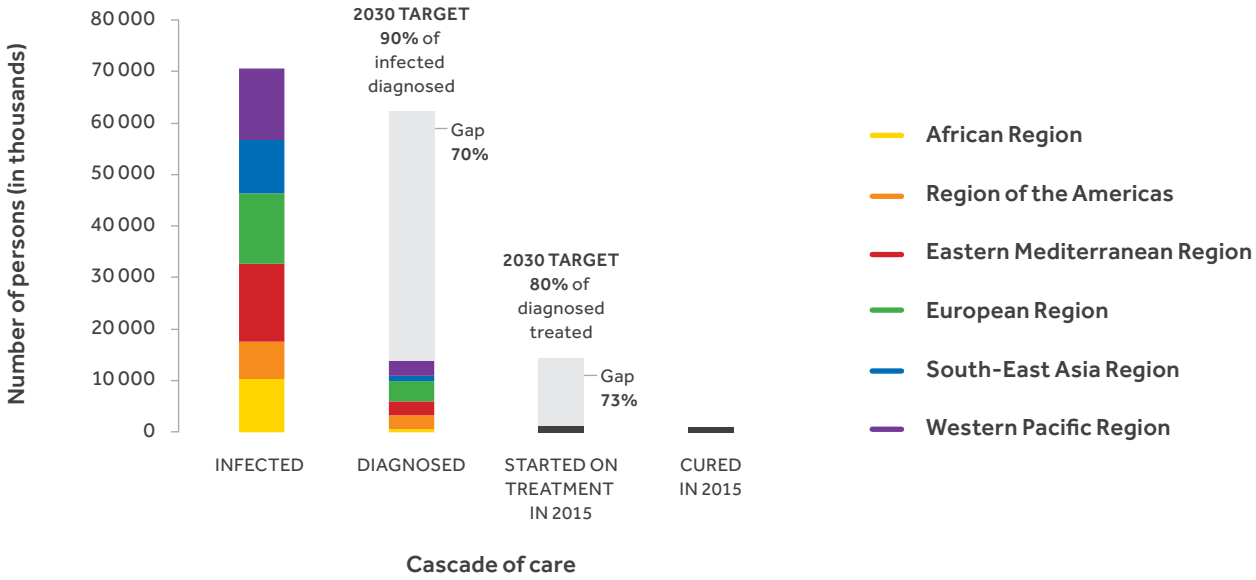
Cascade of care for HCV

In the decades following the discovery of HCV in 1989, the treatment of persons with HCV infection became possible. The first HCV treatments were based on various types of interferon. The addition of ribavirin, an antiviral drug, increased cure rates. However, treatments based on interferon/ribavirin were poorly tolerated, associated with severe adverse effects, and resulted in cure rates of between 40% and 65%, depending on various factors. A dramatic improvement in HCV therapy followed the introduction of oral medicines that directly inhibited the replication cycle of HCV, called direct-acting antivirals (DAAs). In 2013, sofosbuvir was registered in the United States of America. DAAs are usually used in combination. As of October 2015, eight separate DAAs had been approved for the treatment of persons with HCV infection. WHO released its first guidelines on HCV treatment in 2014 *(100)*, and updated these in 2016 *(54)*.

Access to HCV treatment is improving, but remains limited. In 2015, of the 71 million persons living with HCV infection globally, 20% (14 million) knew their diagnosis. The Region of the Americas had the highest proportion of those diagnosed (36%), while the African Region had the lowest (6%, Fig. 8). Worldwide, 7% of those diagnosed (1.1 million) were started on treatment in 2015. The Eastern Mediterranean Region accounted for the largest proportion of those started on treatment (12%), boosted by the large-scale elimination plans in Egypt *(101)*. Of those started on treatment in 2015, about half received DAAs. Given that more people were initiated on treatment the following year, in 2016, the WHO global report on access to hepatitis C treatment estimated that about 1 million persons had accessed DAAs in selected countries *(102)*. However, there is wide variation in terms of access to DAAs from country to country. For example, in 2015, the HCV elimination programme in Egypt was based on the use of DAAs.

Globally, over the years, the cumulative number of those placed on treatment reached 5.4 million persons in 2015. Most of the patients treated before 2015 received older treatments, primarily interferon-based therapies. Of the persons that completed treatment in 2015, it is projected that 80% (843 000) overall achieved a sustained virological response (SVR). The projected proportion of those with an SVR was highest in the Region of the Americas (88%) and lowest in the Western Pacific Region (63%). These regional differences in SVR reflect differences in access to newer DAAs.

Fig. 8. Cascade of care for HCV infection, by WHO region, 2015



Source: WHO estimates, conducted by the Center for Disease Analysis. *See* Annex 2.

LONG-TERM FOLLOW UP AND CHRONIC CARE

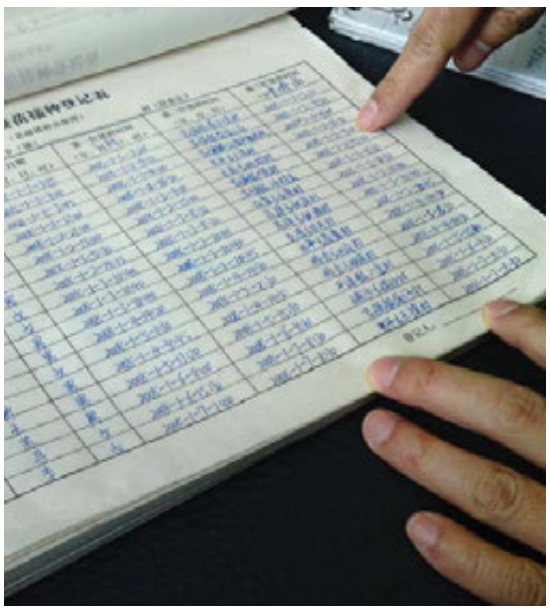
Patients with chronic hepatitis infection who do not initiate antiviral treatment or for whom treatment is unsuccessful, may require ongoing care. This care will include services such as monitoring for hepatocellular carcinoma, management of symptoms and palliative care. Monitoring the cascade of care beyond treatment will ensure that services remain comprehensive and patient-centred.

WHAT CAN BE DONE TO REACH SUFFICIENT COVERAGE LEVELS FOR ELIMINATION?

- Reaching those who have not yet been reached with hepatitis B immunization, particularly in the African, European and Eastern Mediterranean regions
- Expanding access to the birth dose of hepatitis B vaccine so that it becomes a standard of care beyond the Region of the Americas and Western Pacific Region
- Provision of safe blood and safe injections to ensure that the viruses causing hepatitis are not spread through unsafe health care
- Scaling up harm reduction services (particularly access to sterile injecting equipment and opioid substitution therapy for opioid users), with full documentation and supportive policies
- Provision of testing services to identify those who do not know their infection status
- Ensuring secure access to safe, effective treatment for those identified with infection

WHICH DATA SYSTEMS ARE NEEDED FOR MONITORING AND EVALUATION OF A NATIONAL RESPONSE?

- UNICEF/WHO reporting of immunization coverage
- Indicators of harm reduction
- Proportion of injections given with devices reused without sterilization (from health-facility surveys)
- Data on the cascade of care for HBV and HCV, from patients' databases.



14 – What gets measured gets done: register of the timing of the hepatitis B birth dose, China.

04

DELIVERING FOR EQUITY: NEED FOR A PUBLIC HEALTH APPROACH

15 – People who inject drugs continue to face stigma, discrimination and limited access to appropriate services.

KEY FINDINGS

- Within countries, some population groups differ in terms of incidence or prevalence of HBV or HCV infection. Vulnerability and needs vary also. Groups in need of specific prevention, testing, care and treatment approaches include health-care workers, persons who inject drugs, indigenous peoples and minorities, prisoners, migrants, men who have sex with men, persons coinfected with HIV and hepatitis and blood donors.
- The hepatitis C epidemic and injection drug use are two public health issues interconnected at the levels of transmission, management and mortality. Worldwide, 11.8 million persons who inject drugs are in need of prevention and treatment services. Injection drug use accounts for 1% of new HBV infections and 23% of new HCV infections. Among persons with chronic infection, 0.5% of those living with HBV and 8% of those living with HCV currently inject drugs.
- Low- and middle-income countries account for the largest proportion of persons living with HBV (96%) and HCV (72%), yet access to testing and treatment is more limited in these countries.
- To increase access and reduce health inequities, delivery of hepatitis and harm reduction services can be tailored to different populations and settings through integration, decentralization and task-shifting.

VIRAL HEPATITIS DISPROPORTIONALLY AFFECTS CERTAIN POPULATION GROUPS

A number of population groups have specific profiles in terms of incidence and prevalence, which differ for HBV and HCV. Vulnerabilities and needs also vary across groups. Disaggregated data should be used at country level to describe these populations in terms of incidence, prevalence, vulnerability and needs. This information makes it possible to focus resources where they are needed the most, and adapt services to achieve the highest impact. Groups with high incidence especially need intensified prevention services. Groups with high prevalence need improved testing and treatment services. Other individuals, communities and populations more vulnerable to hepatitis because of their poor access to appropriate health care or because they are marginalized or stigmatized need access to client-friendly care, without discrimination.

Health-care workers: protecting those at the frontline of the response

Health-care workers are at higher risk of infection with HBV and HCV because of exposure to blood and body fluids, usually through needle-stick injuries *(103)*. A safe working environment for health-care workers should include the offer of HBV immunization *(104)*. With respect to HBV, health-care workers often have a higher prevalence of serological evidence of past or present infection, which reflects a higher cumulative risk of infection during their lifetime *(105)*. With respect to HCV, the higher risk of infection does translate into a higher prevalence *(106)*, which could be taken into account while defining population groups that should be tested for HCV infection.

Persons who inject drugs: comprehensive care needed for prevention and treatment

Injection drug use affects the three components of the HBV and HCV epidemics in different ways (Table 7).

1. **New infections.** Injection drug use accounts for 1% of new HBV infections and 23% of new HCV infections. In settings with intermediate and high HBV endemicity, by the time potential drug injectors reach adulthood, most are chronically infected with HBV or were infected in the past *(107)*.
2. **Chronic infections.** A lower proportion of those with HBV infection (0.5%) are current or recent injection drug users than those with HCV infection (8%). Unlike for HCV, most adults who acquire HBV infection through injection drug use are likely to clear the infection because of their age. Testing and treatment services for those with chronic HCV infection need to link with services for the management of drug dependence, such as opioid substitution therapy, to improve treatment adherence and outcomes.
3. **Mortality.** Of all the deaths from cirrhosis and hepatocellular carcinoma, 0.9% of deaths due to HBV infection and 31% of deaths due to HCV infection are attributable to a lifetime history of injection drug use. Overall, the high incidence of HCV infection and the high probability of chronic HCV infection in persons who inject drugs mean that injection drug use explains a much larger share of viral hepatitis mortality than HBV infection. Therefore, reaching the mortality target of HCV elimination will be possible only if injection drug use is addressed from a public health perspective, within a broad policy context that includes prevention of initiation of injection drug use, prevention of stigma and discrimination, and the provision of a full spectrum of harm reduction interventions *(94)*.

Table 7. Role of injection drug use in acquisition of new infections, chronic infections and deaths from HBV and HCV, 2015

	New infections			Chronic infections			Deaths from cirrhosis and hepatocellular carcinoma		
	Total	Attributable to current injection drug use		Total	Among persons who currently inject (or recently injected) drugs		Total	Attributable to lifetime injection drug use	
	# (million)	# (million)	%	# (million)	# (million)	%	# (000s)	# (000s)	%
HBV	N/A	N/A	1.2	257	1.3	0.5	890	8.1	0.9
HCV	1.7	0.39	23.0	71	5.6	8	400	126.0	31.5

Source: Calculation based on published data *(107, 108)* (see Annex 2 at the end of this report).

In 2009, WHO, the United Nations Office on Drugs and Crime (UNODC) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) defined a package of nine interventions for people who inject drugs, which includes access to sterile injecting equipment, opioid substitution therapy for opioid users and other drug dependence treatment, and risk reduction information and education *(109)*. Opioid substitution therapy reduces the frequency of injecting behaviour, thereby reducing the transmission of bloodborne pathogens among people who use opioids. In addition, in countries with low HAV endemicity, people who inject drugs should also receive hepatitis A vaccine *(110)*. A study estimated that the investment in harm reduction in Australia will be entirely recovered in health-care cost savings by 2032 *(111)*. Mathematical modelling indicates that high service coverage for people who inject drugs will be essential for eliminating HCV *(112)*. However, in many countries, political resistance to harm reduction services, stigma, discrimination and criminalization reduce accessibility and coverage.

Indigenous peoples and minorities need adapted approaches

Indigenous populations and minorities in many parts of the world have a high prevalence of HBV infection, including peoples of the Indian Ocean (in the Andaman and Nicobar Islands of India *(113)*), the Arctic *(114, 115)*, the Americas *(116)*, New Zealand (Maori), Australia *(117)* (Aboriginal and Torres Strait Islander peoples) and in Europe (the Roma) *(118–120)*. Some indigenous communities also have a high prevalence of HCV infection *(121, 122)*. These populations are often excluded from or have poor access to health-care services, because they live in remote communities, are discriminated against or because the services are not sensitive to their cultural differences. National viral hepatitis plans need to include specific strategies to facilitate access to prevention, care and treatment for indigenous populations and minorities. Box 3 provides an example from the Amazon region of the Americas *(123)*.

BOX 3. HEPATITIS B AND D AMONG INDIGENOUS PEOPLES OF THE AMAZON BASIN

The Amazon Basin is home to some 385 indigenous groups, totalling approximately 33 million people in nine countries of the Americas *(124)*. These groups are marginalized and live under difficult social and economic conditions. Endemicity of HBV infection in the Amazon Basin is intermediate to high. Prevalence ranges from 1% to over 14% among different indigenous populations and age groups *(123)*. Wide-scale implementation of universal infant hepatitis B vaccination helped to lower the prevalence of HBV infection in several countries of the Amazon Basin *(125)*. Studies have reported reductions in prevalence in indigenous peoples over the past decade. Timely coverage with birth dose vaccination among indigenous peoples varies within countries and communities. Indigenous peoples also have a high endemicity of HBV infection and HDV superinfection *(123)*. HDV prevalence among HBV-infected persons ranges from 7% to 42% *(126, 127)*. Family outbreaks of fulminant hepatitis have been reported in small villages of the western Brazilian Amazon region *(127)*, in other areas of Brazil and Ecuador *(128)*.

Prisoners: higher prevalence in a vulnerable population

In most countries, the prevalence of HBV and HCV infection among prisoners is higher than the prevalence in the general population *(129)*. The overrepresentation of people born in countries with higher endemicity (HBV), other ethnic minorities (HBV) and the higher frequency of injection drug use (HCV) among prisoners may explain this higher prevalence *(130, 131)*. Prisoners are a vulnerable population in need of comprehensive hepatitis prevention, testing and treatment services *(132, 133)*.

Migrants: higher prevalence among persons who struggle to access health care

Persons may migrate from countries with a high prevalence of HBV or HCV infection to countries with a low prevalence. In the European Union, migrants account for an estimated 25% of persons living with HBV and 14% of persons living with HCV. This is higher than the proportion of migrants in the total population, which is 5% for migrants from countries with intermediate and high HBV endemicity, and 8% for migrants from countries with high HCV endemicity. Despite a high prevalence of chronic infection among migrants, the risk of transmission to the population in their countries of arrival is likely to be low since HBV and HCV are not transmitted through casual contact *(134)*. However, given the difficulties migrants face in accessing health care, hepatitis-specific prevention and care services should focus on migrant populations, and provide accessible opportunities for timely testing and treatment.

Blood donors: missed opportunities to link donors diagnosed with hepatitis to care

In voluntary, non-remunerated blood donors recruited with effective education and selection programmes, the prevalence and incidence of HBV and HCV infection should be lower than in the general population. Despite a lower prevalence and incidence, screening of blood donors may lead to tests that are positive for HBV or HCV infection. Globally, an estimated 1.6 million units are discarded annually due to the presence of markers for transfusion-transmitted infections, including HIV, HBV, HCV and syphilis *(80)*. However, donors with reactive tests are not always managed appropriately. Following confirmatory tests, they should either be returned to the pool of blood donors (if not infected) or be further assessed for treatment (if infected) *(135)*.

16 – Viral hepatitis testing in the Amazon, Brazil.

SPECIFIC POPULATION GROUPS DIFFER IN TERMS OF INCIDENCE, PREVALENCE, VULNERABILITY AND NEEDS.

Men who have sex with men: higher risk of HAV and HBV infection, and recent reports of HCV infections

Men who have sex with men are at higher risk of HAV and HBV infection *(136)*. In addition, an increased incidence of HCV infection has been reported among those who are HIV-infected *(50)*. Where feasible, men who have sex with men should be considered for hepatitis B catch-up vaccination *(1)*. In countries with low HAV endemicity, they should also receive hepatitis A vaccination *(110)*. Since HBV infection acquired during adulthood uncommonly leads to chronic infection, the prevalence of chronic HBV infection among men who have sex with men is unlikely to differ from the prevalence in the general population. With respect to HCV infection, HIV-positive men who have sex with men would benefit from testing for HCV infection, and more extensive risk behaviour counselling and targeted HCV prevention services, as well as access to treatment.

Coinfection

Persons with HIV–HBV or HIV–HCV coinfection are at risk for accelerated disease progression, stigma and, in some instances, compromised access to health services. They may also belong to population groups that are stigmatized because of injection drug use or sexual behaviours.

MEASURING HEALTH INEQUALITIES AMONG VULNERABLE POPULATIONS

Monitoring the indicators of the cascade of care for population subgroups ensures that the response addresses all those in need. Information on access to hepatitis care disaggregated by population subgroups is limited and mostly available from high-income countries (although it would be relevant everywhere). Investigators have examined the cascade of care for HBV and that for HCV from two different approaches. Cross-sectional methods look at the overall population *(137)* and examine whether everyone progresses in the same way along the cascade of care. They can provide information on specific subgroups if data are disaggregated according to specific characteristics (e.g. injection drug use *(138)*), health insurance coverage or minority group status *(139)*). Cohort methods tend to be used by those who provide services to these specific populations. Therefore, persons included in cohort cascades are only those who are able to access these services, including transition clinics for individuals recently released from incarceration *(140)*, community-based services for persons who inject drugs *(141)* and dedicated health services for indigenous peoples *(142)*.

17 – Unique identifiers can protect confidentiality while facilitating data management.

VIRAL HEPATITIS DISPROPORTIONALLY AFFECTS PEOPLE LIVING IN LOW- AND MIDDLE-INCOME COUNTRIES

Viral hepatitis affects persons in all countries and from all income levels. However, low- and middle-income countries account for the highest burden and face the greatest challenges in scaling up testing and treatment for affected populations.

LOW-INCOME COUNTRIES HAVE A HIGHER BURDEN OF HBV INFECTION, BUT LIMITED AVAILABILITY OF TESTING AND TREATMENT[a]

The prevalence and incidence of HBV infection are 7.4 and 9.2 times higher, respectively, in low-income countries than in high-income countries. However, the proportion of diagnosed individuals decreases from 18% in high-income countries to 0.8% in low-income countries. Among those diagnosed, the proportion accessing treatment also decreases from 14% in high-income countries to 9% in low-income countries.

LOW- AND MIDDLE-INCOME COUNTRIES HAVE LIMITED AVAILABILITY OF TESTING AND TREATMENT FOR HCV INFECTION[b]

High-, middle- and low-income countries do not differ in terms of incidence or prevalence of HCV infection. However, most persons living with HCV infection live in middle-income countries because most of the world's population lives in middle-income countries. The proportion of persons infected with HCV who are diagnosed is higher (46%) in high-income countries than in low- and middle-income countries (6%). Annual rates of treatment initiation are also higher in high-income countries (8%) than in middle-income and low-income countries (2%). In 2015, access to DAAs was difficult in low- and middle-income countries; therefore, projected cure rates were lower in low- and middle-income countries than in high-income countries. The access patterns are, however, changing rapidly with the decreasing prices of generic formulations.

A PUBLIC HEALTH APPROACH WILL INCREASE ACCESS AND REDUCE HEALTH INEQUITIES

A public health approach balances the best possible standards of care with the feasibility of implementation. This approach uses evidence-based, simplified, standardized, effective, affordable methods that can be scaled up, including in resource-limited settings. Given the limited resources in low- and middle-income countries, elimination of viral hepatitis will be possible only by following a public health approach that strengthens the health system and not through establishing new disease-specific programmes. This approach alone can go beyond individual benefits and reach the largest number of persons possible to reduce inequities. The hallmarks of robust and flexible health systems are:

- **a strong health information system;**
- **efficient service delivery models;**
- **adequate numbers of an appropriately trained workforce that is well distributed and has the appropriate skills mix (Box 4);**
- **reliable and uninterrupted access to essential medical products and technologies;**
- **adequate health financing;**
- **strong leadership and governance.**

a WHO estimates conducted in collaboration with LSHTM, data not shown

b WHO estimates conducted in collaboration with Center for Disease Analysis, data not shown

BOX 4. TASK-SHIFTING TO DECENTRALIZE CARE CAN INCREASE EQUITY, REDUCE COSTS AND ENSURE THE QUALITY OF HEPATITIS SERVICES IN SOME SETTINGS

Telemedicine distance-learning systems can expand the capacity to treat chronic hepatitis *(143)*. Models have been proposed based on four pillars: (i) use of technology to leverage scarce resources; (ii) sharing best practices to reduce disparities; (iii) mastering complexity through case-based learning; and (iv) monitoring outcomes. Telemedicine distance-learning systems build capacity among physicians, physician assistants, nurse practitioners, nurses, community health workers, and other health-care professionals so that patients are treated by local providers they already know and trust. Videoconferences can be accessible through most platforms, including cellular phones. Capacity-building sessions can include a brief lecture, guided practice and mentoring through case-based learning. In addition to addressing viral hepatitis, they can also touch on substance use disorders, which can help in integrating services for patients *(144)*. Telemedicine distance-learning systems have been used in more than 110 academic medical centres in over 20 countries, including Egypt, India, Georgia, Kazakhstan, Kenya, Namibia, Tanzania, Ukraine and Viet Nam. Evaluation has indicated that the outcome of patients treated by providers trained using these methods is no different from the outcome of patients treated by specialists *(145)*. Further, such task-shifting reduces disparities in treatment practices, increases access, including in prisons and rural areas, improves quality and reduces costs.

Interventions for addressing hepatitis are most effective when they are tailored to specific populations and settings, and implemented within social, legal and policy frameworks that enable all people to access and use services.

HOW CAN A PUBLIC HEALTH APPROACH REDUCE INEQUITIES?

There are differences between and within countries in terms of incidence, prevalence, vulnerable populations and capacity to respond. The highest burden from viral hepatitis is found in low- and middle-income countries. Eliminating hepatitis will be possible if these countries follow a public health approach that strengthens health systems and reduces inequities. Progress in reducing inequities can be measured by disaggregating incidence, prevalence and service coverage data at country level for specific populations. Hepatitis services should be prioritized for those populations with a higher incidence, prevalence and/or increased vulnerability, and adapted to specific needs.

05

FINANCING FOR SUSTAINABILITY: MAKING ELIMINATION AFFORDABLE

18 – NOhep: a global movement to call for action.

KEY FINDINGS

- There is currently limited funding available at the international level to support national hepatitis elimination plans. Therefore, countries will need to finance most of their response through domestic sources. Economic analyses can be used to make an investment case.
- The prices of medicines and diagnostics are the key drivers that influence the economic analysis of viral hepatitis elimination plans.
- WHO-recommended treatment for HBV infection is available as generics in most low- and middle-income countries and costs as little as US$ 48 for a year of treatment. The prices of WHO-recommended DAAs for HCV vary substantially (US$ 200–45 000 for a curative course), but prices have been falling rapidly, and most low- and middle-income countries should be able to procure generic medicines at affordable prices.
- The cost of prequalified serological tests used to identify those with HBV and HCV infection varies from US$ 0.5 to US$ 3. Nucleic acid tests that are required to make treatment decisions are more expensive (US$ 25–200), and need to be made available at lower cost.
- There are opportunities for the public sector to procure medicines and diagnostics on the international market at low cost. When this is the case, treatment can be cost effective, or even cost-saving, from a health-care perspective.

THE ECONOMICS OF ELIMINATION OF VIRAL HEPATITIS ARE CHANGING

New treatments for HBV and HCV infection offer new opportunities. However, the costing, budgeting and financing of viral hepatitis services have changed. New medicines and diagnostics bring additional costs, but they can lead also to savings, improved health outcomes and increased productivity.

CURRENT INVESTMENTS IN HEPATITIS REMAIN LIMITED

In 2017, despite the large burden of disease, investments in hepatitis remain limited at the national and international levels when compared with some other major infectious diseases.

FUNDED NATIONAL PLANS: MOSTLY IN HIGH-INCOME COUNTRIES, BUT ALSO IN A FEW LOW- AND MIDDLE-INCOME COUNTRIES

At the national level, apart from high-income countries that have formulated national elimination plans, such as France, Australia and the United States, the number of low- and middle-income countries that have currently secured funds for a scaled-up response is limited. However, a number of high-burden countries have elaborated financing plans that include testing and treatment, including Brazil, Egypt, Georgia, Mongolia and Myanmar. In the absence of financing plans in many countries, patients organize themselves to procure medicines through "buyers' clubs" or, those who can afford travel, seek treatment in countries that offer medicines at low prices. These initiatives may provide access to treatment for individuals but do not secure access to quality medicines for all those who need them.

Funding an increase in HCV treatment uptake in Australia

In 2016, an economic analysis in Australia used a mathematical model to study which treatment strategies would most effectively and efficiently eliminate hepatitis C in the country, based on the WHO strategy's targets *(112)*. On the basis of the results of this analysis, in March 2016, the Australian Pharmaceutical Benefits scheme listed a number of DAAs for the treatment of hepatitis C for which it covers the majority of the drug costs. As a result, in 2016, from March to September, an estimated 25 900 persons were started on treatment, representing 11% of those living with HCV infection *(146)*.

Perspectives for universal hepatitis C treatment in France

France has a national viral hepatitis plan that addresses HBV and HCV. The plan includes reimbursement of the cost of DAAs against HCV by the national health insurance scheme *(147)*, and specific approaches to reach injecting drug users, persons in prisons, migrants and persons coinfected with HIV. Treatment of all persons infected with HCV, irrespective of fibrosis, is also considered as part of operational research.

WHO-recommended medicines for treatment of hepatitis B included under health insurance in China

More than 90 million persons are chronically infected with HBV in China. Ninety-eight per cent of the population is covered by basic health insurance. In February 2017, entecavir and tenofovir, the WHO-recommended medicines for the treatment of hepatitis B, were included in the updated national list of reimbursable medicines. The decision signifies critical progress towards universal coverage for hepatitis B treatment in the country. However, implementation is complex. Provinces and health facilities have the flexibility to make further decisions and the health insurance systems are undergoing reform. In 2018, when tenofovir comes off-patent in China, the costs of medicines are expected to drop, which should further increase treatment access.

INTERNATIONAL RESPONSE: LIMITED FUNDS AVAILABLE

The Global Fund to Fight AIDS, Tuberculosis and Malaria does not currently provide funding for the viral hepatitis response, other than for persons who also have HIV infection.

UNITAID was one of the first donors in the field of HCV to accelerate access to innovative new health products, which is at the heart of its role. UNITAID supports a number of partners with a mandate to work on HIV–HCV coinfection. These include Médecins Sans Frontières, with a project to treat HCV infection in HIV-infected people in resource-limited settings using simplified models of care, Coalition Plus to increase general awareness about hepatitis, and the Foundation for Innovative New Diagnostics (FIND), to develop easy-to-use diagnostics and facilitate diagnosis in health facilities with limited laboratory infrastructure. Together, these projects will help jump-start the cycle of demand and supply *(148)*.

In June 2016, a collaborative effort by the United States Centers for Disease Control and Prevention, WHO and the ZeShan Foundation led to the first International Roundtable Summit on Funding for Elimination of Viral Hepatitis *(149)*.

MAKING THE CASE TO INVEST IN TESTING AND TREATMENT

Economic analyses guide decision-making and determine acceptable pricing levels

Economic analyses have helped to secure additional investment for the elimination of viral hepatitis. Given the large share of commodities in the costing of the response to viral hepatitis, economic analyses can also estimate the price at which these commodities can be affordable from a health-care perspective. WHO has proposed key principles to be taken into account for cost–effectiveness analyses *(150)*. The results of such cost–effectiveness analyses can be considered along with other criteria used to allocate resources within the health sector *(151)* to set priorities within the limited budget envelope of the health system.

Economic analyses make the case for care and treatment

In Egypt, the prevalence of hepatitis C infection is very high and direct health-care costs for hepatitis already consume 4% of the total health expenditure. As indirect costs represent twice the direct costs, the total costs amount to 1.4% of the gross national product. An economic analysis, however, indicated that treating 328 000 persons with hepatitis C infection annually by 2018 with direct-acting antivirals could reduce the prevalence of infection by 94% and liver-related deaths by 75% by 2030 *(101)*. Treatment is highly cost effective from health-care perspective, and when indirect costs are taken into account, the intervention is cost-saving. Since 2015, treatment has been based on direct-acting antivirals and, as of March 2017, at least a million persons have already received treatment in the public sector (with more being treated in the private sector). Since the waiting lists for treatment have been cleared, Egypt is now actively testing in the general population as the next step towards elimination.

In the Gambia, a study examined the cost–effectiveness of a community-based programme for testing and treatment for HBV infection *(99)*. The results of the analysis suggest that this intervention is cost effective. A reduction in the prices of key commodities and stronger integration within the health-care services could make the intervention highly cost effective or cost-saving.

In India, where the cost of a curative course of HCV treatment was US$ 200 in 2016, a study examined the cost–effectiveness of hepatitis C treatment. (Aggarwal R, Chen Q, Goel A, Seguy N, Pendse R, Ayer T, Chhatwal J. Cost-effectiveness of hepatitis C treatment using generic DAAs available in India, Manuscript submitted for publication). The results of the analysis suggest that this intervention is cost-saving. Treatment is cost effective after 2 years and the threshold for cost-saving is reached after 10 years.

In China, the annual treatment for hepatitis B with branded tenofovir costs US$ 2920 per year when purchased by patients, but only US$ 360 when purchased for HIV treatment by government programmes. In addition to the reduction in human suffering, cost–effectiveness analyses indicated that at the lower price at which tenofovir could be acquired, hepatitis B treatment would be cost-saving, with a return on investment of approximately US$ 1.3 for every dollar invested *(71, 152)*. In 2017, China announced that the costs of hepatitis B treatment could be reimbursed by health insurance.

From economic analyses to financial dialogue in Mongolia

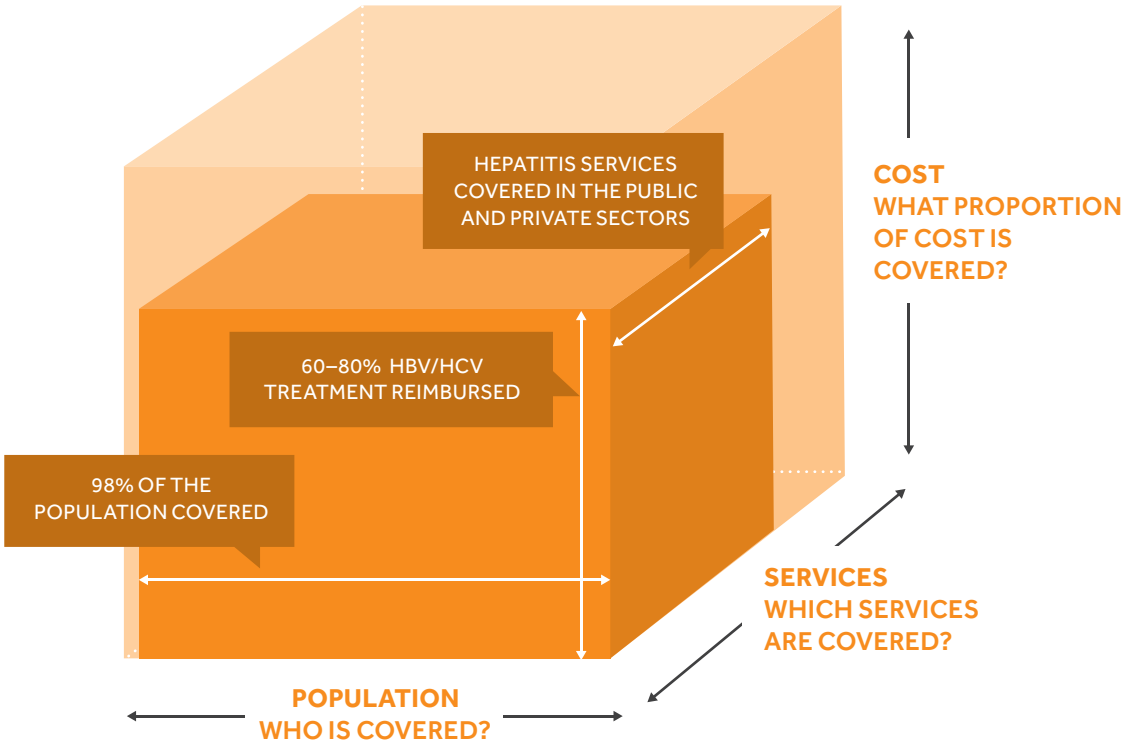
The national viral hepatitis programme in Mongolia illustrates a comprehensive approach to financing the hepatitis response, using economic analyses to advocate for adequate domestic funding, financial protection for individuals to ensure access to services, and achieving affordable prices for hepatitis medicines (Fig. 9 and Box 5).

BOX 5. INVESTMENT CASE LEADING TO REIMBURSEMENT FOR HBV AND HCV MEDICINES BY THE NATIONAL HEALTH INSURANCE IN MONGOLIA

Mongolia followed a sequential approach to financing its hepatitis response. This included making an epidemiological assessment, modelling the future impact of interventions, identifying costs, conducting economic analyses, estimating the impact on the budget and holding a financial dialogue between stakeholders. This dialogue was used to identify funding mechanisms to minimize out-of-pocket costs and determine whether the health sector could invest more in hepatitis or whether external funding sources would be needed. At the end of 2016, there were four generic companies and one originator company manufacturing HCV DAAs in Mongolia. Generic tenofovir costs US$ 84/year and generic DAAs (sofosbuvir/ledispavir) cost US$ 450/course. By the end of 2016, the Mongolian Government had included HBV and HCV medicines in the national health insurance, which covers 98% of the population. It reimburses individuals seeking treatment in both the public and private sectors. For HCV, around 60% of the cost is reimbursed (~US$ 265). However, this reimbursement is fixed so the proportion of out-of-pocket expenses will decrease as wholesale prices come down. For HBV, 80% of the cost of generic medicines is reimbursed. During 2016, around 4000 people were treated for HBV, and around 8000 people for HCV in Mongolia. The cure rate for treatment of HCV infection was 92–99%. Overall, integration of the coverage of viral hepatitis services in the national health insurance illustrates the three dimensions of universal health coverage (Fig. 9).

19 – While there is a call for action to end hepatitis, funding available remains limited.

Fig. 9. Viral hepatitis services in the three dimensions of universal health coverage in Mongolia



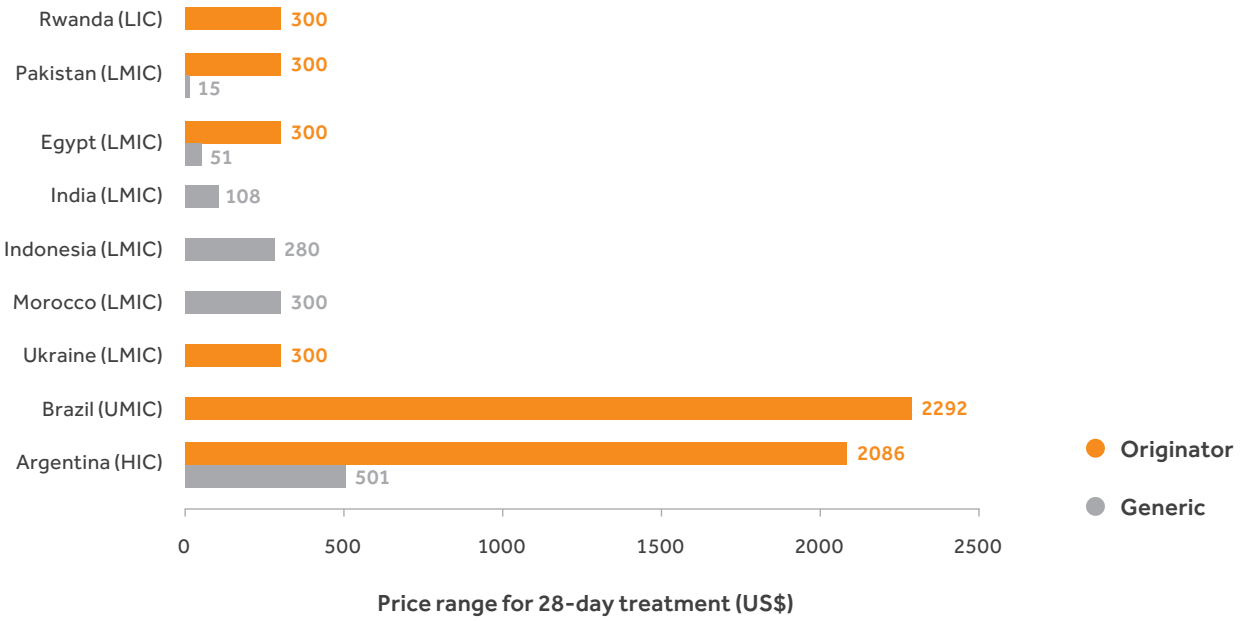
REDUCING THE PRICES OF COMMODITIES

PRICES OF MEDICINES

Prices of HCV medicines are falling but vary, and remain high in some countries

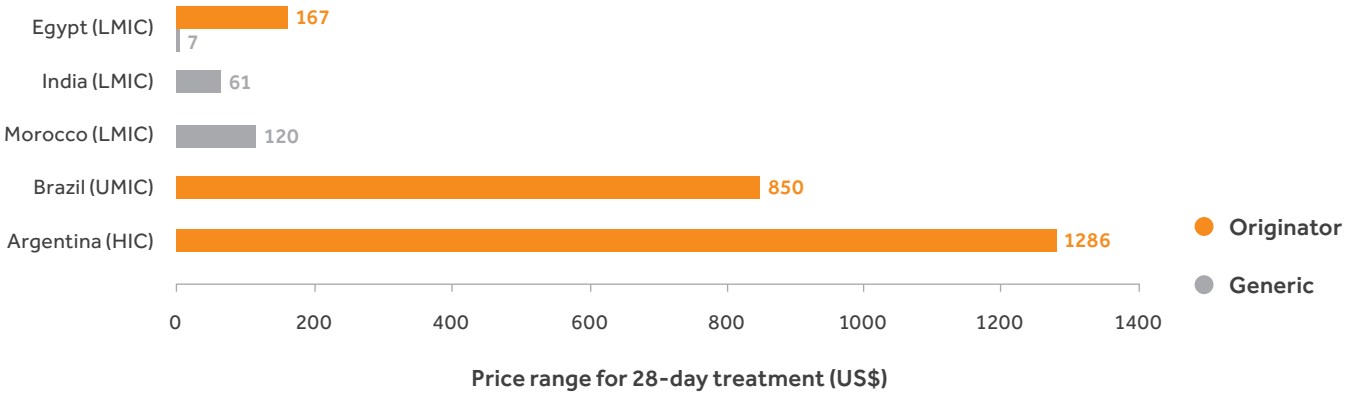
While the prices of DAAs against HCV recommended by WHO have decreased rapidly in some countries, they remain variable and are still unaffordable in others *(153)*. In 2015, the US$ forex price (with a 23% rebate) for the combination of ledipasvir/sofosbuvir ranged from US$ 68 834 to US$ 655 *(153)*. In October 2016, results of the analysis of data collected for the first WHO global report on access to hepatitis C treatment indicated that, despite challenges, some pioneering low- and middle-income countries were starting to deliver new hepatitis C treatment, reaching over one million in 2016 *(102)*. Increasing generic competition is starting to lower the prices of DAAs, which are becoming more affordable. Prices remain high in high-income countries and those middle-income countries that do not have access to generic formulations and who fall outside of license agreements, placing a heavy burden on health systems and leading to treatment rationing. As of October 2016, the lowest price reported for a 28-day supply of sofosbuvir (Fig. 10 and Fig. 11) was US$ 300 in Pakistan and Rwanda from originator companies, and US$ 15–42 in Pakistan from generic companies. The lowest price reported for a 28-day supply of daclatasvir was reported from Egypt; US$ 167 from the company that developed the medicine and US$ 7 from a generic company. Without lower prices, countries are unlikely to be able to increase investment to minimize the burden of hepatitis C. Sofosbuvir, daclatasvir and the sofosbuvir/ledipasvir combination, which are part of the preferred regimens in the WHO guidelines *(54)*, are included in the 19th WHO model list of essential medicines and in the WHO prequalification programme. However, as of March 2017, only one prequalified generic formulation was available. There are opportunities for the public sector to optimize procurement of medicines (Box 6).

Fig. 10. Reported prices (originators and generics) for a 28-day supply of sofosbuvir in selected countries, per country income group (price information updated as of November 2016)



HIC: high-income country; LIC: low-income country; LMIC: lower–middle-income country; UMIC: upper–middle-income country
Source: Global report on access to hepatitis C treatment: focus on overcoming barriers. Geneva: World Health Organization; October 2016 *(102)*

Fig. 11. Reported prices (originators and generics) for a 28-day supply of daclatasvir in selected countries, per country income group (price information updated as of November 2016)



HIC: high-income country; LIC: low-income country; LMIC: lower–middle-income country; UMIC: upper–middle-income country
Source: Global report on access to hepatitis C treatment: focus on overcoming barriers. Geneva: World Health Organization; October 2016 *(102)*

Medicines for hepatitis B are available and inexpensive in most high-prevalence countries

Since 2015, the WHO treatment guidelines for hepatitis B *(22)* recommend antinucleos(t)ides with a high barrier to resistance as first-line therapy for patients with hepatitis B who are eligible for treatment. In most patients that are eligible, the treatment is lifelong. Two medicines are available: entecavir and tenofovir. Entecavir is off-patent, but availability and costs vary widely. Tenofovir is protected by a patent until 2018 in most upper–middle- and high-income countries, where the cost ranged from US$ 400 to US$ 1500 for a year of treatment in February 2017. In most low- and middle-income countries, generic tenofovir produced by eight companies is available, and approved through the WHO prequalification programme or tentatively approved by the United States Food and Drug Administration (USFDA). While some middle-income countries (e.g. Russian Federation, China) still face patent barriers in accessing tenofovir, generic tenofovir is affordable in most countries where it is accessible. The Global Price Reporting Mechanism (GPRM) indicates that the cost for a year of quality-assured treatment was US$ 48 in February 2017. Overall, tenofovir has the potential to be more widely used in the countries where it is available as a generic (Box 6). Ultimately, generic tenofovir should be available in all retail pharmacies. However, fears of reimportation in countries where the product is more expensive could be an obstacle to such distribution mechanisms until the patent expires.

BOX 6. OPPORTUNITIES TO OPTIMIZE PUBLIC SECTOR PROCUREMENT OF MEDICINES FOR HBV AND HCV INFECTION

There are opportunities for the public sector to optimize the procurement of medicines against HBV and HCV infection at country level. Elements that can contribute to this optimization include:

Formulating national treatment guidelines that specify and recommend which medicines should be used; estimating the size of the infected population eligible for treatment; including medicines needed in the national essential medicines list; registering the medicines;[a] procuring and supplying hepatitis medicines through launching a tender to invite manufacturers to bid or purchasing through a pooled procurement mechanism.[b]

[a] Including manufacturers of generic medicines if there is no patent or if the country is eligible for voluntary licensing

[b] Examples include the strategic fund of the Pan American Health Organization and the Global Procurement Fund (GPRO fund, www.gprofund.org) that negotiates prices for products and services based on a guaranteed volume.

20 – Dispensing generic medicines in a public sector hospital, the Philippines.

PRICES OF DIAGNOSTICS

Although access to essential medicines for the treatment of persons living with hepatitis is improving, access to affordable, quality-assured diagnostics remains a barrier. The GHSS on viral hepatitis clearly spells out the need to reach out and test the population to identify asymptomatic persons living with viral hepatitis. However, this requires testing services and commodities. In a WHO-commissioned economic assessment of the cost of elimination, testing services accounted for a substantial share of the total cost *(71,72)*.

The price of serological tests used for the initial diagnosis of HBV and HCV infection is low

HBV. The reagent costs for HBsAg assays are similar for rapid diagnostic tests (between US$ 0.95 and US$ 3.00) and laboratory-based assays (between US$ 0.40 and US$ 2.80). Machines that can handle high volumes of specimens in laboratories require additional infrastructure and equipment, and precision and expertise in operation.

In contrast, rapid diagnostic tests do not require capital investment and can be performed by non-laboratory staff, such as trained health-care workers and lay providers. Up till March 2017, WHO had prequalified a number of laboratory-based assays for HBsAg, but to date, no rapid diagnostic tests have met the WHO prequalification requirements. A number of rapid diagnostic tests are unable to detect low levels of HBsAg, which limits their use for testing asymptomatic individuals.

HCV. The cost of laboratory-based tests for HCV antibodies ranges from US$ 0.50 to US$ 1.70. As for HBV, they require laboratory infrastructure and equipment. The cost of rapid diagnostic tests for HCV antibodies ranges from US$ 0.50 to US$ 2.00 for assays using capillary whole blood, and US$ 10 for assays using oral fluids. As of March 2017, WHO had prequalified a number of laboratory-based assays and two rapid diagnostic tests for HCV antibodies.

Nucleic acid tests needed for treatment decisions are still expensive

The cost of tests that quantify the nucleic acids of HBV to make treatment decisions ranges from US$ 60 to US$ 200. The cost of the tests that quantify the nucleic acids of HCV to rule in HCV infection among individuals with HCV antibodies ranges from US$ 30 to US$ 200. The laboratory equipment needed for these nucleic acid tests is also expensive. They are operated by technicians with specialized training. Countries can reduce prices by using existing infrastructure and equipment that have been used to measure HIV viral load and detect tuberculosis. For HCV, another option would be to use a simpler test that detects HCV core antigen. The cost of testing for HCV core antigen ranges from US$ 25 to US$ 50, which is comparable to qualitative HCV RNA testing (US$ 43–51). However, these high prices remain a barrier to large-scale use.

A BLOOD TEST FOR AN INITIAL DIAGNOSIS OF HEPATITIS STARTS AT

US$ 0.5.

WHAT MECHANISMS WOULD SECURE FINANCING FOR ELIMINATION?

Given the limited availability of donor funds at the global level, most national viral hepatitis elimination plans will need to be funded through national resources. This will require a robust viral hepatitis investment case to advocate for adequate allocation of resources. Where appropriate, integration with other programmes should lead to opportunities for cost and programme efficiencies. Optimized procurement of commodities through the public sector should also decrease cost, as medicines and diagnostics account for a large share of the cost.

06

INNOVATIONS FOR ACCELERATION

21 – Newer, more affordable diagnostics is a high research priority.

KEY FINDINGS

Major research and development innovations have transformed the field of viral hepatitis in recent years. Pangenotypic HCV medicines are being introduced. Products that could further accelerate elimination include newer and cheaper point-of-care virological tests for HBV and HCV, a functional cure for HBV infection (aimed for by 2020–2025), and a vaccine for preventing HCV infection.

These innovations in research and development need to be followed downstream and in sequence by (i) trials that evaluate new products for efficacy, quality and safety to seek approval of products by national regulatory authorities, and (ii) field assessments that evaluate the impact of introduction of new technologies on outcome and cost, so that innovations can reach the field as quickly as possible.

1. RESEARCH AND DEVELOPMENT IS DYNAMIC

RECENT INNOVATIONS HAVE ENABLED THE COMMITMENT TO ELIMINATION

Major innovations have occurred in the field of viral hepatitis. For hepatitis C, innovations have transformed the field and opened avenues previously thought impossible. New medicines for treating chronic hepatitis C infection have become available for use so rapidly that the first WHO hepatitis C treatment guidelines released in 2014 *(100)* were updated in 2016 *(54)* and will be updated again in 2017. Other key recent innovations have included rapid serological tests that detect antibodies to HCV and point-of-care tests for the diagnosis of HCV infection (HCV RNA). Pangenotypic HCV medicines are being introduced progressively.

NEWER PRODUCTS COULD FURTHER ACCELERATE ELIMINATION

Newer products that could accelerate elimination include newer and cheaper point-of-care rapid tests, including new ones for HBV DNA and affordable ones for HCV RNA, a functional cure for HBV (aimed for by 2020–2025) and a vaccine for preventing HCV infection. A functional cure for HBV infection could change the proportion of those infected who are eligible for treatment, with major consequences for elimination plans. In addition, there is a need for novel therapies for HDV coinfection as the net effect of HDV is to make the underlying HBV disease worse, including higher rates of cirrhosis and hepatocellular carcinoma.

2. TRIALS: INITIATIVES IN MIDDLE-INCOME COUNTRIES

Trials evaluate the efficacy, quality and safety of new technologies with a view to obtaining regulatory approval. This ensures that the new products work and are safe (Box 7).

BOX 7. A CLINICAL TRIAL IN MALAYSIA AND OTHER COUNTRIES TO EXAMINE OPTIONS FOR ALTERNATIVE TREATMENT OF HCV INFECTION

Malaysia is working with the Drugs for Neglected Diseases initiative (DNDi) on a clinical trial (NCT02961426). This trial aims to facilitate the use of cheaper medicines suited to low- and middle-income country markets. It will assess the efficacy and safety of a generic DAA (sofosbuvir) combined with ravidasvir, a new chemical entity, across all genotypes of HCV, among HCV-infected and HCV–HIV-coinfected persons. Shorter treatment schemes will be examined to facilitate future uptake and reduce cost. The treatment duration will be 12 weeks for subjects without cirrhosis and 24 weeks for subjects with compensated cirrhosis. Efficacy will be judged on the basis of virological response 12 weeks after completion of treatment. Similar trials are also planned in Thailand, South Africa and Viet Nam to obtain safety and efficacy data across all genotypes. Ultimately, the data generated from these trials should be useful for the registration of this combination of medicines in these countries, which should facilitate procurement and open the way for use on a larger scale.

3. FIELD ASSESSMENT

Through the support of UNITAID, field assessment projects evaluate the impact of the introduction of new technologies on public health outcomes, cost and cost–effectiveness. For example, once a new diagnostic (such as a point-of-care test to measure HCV RNA) has been approved for use, its impact on increasing service coverage can be quantified (e.g. by measuring how its use in the field can lead to better diagnosis and linkage to care for injection drug users approached through outreach services).

4. LARGE-SCALE DISSEMINATION AND OPTIMIZATION

Prequalification

The WHO prequalification system helps in increasing access to new medicines and diagnostics by assuring their quality and safety. As of March 2017, WHO had prequalified a number of serological tests for HBV and HCV infection, two first rapid diagnostic tests for HCV infection and generic tenofovir for the treatment of HBV infection. However, as of March 2017, only one generic DAA was prequalified. Further work is needed to ensure the large-scale availability of prequalified products.

Optimization

Research also includes work to optimize the use of technologies in health-care service delivery. Once diagnostics and medicines have been made available, the best service delivery models need to be identified to improve service coverage and maximize health outcomes.

Long-term follow up of treated patients

New treatment protocols for HBV and HCV infection need to be evaluated also in the long term through cohorts of patients. This will allow assessment of the adverse effects of treatment on patients, risk of hepatocellular carcinoma after treatment, and prognosis after treatment of patients with advanced disease.

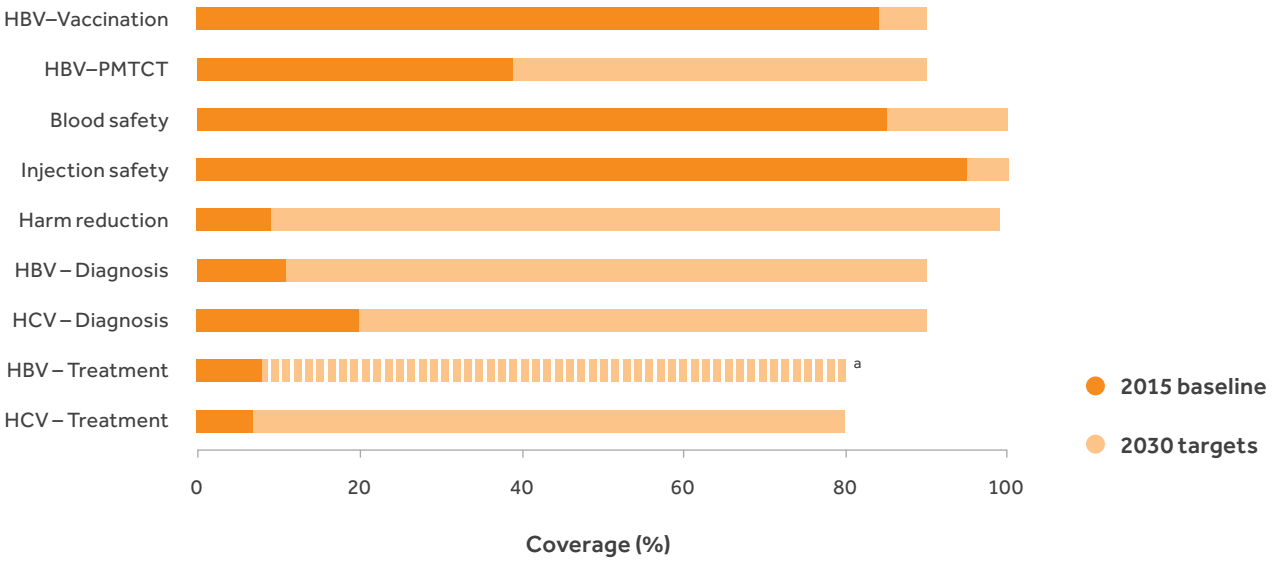
HOW CAN INNOVATIONS ACCELERATE ELIMINATION?

- Generate innovative products through research and development.
- Evaluate new products for quality and safety in view of approval by national regulatory authorities.
- Assess how new technologies improve health outcomes and reduce costs in the field.
- Disseminate and optimize new commodities and monitor their impact in terms of long-term outcomes of patients.

07

THE ROAD TO ELIMINATION BY 2030

Fig. 12. Global Health Sector Strategy on viral hepatitis: 2015 baseline towards the 2030 targets



[a] Measurement of progress on HBV treatment target currently limited by the absence of data on the proportion of persons eligible and the absence of a functional cure

22 – Collaboration between the government, civil society, nongovernmental organizations and WHO facilitates strong national elimination plans.

1. A GLOBAL PICTURE IS TAKING SHAPE BUT KEY DATA FOR ACTION ARE MISSING IN MANY COUNTRIES

In terms of strategic information, WHO is now in a position to formulate global and regional estimates for key indicators. However, many countries, lack data of sufficient quality. Strategic information systems that collect surveillance and programme data will guide elimination.

2. GAPS IN PREVENTION NEED TO BE CLOSED; TESTING AND TREATMENT NEED TO BE SCALED UP

The elimination strategy has identified the core interventions. Coverage gaps in prevention need to be closed, particularly for the birth dose of hepatitis B vaccine, health-care injection safety and harm reduction, if the target of 90% reduction in new infections is to be reached. Rapid scaling up of testing and treatment is needed to reach the 65% mortality reduction component of the elimination target.

3. EXISTING OPPORTUNITIES NEED TO BE LEVERAGED USING A PUBLIC HEALTH APPROACH THAT REDUCES INEQUITIES

Recent years have been marked by an unprecedented increase in persons who access prevention and care services for hepatitis. However, this access has been fragmented and not equitable. Only a few countries have taken proactive steps to move towards elimination using a public health approach that benefits all those in need, including populations that have limited access to health services.

4. SUSTAINABLE FINANCING OF ELIMINATION PLANS LEADS TO UNIVERSAL HEALTH COVERAGE

Universal health coverage provides an overarching framework for health in the 2030 Agenda for Sustainable Development. This requires both strong health systems and disease-specific actions. An effective hepatitis response will depend on the integration of hepatitis services into broader health programmes and funding through adequate national health budgets. Hence, the focus needs to be on improving the efficiency, reach and quality of hepatitis services, on reducing prices, and on optimizing the procurement of commodities for testing and treatment of hepatitis. National health budgets need to cover the costs, and ensure relevant services without financial hardship to the patient.

5. A DYNAMIC RESEARCH AGENDA LEADS TO NEW PRODUCTS AND APPROACHES

Research in the field of viral hepatitis has been highly active, generating new products at a rapid pace. Further innovation is needed to optimize vaccines and other prevention interventions, diagnostics, medicines, and models of service delivery, with a focus on improving efficacy, quality, safety and access, and efficiently documenting and achieving public health impact. Priorities include rolling out pangenotypic medicines for HCV and developing newer and cheaper point-of-care tests, including for HBV DNA. In the future, a functional cure for HBV and, ultimately, a vaccine against HCV infection would complete the set of tools available for elimination.

ANNEX 1. BASELINE ESTIMATES TOWARDS THE TARGETS OF THE GLOBAL HEALTH SECTOR STRATEGY

Table A1. Summary of the 2015 baseline estimates of the indicators of the global health sector strategy on viral hepatitis, by region

			Regional estimates						Global	Targets required for elimination	
	Interventions	Indicator	African Region	Region of the Americas	Eastern Mediterranean Region	European Region	South-East Asia Region	Western Pacific Region	2015 baseline	2020	2030
1	**Hepatitis B vaccination**	HEPB3 coverage	76%	89%	80%	81%	87%	90%	84%	90%	90%
2	**HBV PMTCT**[a]	HEP vaccine birth dose coverage	10%	72%	23%	39%	34%	83%	39%	50%	90%
3	**Blood safety**	Donations screened with quality assurance	80%	98%	81%	99.9%	85%	98%	97%	95%	100%
	Injection safety	Proportion of unsafe injections	3.7%	3.4%	14.0%	4.6%	5.2%	3.2%	5% *(40)*	0%	0%
4	**Harm reduction**	Syringes & needles distributed/PWID/year	6	22	25	59	29	57	27	200	300
5	**Testing services**	% HBV-infected diagnosed	0.3%	10%	2%	13%	3%	2%	9%	30%	90%
		% HCV-infected diagnosed	6%	36%	18%	31%	9%	21%	20%	30%	90%
	Treatment	% diagnosed with HBV on treatment	N/A	N/A	N/A	N/A	N/A	N/A	8%	–[c]	80%[d]
		% diagnosed with HCV started on treatment	2%	11%	12%	5%	7%	5%	7%[b]	–[c]	80%[d]

HEPB3: three doses of hepatitis B vaccine; PMTCT: prevention of mother-to-child transmission; PWID: person who injects drugs

[a] Interventions to prevent the mother-to-child transmission of HBV

[b] Less than 20% of persons living with HBV infection are eligible for treatment with antinucleos(t)ides available today.

[c] 5 million treated for HBV and 3 million treated for HCV (cumulative targets)

[d] Of those eligible for treatment

ANNEX 2. HOW WERE THESE ESTIMATES GENERATED?

ALSO SEE THE METHODOLOGICAL ANNEX AVAILABLE ONLINE AT:
http://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/

GENERAL APPROACH

WHO used systematic methods to generate the evidence consolidated in this global report on viral hepatitis. The Reference Group for Strategic Information and Modelling advised WHO on the scope of the report, its technical content and the epidemiological methods used. This included the use of Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) *(154)* checklist. The WHO department of Information, Evidence and Research systems reviewed and cleared the report.

DATA COLLECTION AND ANALYSIS

MORTALITY

To estimate the current mortality due to past infections, we used WHO global health estimates methods based on the "mortality envelope" *(2)*. In short, the proportion of sequelae (cirrhosis and hepatocellular carcinoma) attributable to HBV and HCV infections was applied to the mortality data from these sequelae obtained from vital registration services and modelling *(68, 155)*. All WHO global health estimates data are available from the WHO Internet site at: http://www.who.int/gho/mortality_burden_disease/en/.

PREVALENCE AND INCIDENCE OF HBV INFECTION

WHO commissioned the London School of Hygiene & Tropical Medicine (LSHTM) to generate estimates of the prevalence and incidence of HBV infection. LSHTM investigators conducted a systematic review of all biomarker surveys that estimated the prevalence of HBsAg in the general population before implementation of vaccination, and in children under 5 years of age after vaccination. To generate estimates in countries and territories without empirical data, modellers extrapolated the available data using mathematical models on the basis of geographical proximity to countries that had data, and income levels. In the absence of better data, the prevalence of HBsAg among children under 5 years of age was used as a surrogate indicator of the cumulative incidence of chronic HBV infection at five years of age *(8)*. This represents a slight variation from the core indicator of the monitoring and evaluation framework of the GHSS on viral hepatitis *(8)*.

PREVALENCE AND INCIDENCE OF HCV INFECTION

WHO commissioned the Center for Disease Analysis (CDA) to generate estimates of the prevalence and incidence of HCV infection. The CDA conducted a systematic review of biomarker surveys estimating the prevalence of HCV infection *(53)*. On the basis of the prevalence data, investigators constructed a country-by-country HCV infection model that predicted incidence and prevalence. In-country experts reviewed these models and provided comments and suggestions on the process, and on the outcome. Estimates for countries and territories without empirical data were extrapolated on the basis of Global Burden of Disease regional averages.

CASCADE OF CARE FOR HBV AND HCV INFECTION

WHO commissioned the CDA for estimates of the cascade of care. Investigators modelled estimates of the cascade of care for HBV and HCV infection using country-level models, sales of medicines, expert opinions from national stakeholders and extrapolations.

PREVENTION INDICATORS

To estimate the coverage of prevention interventions, sources of data included vaccine coverage reported to WHO and UNICEF *(156)*, data on the coverage of screening of blood donations reported to WHO in the Global Database on Blood Safety *(80)*, systematic reviews that estimated the frequency of unsafe injections *(40)*, and coverage of harm reduction indicators *(93)*.[a]

[a] The original GHSS indicator is the on the use of injection devices with reuse prevention features. In the absence of data on this indicator, data are presented on the proportion of unsafe injections with targets at 0% for 2020 and 2030.

COUNTRY INTELLIGENCE

To update the previous policy report *(157)*, WHO collaborated with the World Hepatitis Alliance to approach Member States and generate "country profiles". These examined inputs, processes and outputs that described the status of implementation of the GHSS on viral hepatitis, including the availability of a national viral hepatitis plan.

ROLE OF INJECTION DRUG USE IN THE EPIDEMIC OF VIRAL HEPATITIS

New infections. To estimate the proportion of new HBV and HCV infections attributable to injection drug use, we used the fraction of disability-adjusted life-years (DALYs) from acute HBV and HCV infections attributable to injection drug use in the Global Burden of Disease study, 2013 *(107)*.

Chronic infections. To estimate the proportion of chronic HBV and HCV infections among persons who currently inject drugs, we extracted the prevalence of HBsAg and anti-HCV among persons who inject drugs *(108)*, adjusted for the proportion of anti-HCV-positive persons who have HCV infection *(53)*, multiplied this prevalence by the 2015 estimates of the number of people who inject drugs worldwide, and divided this estimated number of people who inject drugs with HBV and HCV infection by the total number estimated by WHO of HBV and HCV infections worldwide.

Deaths. To estimate the proportion of deaths from the sequelae of HBV and HCV infections attributable to injection drug use, we applied the fraction of HBV- and HCV-induced cirrhosis and hepatocellular carcinoma attributable to lifetime injection drug use from the Global Burden of Disease study *(107)* to the 2015 WHO global health estimates for mortality available from the WHO Internet site (http://www.who.int/gho/mortality_burden_disease/en/).

WHY AND HOW DO WORLD HEALTH ORGANIZATION ESTIMATES CHANGE?

Estimates formulated or quoted by WHO evolve over time. In general, this is due to improvement in criteria, availability of higher-quality data, improved review methods and stronger analysis techniques. This report contains new or updated estimates from WHO. Key changes and updates are given in the following paragraphs.

HBV ESTIMATES

In the past, WHO estimated that there were 240 million persons with HBV infection in the world *(125)*. The new estimate (257 million) is not far from the previous one. It reflects that more data have been made available, that more complex methods have been used (modelling) and that the size of the population has been increasing.

HCV ESTIMATES

WHO had not formulated estimates of the number of persons living with HCV before. However, WHO quoted a number of publications that were based on the use of anti-HCV (serological evidence of past or present infection) *(158)* rather than HCV RNA (evidence of HCV infection). Use of HCV RNA as a criterion to define HCV infection is a better reflection of the public health implications of the HCV epidemic and explains a decrease in the estimates. A 2014 study estimated that 80 million persons were living with HCV infection *(159)*. The 2015 estimate published by WHO in this report in 2017 (71 million) is a small adjustment that reflects the availability of better data from large countries that substantially influence the global estimates.

MORTALITY ESTIMATES

For many years, WHO did not have a mechanism to count deaths from cirrhosis and hepatocellular carcinoma associated with HBV and HCV infection. As methods evolved to measure the proportion of cirrhosis and hepatocellular carcinoma associated with HBV and HCV infection, estimates have also progressively evolved. For the GHSS on viral hepatitis, WHO quoted estimates from the Global Burden of Disease (1.46 million deaths in 2013) *(155)*. The new estimate has been formulated by WHO (1.34 million deaths). It takes into account a recent publication on the proportion of hepatocellular carcinomas that are attributable to HBV and HCV infection *(68)*. The WHO estimate for 2015 is slightly lower than the one previously used but the trends over time, estimated retrospectively, are on the increase. The new estimate also correctly identifies the relative proportion of deaths attributable to HBV and HCV infections. The proportion of deaths from HBV is now higher than the proportion of deaths from HCV. These changes are explained mostly by the remaining areas of uncertainty regarding the fraction of cirrhosis and hepatocellular carcinoma attributable to HBV and HCV infections versus other causes of chronic liver disease, such as alcohol or the metabolic syndrome. While the exact number of deaths for a given year may change according to the methods used, an upward trend in mortality is seen, irrespective of the method used *(155)*.

CASCADE OF CARE

The GHSS on viral hepatitis was published in 2016 *(7)*. It contained approximations in terms of the proportion of infected persons diagnosed, treated, and virologically suppressed or cured. These were not based on systematic reviews. In this report, WHO for the first time makes an attempt to use the best possible data available to estimate the cascade for HBV and HCV infection.

These estimates are imperfect because the data systems that should generate them are not in place in most countries. The quantity and quality of data available are better for HCV than for HBV. In some regions, such as the African Region, data are particularly scarce. Therefore, WHO will continue to collect more data of better quality in order to update and refine these estimates.

A FRAMEWORK TO REPORT ON THE GLOBAL STRATEGY AND FROM A COUNTRY PERSPECTIVE

THE FIVE STRATEGIC DIRECTIONS OF THE GLOBAL HEALTH SECTOR STRATEGY ON VIRAL HEPATITIS

We structured this report as per the five strategic directions of the 2016 GHSS on viral hepatitis, which fits in with the context of the 2015 Sustainable Development Goals (SDGs, Target 3.3) *(16, 160)*. This framework is relevant for comprehensive reporting on the global progress of the GHSS on viral hepatitis.

THE 10 CORE INDICATORS OF THE MONITORING AND EVALUATION FRAMEWORK FOR VIRAL HEPATITIS B AND C

WHO prepared a monitoring and evaluation framework *(8)* for viral hepatitis B and C. This follows the result chain, from (a) context and needs (indicator C.1 on prevalence) to (b) input (indicator C.2 on testing capacity), (c) output and outcomes (indicators C.3–C.5 on prevention, and indicators C.7–C.8 on the cascade of care), and (d) impact (indicator C.9 on incidence and indicator C.10 on mortality). This framework is adapted more to reporting at the country level and was not used for the policy report.

REMAINING AREAS OF UNCERTAINTY

This first-ever global report on viral hepatitis describes what is known of the current status of viral hepatitis in the world. However, data systems are not in place in many parts of the world to generate the necessary strategic information. Limitations explain why this initial report provides estimates only at the regional level. They also point to the need for stronger mechanisms to collect, transfer, analyse and disseminate data on viral hepatitis.

MORTALITY IS POORLY MEASURED IN ROUTINE REPORTING AT THE NATIONAL LEVEL

Methods to estimate mortality use a combination of data from two types of sources. First, the "mortality envelope" from the vital registration, and second, the "attributable fraction" generated by clinical centres. At the global level, this method has been adopted by the Global Burden of Disease, the International Agency for Research on Cancer *(68)* and WHO. Routine systems are needed to measure this attributable fraction at the country level and to link these data with "mortality envelope" data so that in the future, sound, robust estimates can be generated, which can be accepted by all partners involved.

SOME COUNTRIES STILL LACK POPULATION-BASED ESTIMATES OF THE PREVALENCE OF INFECTION

Biomarker surveys are the reference epidemiological tool for estimating the prevalence of HBV and HCV infection. These prevalence estimates are key for planning testing and treatment. However, in the body of evidence that led to this report, reliable population-based estimates of the prevalence of HBV and HCV infection were available only from some countries. In others, regional averages or other sources of data were obtained through the use of extrapolation techniques. While the absence of information on the prevalence of HBV or HCV infection in a country is unlikely to affect global estimates to a large extent, they can prevent the engagement of stakeholders at the national level. Hence, countries that do not have a national, population-based estimate of the prevalence of HBV and HCV infection may need to consider planning a biomarker survey (*see* Box 1, page 18). This is particularly relevant in Africa where the impact of the third dose of hepatitis B vaccine in the absence of a timely birth dose is poorly understood because of a lack of biomarker surveys. WHO has developed template protocols for these biomarker surveys, which are available upon request.

KEY PREVENTION MEASURES ARE POORLY MONITORED

Two health interventions are particularly critical for the prevention of HCV infection: safe and appropriate use of injections, and harm reduction. However, service coverage for these two interventions is poorly monitored.

Monitoring health-care injection safety is still based on ad-hoc surveys

With respect to health-care injection safety, two methods are available to estimate the proportion of injections that are given with syringes and needles reused without sterilization. The first is based on population surveys where individuals selected in samples recall during an interview the circumstances of the last injection that they received *(40)*. The second is based on surveys of health-care facilities during which evaluators attend health-care facilities and inspect injection techniques *(161)*. None of these methods are easy to use routinely for monitoring. Hence, the proportion of injections that are unsafe remains a poorly measured indicator and global estimates need to rely on systematic reviews of surveys done ad hoc.

Harm reduction indicators suffer from data gaps

While UNAIDS collects data from critical indicators on harm reduction in the context of the Global AIDS Response Progress Monitoring (GARPR) *(162)*, systems to routinely collect, transmit and analyse data to provide feedback on indicators for measuring harm reduction are still weak. As a result, global estimates are not updated regularly and are based on systematic reviews of ad-hoc studies that have gaps *(93)*.

THE INCIDENCE OF HCV INFECTION IS TECHNICALLY DIFFICULT TO MEASURE

Measuring the incidence of HCV infection is technically difficult. Most methods rely on mathematical models. However, modelling the incidence of HCV infection poses several methodological challenges. First, new HCV infections are most often asymptomatic *(163)*. Second, there is no biomarker that can be used to identify recent HCV infection *(164)*. Third, the incidence of HCV infection is probably low from a statistical point of view, which complicates measurement with precision because of the small sample size *(150)*. As a result, this report

publishes modelled estimates of incidence that suffer from substantial uncertainty and are not validated in most countries. Trends in incidence identified through modelling need to be verified using surveillance data, albeit with some limitations. Data from surveillance for acute hepatitis C, which reflect new infections, are useful for this validation. The number of cases of acute hepatitis C is underreported as a large proportion of infections are symptomatic. However, when considered in light of these limitations, the reported number of cases of acute hepatitis C provides information on time trends that are hard to obtain from other data sources. In the United States, surveillance for acute hepatitis C showed a re-emergence of new HCV infections associated with injection drug use in rural areas *(45)*.

SYSTEMS TO MONITOR THE CASCADE OF CARE ARE STILL BEING ESTABLISHED

Most of the data used in this report to estimate the cascade of care for HBV and of cure for HCV are based on a variety of ad-hoc sources that are often cross-sectional. WHO is in the process of providing countries with standardized tools to set up patients' databases, which could be used to generate estimates for these core indicators of the cascade of care. As a result, estimates of the cascade of care in this report should be considered as preliminary. They should be used with caution and, in the future, ad-hoc sources of information should be replaced by data obtained from patients' databases.

THE CAPACITY TO TEST FOR HBV AND HCV INFECTION AT COUNTRY LEVEL IS UNCLEAR

One of the most challenging service coverage targets of the GHSS on viral hepatitis is to increase the proportion of those infected who are diagnosed (30% by 2020 and 90% by 2030) *(7)*. This will require a substantial increase in the capacity to test individuals for viral hepatitis, which will require investment in resources and capacity for in-vitro diagnosis. Hence, among other inputs to the response to viral hepatitis that can be considered (e.g. governance, essential medicines, service delivery models, financing), the core indicator selected by WHO as part of the monitoring and evaluation framework for viral hepatitis is the infrastructure for testing for HBV and HCV infection *(8)*. Core indicator C.2 monitors the infrastructure for HBV and HCV testing. It is defined as the ratio of facilities with the capacity to test individuals for chronic hepatitis HBV and/or HCV per 100 000 population according to molecular methods (HCV RNA, HBV DNA) and serological methods (HBsAg, anti-HBc, anti-HCV). This indicator is structured like other indicators that estimate the capacity for laboratory diagnosis for the SDGs *(8)*. It can be measured through health-care facility surveys, such as the Service Availability and Readiness Assessment (SARA) tool in the future *(165)*. However, data are not yet available, and thus in 2015, the capacity for countries to test for HBV and HCV infection remains unclear.

REFERENCES

1. HBV vaccines: WHO position paper. Wkly Epidemiol Rec. 2009;84:405–20.
2. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contribution of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol. 2006; 45:529–38.
3. Resolution WHA58.13. Blood safety: proposal to establish World Blood Donor Day. In: Fifty-eighth World Health Assembly, Geneva, 16–25 May 2005. Resolutions and decisions, annexes. Geneva: World Health Organization; 2005 (http://www.who.int/bloodsafety/WHA58_13-en.pdf?ua=1, accessed 10 March 2017).
4. Hutin Y, Chen RT. Injection safety: a global challenge: Bull World Health Organ. 1999;77 (10):787–8.
5. Resolution WHA63.18. Viral hepatitis. In: Sixty-third World Health Assembly, Geneva, 17–21 May 2010. Resolutions and decisions, annexes. Geneva: World Health Organization; 2010 [Agenda item 11.12] (http://apps.who.int/gb/ebwha/pdf_files/WHA63-REC1/WHA63_REC1-en.pdf, accessed 10 March 2017).
6. Resolution WHA67.6. Hepatitis. In: Sixty-seventh World Health Assembly. Geneva, 19–24 May 2014. Resolutions and decisions, annexes. Geneva: World Health Organization; 2014 [Agenda item 12.3] (http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R6-en.pdf, accessed 10 March 2017).
7. Global Health Sector Strategy on viral hepatitis, 2016–2021. Geneva: World Health Organization; 2016 [WHO/HIV/2016.06] (http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf?ua=1, accessed10 March 2017).
8. Monitoring and evaluation for viral hepatitis B and C: recommended indicators and framework. Technical report. Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/10665/204790/1/9789241510288_eng.pdf, accessed 10 March 2017).
9. Hepatitis A fact sheet. In: World Health Organization: media centre [website] (http://www.who.int/mediacentre/factsheets/fs328/en/, accessed 10 March 2017) July 2016 update.
10. Farzi P. Delta hepatitis: an update. J Hepatol. 2003;39:S212–S219.
11. Chen X, Oidovsambuu O, Liu P, Grosely R, Elazar M, Winn VD et al. A novel quantitative microarray antibody capture (Q-MAC) assay identifies an extremely high HDV prevalence amongst HBV infected Mongolians. Hepatology. 2016 Nov 23. doi:10.1002/hep.28957. [Epub ahead of print]
12. Hepatitis D fact sheet. In: World Health Organization: media centre [website] http://www.who.int/mediacentre/factsheets/hepatitis-d/en/, accessed 10 March 2017) July 2016 update.
13. Rein DB, Stevens GA, Theaker J, Wittenborn JS, Wiersma ST. The global burden of hepatitis E virus genotypes 1 and 2 in 2005. Hepatology. 2012;55:988–97.
14. Hepatitis E fact sheet. In: World Health Organization: media centre [website] (http://www.who.int/mediacentre/factsheets/fs280/en/, accessed 10 March 2017) July 2016 update.
15. Beasley RP, Trepo C, Stevens CE, Szmuness W. The e antigen and vertical transmission of hepatitis B surface antigen. Am J Epidemiol. 1977;105(2):94–8.
16. World health statistics 2016: monitoring health for the SDGs, sustainable development goals. Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/10665/206498/1/9789241565264_eng.pdf?ua=1, accessed 10 March 2017).
17. Okada K, Kamiyama I, Inomata M, Imai M, Miyakawa Y. e antigen and anti-e in the serum of asymptomatic carrier mothers as indicators of positive and negative transmission of hepatitis B virus to their infants. N Engl J Med. 1976;294(14):746-9.
18. Keane E, Funk AL, Shimakawa Y. Systematic review with meta-analysis: the risk of mother-to-child transmission of hepatitis B virus infection in sub-Saharan Africa. Aliment Pharmacol Ther. 2016, 44(10):1005-1017.
19. Machaira M, Papaevangelou V, Vouloumanou EK, Tansarli GS, Falagas ME. Hepatitis B vaccine alone or with hepatitis B immunoglobulin in neonates of HBsAg+/HBeAg- mothers: a systematic review and meta-analysis. J Antimicrob Chemother. 2015;70:396-404.
20. LeeC,Gong Y, Brok J, Boxall EH,GluudC.Hepatitis B immunisation for newborn infants of hepatitis B surface antigen-positivemothers.Cochrane Database Syst Rev. 2006;(2):004790.DOI: 10.1002/14651858.CD004790.pub2.
21. Brown RS Jr, McMahon BJ, Lok AS et al. Antiviral therapy in chronic hepatitis B viral infection during pregnancy: A systematic review and meta-analysis. Hepatology. 2016; 63:319-33.
22. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. Geneva: World Health Organization; March 2015 (http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059_eng.pdf?ua=1&ua=1, accessed 10 March 2017).
23. Lemoine M, Shimakawa Y, Njie R, Taal M, Ndow G, Chemin I et al. Acceptability and feasibility of a screen-and-treat programme for hepatitis B virus infection in The Gambia: the Prevention of Liver Fibrosis and Cancer in Africa (PROLIFICA) study. Lancet Glob Health. 2016;4 (8):e559–67. doi: 10.1016/S2214-109X(16)30130-9.
24. Shankar H, Blanas D, Bichoupan K, et al. A Novel Collaborative Community-Based Hepatitis B Screening and Linkage to Care Program for African Immigrants. Clin Infect Dis. 2016; 62 Suppl 4:S289-97.
25. Spradling PR, Xing J, Rupp LB, Moorman AC, Gordon SC, Teshale ET et al. Infrequent clinical assessment of chronic hepatitis B patients in United States general healthcare settings. Clin Infect Dis. 2016; 63:1205–8.
26. Easterbrook P, Platt L, Gower E, Razavi H, Sabin K, Vickerman P. Global systematic review and metaanalysis of the seroprevalence of HBV and HCV infection in HIV-infected persons. [TUPEB 254 abstract]. 8th IAS Conference on Pathogenesis, Treatment and Prevention, 19–22 July 2015, Vancouver, Canada.

27. Nikolopoulos GK, Paraskevis D, Hatzitheodorou E, Moschidis Z, Sypsa V, Zavitsanos X et al. Impact of hepatitis B virus infection on the progression of AIDS and mortality in HIV-infected individuals: a cohort study and meta-analysis. Clin Infect Dis. 2009;48:1763–71.

28. Easterbrook P, Sands A, Harmanci H. Challenges and priorities in the management of HIV/HBV and HIV/HCV coinfection in resource-limited settings. Semin Liver Dis. 2012;32(2):147–57. doi: 10.1055/s-0032-1316476.

29. Sulkowski MS. Viral hepatitis and HIV coinfection. J Hepatol. 2008;48: 353–67.

30. Thio CL. Hepatitis B and human immunodeficiency virus coinfection. Hepatology. 2009;49(5 Suppl):S138–S145. doi: 10.1002/hep.22883.

31. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach, second edition. Geneva: World Health Organization; June 2016. (http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf?ua=1, accessed 10 March 2017).

32. Progress report 2016. Prevent HIV, test and treat all. WHO support for country impact. Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/10665/251713/1/WHO-HIV-2016.24-eng.pdf?ua=1, accessed 2 April 2017).

33. Wang L, Wiener J, Bulterys M, Wei X, Chen L, Liu W et al. Hepatitis B virus (HBV) load response to 2 antiviral regimens, tenofovir/lamivudine and lamivudine, in HIV/HBV-coinfected pregnant women in Guangxi, China: The Tenofovir in Pregnancy (TiP) Study. J Infect Dis. 2016; 214:1695–9.

34. Bruggmann P, Berg T, Øvrehus AL, Moreno C, Brandao Mello CE, Roudot-Thoraval F et al. Historical epidemiology of hepatitis C virus (HCV) in selected countries. J Viral Hepat. 2014; 21 Suppl 1:5–33.

35. Saraswat V, Norris S, de Knegt RJ, Sanchez Avila JF, Sonderup M, Zuckerman E et al. Historical epidemiology of hepatitis C virus (HCV) in select countries - volume 2. J Viral Hepat. 2015; Suppl 1:6–25.

36. Liakina V, Hamid S, Tanaka J, Olaffson S, Sharara AI, Alavian SM et al. Historical epidemiology of hepatitis C virus (HCV) in select countries - volume 3. J Viral Hepat. 2015; Suppl 4:4–20.

37. Armstrong GL, Alter MJ, McQuillan GM, Margolis HS. The past incidence of hepatitis C virus infection: implications for the future burden of chronic liver disease in the United States. Hepatology. 2000; 31:777–82.

38. Williams IT, Bell BP, Kuhnert W, Alter MJ. Incidence and transmission patterns of acute hepatitis C in the United States, 1982-2006. Arch Intern Med. 2011; 171(3):242–8.

39. Ministry of Health and Population [Egypt], El-Zanaty and Associates [Egypt], and ICF International. 2015. Egypt Health Issues Survey 2015. Cairo, Egypt and Rockville, Maryland, USA: Ministry of Health and Population and ICF International; 2015 (https://dhsprogram.com/pubs/pdf/FR313/FR313.pdf, accessed 2 April 2017).

40. Pépin J, Abou Chakra CN, Pépin E, Nault V, Valiquette L. Evolution of the global burden of viral infections from unsafe medical injections, 2000–2010. PLoS One. 2014;9(6):e99677. doi: 10.1371/journal.pone.0099677.

41. Mohsen A, Bernier A, LeFouler L, Delarocque-Astagneau E, El-Daly M, El-Kafrawy S et al. Hepatitis C virus acquisition among Egyptians: analysis of a 10-year surveillance of acute hepatitis C. Trop Med Int Health. 2015;20(1):89–97.

42. Khan AJ, Luby SP, Fikree F, Karim A, Obaid S, Dellawala S et al. Unsafe injections and the transmission of hepatitis B and C in a periurban community in Pakistan. Bull World Health Organ. 2000;78:956–63.

43. Mitruka K, Tsertsvadze T, Butsashvili M, Gamkrelidze A, Sabelashvili P, Adamia E et al. Launch of a nationwide hepatitis C elimination program—Georgia, April 2015. MMWR Morb Mortal Wkly Rep. 2015;64(28):753–7.

44. National Academies of Sciences, Engineering, and Medicine. Eliminating the public health problem of hepatitis B and C in the United States: phase one report. Washington, DC: The National Academies Press; 2016.

45. Zibbell JE, Iqbal K, Patel RC, Suryaprasad A, Sanders KJ, Moore-Moravian L et al. Increases in hepatitis C virus infection related to injection drug use among persons aged ≤30 years – Kentucky, Tennessee, Virginia, and West Virginia, 2006–2012. MMWR Morb Mortal Wkly Rep. 2015;64:453–8.

46. Suryaprasad AG, White JZ, Xu F, Eichler BA, Hamilton J, Patel A et al. Emerging epidemic of hepatitis C virus infections among young nonurban persons who inject drugs in the United States, 2006–2012. Clin Infect Dis. 2014;59:1411–9.

47. Van Handel MM, Rose CE, Hallisey EJ, Kolling JL, Zibell JE, Lewis B et al. County-level vulnerability assessment for rapid dissemination of HIV or HCV infections among persons who inject drugs, United States. J Acquir Immune Defic Syndr. 2016;73:323–31.

48. Harris AM, Iqbal K, Schillie S, Britton J, Kainer MA, Tressler S, Vellozzi C. Increases in acute hepatitis B virus infections – Kentucky, Tennessee, and West Virginia, 2006–2013. MMWR Morb Mortal Wkly Rep. 2016;65:47–50.

49. Chan DP, Sun HY, Wong HT, Lee SS, Hung CC. Sexually acquired hepatitis C virus infection: a review. Int J Infect Dis. 2016;49:47–58.

50. Ingiliz P, Martin TC, Rodger A, Stellbrink HJ, Mauss S, Boesecke C et al.; NEAT study group. HCV reinfection incidence and spontaneous clearance rates in HIV-positive men who have sex with men in Western Europe. J Hepatol. 2017;66:282–7.

51. Salazar-Vizcaya L, Kouyos RD, Zahnd C, Wandeler G, Battegay M, Darling KE et al. Hepatitis C virus transmission among human immunodeficiency virus-infected men who have sex with men: modeling the effect of behavioral and treatment interventions. Hepatology. 2016;64:1856–69.

52. Dore GJ. Hepatitis C treatment as prevention among HIV-infected men who have sex with men: feasible? Hepatology. 2016;64:1834–6.

53. Blach S, Zeuzem S, Manns M. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol. 2016;2:161–76.

54. Guidelines for the screening, care and treatment of persons with chronic hepatitis C infection. Updated version. Geneva: World Health Organization; April 2016 (http://apps.who.int/iris/bitstream/10665/205035/1/9789241549615_eng.pdf?ua=1, accessed 10 March 2017).

55. Platt L, Easterbrook P, Gower E, McDonald B, Sabin K, McGowan C et al. Prevalence and burden of HCV co-infection in people living with HIV: a global systematic review and meta-analysis. Lancet Infect Dis. 2016;16 (7):789–808.

56. Benova L, Mohamoud YA, Calvert C, Abu-Raddad LJ. Vertical transmission of hepatitis C virus: systematic review and meta-analysis. Clin Infect Dis. 2014;59(6):765–73.

57. Floreani A. Hepatitis C and pregnancy. World J Gastroenterol. 2013;19(40):6714–20.

58. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis. 2005;5:558–67.

59. Valle Tovo C, Alves de Mattos A, Ribeiro de Souza A, Ferrari de Oliveira Rigo J, Lerias de Almeida PR, Galperim B et al. Impact of human immunodeficiency virus infection in patients infected with the hepatitis C virus. Liver Int. 2007;27:40–6.

60. Thomas DL, Astemborski J, Rai RM, Anania FA, Schaeffer M, Galai N et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. JAMA. 2000;284:450–56.

61. Greub G, Ledergerber B, Battegay M, Grob P, Perrin L, Furrer H et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. Lancet. 2000;356:1800–5.

62. Guidelines on hepatitis B and C testing. Policy brief. Geneva: World Health Organization; 2016 [WHO/HIV/2016.23] (http://apps.who.int/iris/bitstream/10665/251330/1/WHO-HIV-2016.23-eng.pdf?ua=1, accessed 10 March 2017).

63. Liang X, Bi S, Yang W, Wang L, Ciu G, Ciu F et al. Epidemiological serosurvey of hepatitis B in China--declining HBV prevalence due to hepatitis B vaccination. Vaccine 2009; 27:6550-7.

64. Peto TJ, Mendy ME, Lowe Y, Webb EL, Whittle HC, Hall AJ. Efficacy and effectiveness of infant vaccination against chronic hepatitis B in the Gambia Hepatitis Intervention Study (1986–90) and in the nationwide immunisation program. BMC Infect Dis. 2014;14:7.

65. Luby SP, Qamruddin K, Shah AA, Omair A, Pahsa O, Khan AJ et al. The relationship between therapeutic injections and high prevalence of hepatitis C infection in Hafizabad, Pakistan. Epidemiol Infect. 1997;119:349–56.

66. Paez Jimenez A, Mohamed MK, Eldin NS, Seif HA, El Aidi S, Sultan Y et al. Injection drug use is a risk factor for HCV infection in urban Egypt. PLoS One. 2009;4:e7193. doi: 10.1371/journal.pone.0007193.

67. Logez S, Soyolgerel G, Fields R, Luby S, Hutin Y. Rapid assessment of injection practices in Mongolia. Am J Infect Control. 2004;32:31–7.

68. de Martel C, Maucort-Boulch D, Plummer M, Franceschi S. World-wide relative contribution of hepatitis B and C viruses in hepatocellular carcinoma. Hepatology. 2015;62:1190–200.

69. Kew MC. Aflatoxins as a cause of hepatocellular carcinoma. J Gastrointestin Liver Dis. 2013;22(3):305–10.

70. Technical considerations and case definitions to improve surveillance for viral hepatitis. Technical report. Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/10665/204501/1/9789241549547_eng.pdf?ua=1, accessed 21 June 2016).

71. Combating hepatitis B and C to reach elimination by 2030. Advocacy brief. Geneva: World Health Organization; May 2016 [WHO/HIV/2016.04] (http://apps.who.int/iris/bitstream/10665/206453/1/WHO_HIV_2016.04_eng.pdf?ua=1, accessed 18 March 2017).

72. Nayagam S, Thursz M, Sicuri E, Conteh L, Wiktor S, Low-Beer D et al. Requirements for global elimination of hepatitis B: a modelling study. Lancet Infect Dis. 2016;16:1399–408.

73. Pépin J, Abou Chakra CN, Pépin E, Nault V. Evolution of the global use of unsafe medical injections, 2000-2010. PLoS One. 2013;8 (12):e80948. doi: 10.1371/journal.pone.0080948.

74. GAVI Alliance. GAVI second evaluation report. 2010 (http://www.gavi.org/library/gavi-documents/evaluations/second-gavi-evaluation-2006-2010/, accessed 30 December 2016).

75. WHO Position paper on hepatitis B vaccines. Wkly Epidemiol Rec. 2004;28 (9):255–63.

76. Cui F, Li L, Hadler SC, Wang F, Zheng H, Chen Y, Gong X et al. Factors associated with effectiveness of the first dose of hepatitis B vaccine in China: 1992–2005. Vaccine. 2010; 28(37):5973–8.

77. Miyahara R, Jasseh M, Gomez P, Shimakawa Y, Greenwood B, Keita K et al. Barriers to timely administration of birth dose vaccines in The Gambia, West Africa. Vaccine. 2016; 34:3335–41.

78. Shimakawa Y, Lemoine M, Njai HF, Bottomley C, Ndow G, Goldin RD et al. Natural history of chronic HBV infection in West Africa: a longitudinal population-based study from The Gambia. Gut. 2016;65 (12):2007–16. pii: gutjnl-2015-309892. doi: 10.1136/gutjnl-2015-309892.

79. Van Thi Thuy Nguyen, Ho Quynh Trang, Nguyen Thi Lan Anh, Le Ai Kim Anh, Truong Binh Minh, Nguyen Duc Vuong et al. An innovative approach to triple elimination of mother-to-child transmission of HIV, syphilis and hepatitis B in Viet Nam [Poster] (http://www.who.int/hiv/pub/posters/poster_09.pdf?ua=1, accessed 30 December 2016).

80. Global status report on blood safety and availability 2016. Geneva: World Health Organization; 2017 (http://apps.who.int/iris/bitstream/10665/254987/1/9789241565431-eng.pdf, accessed 7 April 2017).

81. A guide to establishing a national haemovigilance system. Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/10665/250233/1/9789241549844-eng.pdf, accessed 7 April 2017).

82. Establishing external quality assessment programmes for screening of donated blood for transfusion-transmissible infections: implementation guide. Geneva: World Health Organization; 2016 (http://www.who.int/bloodsafety/publications/TTI-blood-screening/en/, accessed 3 April 2017) .

83. Hauri AM, Armstrong GL, Hutin YJ. The global burden of disease attributable to contaminated injections given in health care settings. Int J STD AIDS. 2004;15(1):7–16.

84. Usman HR, Akhtar S, Rahbar MH, Hamid S, Moattar T, Luby SP. Injections in health care settings: a risk factor for acute hepatitis B virus infection in Karachi, Pakistan. Epidemiol Infect. 2003; 130:293-300.

85. Rapiti E, Dhingra N, Hutin YJF, Lloyd S. The global burden of HBV and HCV infection attributable to unsafe blood transfusions. Poster presented at 11th International Symposium on Viral Hepatitis and Liver Disease, Sydney, Australia, 2003 (http://www.hbvadvocate.org/news/reports/International_Symposium.html#36, accessed 2 April 2017).

86. Kiani RA, Anwar M, Waheed U, Asad MJ, Abbasi S, Abbas Zaheer H. Epidemiology of transfusion transmitted infection among patients with beta-thalassaemia major in Pakistan. J Blood Transfus. 2016;2016:8135649 (http://dx.doi.org/10.1155/2016/8135649, accessed 3 April 2017).

87. Tagny CT, Owusu-Ofori S, Mbanya D, Deneys V. The blood donor in sub-Saharan Africa: a review. Transfus Med. 2010; 20:1–10.

88. Gore C, Lazarus JV, Peck RJ, Sperle I, Safreed-Harmon K. Unnecessary injecting of medicines is still a major public health challenge globally. Trop Med Int Health. 2013;18:1157–9.

89. WHO guideline on the use of safety-engineered syringes for intramuscular, intradermal and subcutaneous injections in health-care settings. Geneva: World Health Organization; 2016 (http://apps.who.int/iris/bitstream/10665/250144/1/9789241549820-eng.pdf, accessed 19 March 2017).

90. UNAIDS/WHO Working Group on Surveillance. Guidelines on estimating the size of populations with HIV. Geneva: UNAIDS/WHO; 2010 (http://www.who.int/hiv/pub/surveillance/estimating_populations_HIV_ risk/en/index.html, accessed 03 December 2015).

91. UNODC, World Drug Report 2017 (forthcoming, to be released on 22 June 2017).

92. The global state of harm reduction. London: Harm Reduction International; 2016 (https://www.hri.global/files/2016/11/14/GSHR2016_14nov.pdf, accessed: 30 December 2016).

93. Mathers BM, Degenhardt L, Ali H, Wiessing L, Hickman M, Mattick RP et al. HIV prevention, treatment, and care services for people who inject drugs: a systematic review of global, regional, and national coverage. Lancet. 2010;375(9719):1014–28.

94. Csete J, Kamarulzaman A, Kazatchkine M, Altice F, Balicki M, Buxton J et al. Public health and international drug policy. Lancet. 2016;387(10026):1427–80.

95. Guidelines on hepatitis B and C testing. Geneva: World Health Organization; 2017 (http://www.who.int/hepatitis/publications/guidelines-hepatitis-c-b-testing/en/, accessed 19 March 2017).

96. Zhou K, Fitzpatrick T, Walsh N, Kim JY, Chou R, Lackey M et al. Interventions to optimise the care continuum for chronic viral hepatitis: a systematic review and meta-analyses. Lancet Infect Dis. 2016;16:1409–22.

97. Romero Díaz-Maroto V, Sánchez Cuervo M, Rodríguez Sagrado MÁ, Bermejo Vicedo T. [Adherence to entecavir for chronic hepatitis B and correlation with effectiveness]. Farm Hosp. 2015;39:378-81. doi: 10.7399/fh.2015.39.6.8374. [Article in Spanish]

98. European Association for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. J Hepatol. 2012;57:167–85.

99. Nayagam S, Conteh L, Sicuri E, Shimakawa Y, Suso P, Tamba S et al. Cost-effectiveness of community-based screening and treatment for chronic hepatitis B in The Gambia: an economic modelling analysis. Lancet Glob Health. 2016;4 (8):e568–78. doi: 10.1016/S2214-109X(16)30101-2.

100. Guidelines for the screening, care and treatment of persons with hepatitis C infection. Geneva: World Health Organization; 2014 (http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en/, accessed 19 March 2017).

101. Estes C, Abdel-Kareem M, Abdel-Razek W, et al. Economic burden of hepatitis C in Egypt: the future impact of highly effective therapies. Aliment Pharmacol Ther. 2015; 42:696–706.

102. Global report on access to hepatitis C treatment: focus on overcoming barriers. Geneva: World Health Organization; October 2016 (http://apps.who.int/iris/bitstream/10665/250625/1/WHO-HIV-2016.20-eng.pdf?ua=1, accessed 18 March 2017).

103. Prüss-Ustün A, Rapiti E, Hutin Y. Estimation of the global burden of disease attributable to contaminated sharps injuries among health-care workers. Am J Ind Med. 2005; 48:482-90.

104. Health care worker safety: aide memoire. Geneva: World Health Organization; 2003 (http://who.int/occupational_health/activities/1am_hcw.pdf, accessed 7 April 2017).

105. Coppola N, De Pascalis S, Onorato L, Calò F, Sagnelli C, Sagnelli E. Hepatitis B virus and hepatitis C virus infection in healthcare workers. World J Hepatol. 2016: 8:273-81.

106. Westermann C, Peters C, Lisiak B, Lamberti M, Nienhaus A. The prevalence of hepatitis C among healthcare workers: a systematic review and meta-analysis. Occup Environ Med. 2015; 72:880–8.

107. Degenhardt L, Charlson F, Stanaway J, Larney S, Alexander LT, Hickman M et al. Estimating the burden of disease attributable to injecting drug use as a risk factor for HIV, hepatitis C, and hepatitis B: findings from the Global Burden of Disease Study 2013. Lancet Infect Dis. 2016;16:1385–98.

108. Nelson PK, Mathers BM, Cowie B, Hagan H, Des Jarlais D, Horyniak D et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. Lancet. 2011;378:571–83.

109. WHO, UNODC, UNAIDS technical guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users. Geneva: World Health Organization; 2009 (http://www.unaids.org/sites/default/files/sub_landing/idu_target_setting_guide_en.pdf, accessed 7 April 2017).

110. WHO position paper on hepatitis A vaccines – June 2012. Wkly Epidemiol Rec. 2012; 87:261–76.

111. Kwon JA, Anderson J, Kerr CC, Thein HH, Zhang L, Iversen J et al. Estimating the cost-effectiveness of needle-syringe programs in Australia. AIDS. 2012;26:2201–10.

112. Scott N, McBryde E, Thompson A, Doyle JS, Hellard ME. Treatment scale-up to achieve global HCV incidence and mortality elimination targets: a cost-effectiveness model. Gut. 12 Apr 2016. doi:10.1136/gutjnl-2016-311504. doi: 10.1136/gutjnl-2016-311504. [Epub ahead of print]

113. Murhekar MV, Murhekar KM, Sehgal SC. Epidemiology of hepatitis B virus infection among the tribes of Andaman and Nicobar Islands, India. Trans R Soc Trop Med Hyg. 2008;102:729–4.

114. McMahon BJ. Viral hepatitis in the Arctic. Int J Circumpolar Health. 2004;63(Suppl 2):41–8.

115. Børresen ML, Andersson M, Wohlfahrt J, Melbye M, Biggar RJ, Ladefoged K et al. Hepatitis B prevalence and incidence in Greenland: a population-based cohort study. Am J Epidemiol. 2015;181:422–30.

116. Scott JD. Chronic liver disease in aboriginal North Americans. World J Gastroenterol. 2008;14(29):4607–15.

117. Graham S, Guy RJ, Cowie B, Wand HC, Donovan B, Akre SP et al. Chronic hepatitis B prevalence among Aboriginal and Torres Strait Islander Australians since universal vaccination: a systematic review and meta-analysis. BMC Infect Dis. 2013;13:403.

118. Veselíny E, Janicko M, Drazilová S et al. High hepatitis B and low hepatitis C prevalence in Roma population in eastern Slovakia. Cent Eur J Public Health. 2014;22 Suppl:S51–6.

119. Michos A, Terzidis A, Kalampoki V, Pantelakis K, Spanos T, Petridou ET. Seroprevalence and risk factors for hepatitis A, B, and C among Roma and non-Roma children in a deprived area of Athens, Greece. J Med Virol. 2008;80:791–7.

120. Husa P, Ovesná P. Prevalence and risk factors of hepatitis C in Roma people in Brno. Klin Mikrobiol Infekc Lek. 2011;17:201–7. [Article in Czech]

121. Mera J, Vellozzi C, Hariri S, et al. Identification and clinical management of persons with chronic hepatitis C virus infection – Cherokee Nation, 2012–2015. MMWR Morb Mortal Wkly Rep. 2016;65:461–6.

122. Wu JS, Lu CF, Chou WH et al. High prevalence of hepatitis C virus infection in aborigines in Taiwan. Jpn J Med Sci Biol. 1992;45:165–74.

123. Hepatitis B and C in the spotlight. A public health response in the Americas, 2016. Washington, DC: Pan American Health Organization; 2016, updated Jan 2017 (http://iris.paho.org/xmlui/handle/123456789/31449, accessed 10 March 2017).

124. Amazonia 2015 Protected Areas Indigenous Terriories, 2015. In: Amazon Geo-Referenced Socio-Environmental Information Network [website] (https://raisg.socioambiental.org/amazonia2015-deforestacion2000-2013, accessed 10 March 2017).

125. Ott J, Stevens G, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine. 2012;30 (12):2212–9.

126. Viana S, Paraná R, Moreira R, Compri AP, Macedo V. High prevalence of hepatitis B virus and hepatitis D virus in the western Brazilian Amazon, Am J Trop Med Hyg. 2005;73 (4):808–14.

127. Braga WS, Castilho Mda C, Borges FG, Martinho AC, Rodrigues IS, Azevedo EP et al. Prevalence of hepatitis B virus infection and carriage after nineteen years of vaccination program in the Western Brazilian Amazon, Rev Soc Bras Med Trop. 2012;45 (1):13–7.

128. Manock SR, Kelley PM, Hyams KC, Douce R, Smalligan RD, Watts DM et al. An outbreak of fulminant hepatitis delta in the Waorani, an indigenous people of the Amazon basin of Ecuador. Am J Trop Med Hyg. 2000;63 (3–4):209–13.

129. Bair RM, Baillargeon JG, Kelly PJ et al. Prevalence and risk factors for hepatitis C virus infection among adolescents in detention. Arch Pediatr Adolesc Med. 2005; 159:1015–8.

130. European Centre for Disease Prevention and Control. Systematic review on hepatitis B and C prevalence in the EU/EEA. Stockholm: ECDC; 2016. (http://ecdc.europa.eu/en/publications/Publications/systematic-review-hepatitis-B-C-prevalence.pdf, accessed 3 April 2017).

131. Zampino R, Coppola N, Sagnelli C, Di Caprio G, Sagnelli E. Hepatitis C virus infection and prisoners: Epidemiology, outcome and treatment. World J Hepatol. 2015; 7 (21):2323-2330.

132. Prevention and control of infectious diseases among people who inject drugs. Stockholm: EMCDDA/ECDC; 2011 (http://www.emcdda.europa.eu/publications/ecdc-emcdda-guidance, accessed 3 April 2017).

133. Hepatitis C among drug users in Europe: epidemiology, treatment and prevention. Lisbon: EMCDDA; 2016 (http://www.emcdda.europa.eu/publications/insights/hepatitis-c-among-drug-users-in-europe, accessed 3 April 2017).

134. European Centre for Disease Prevention and Control. Epidemiological assessment of hepatitis B and C among migrants in the EU/EEA. Stockholm: ECDC; 2016.

135. WHO, CDC, IFRC. Blood donor counselling: implementation guidelines. Geneva: World Health Organization; 2014 (http://www.who.int/bloodsafety/voluntary_donation/Blooddonorcounselling.pdf?ua=1, accessed 3 April 2017).

136. Urbanus AT, van Houdt R, van de Laar TJ, Coutinho RA. Viral hepatitis among men who have sex with men, epidemiology and public health consequences. Euro Surveill. 2009; 14 (47):19421.

137. Maier MM, Ross DB, Chartier M, Belperio PS, Backus LI. Cascade of care for hepatitis C virus infection within the US Veterans Health Administration. Am J Public Health. 2016;106:353–8.

138. Januja NZ, Kuo M, Yu A, Alvarez M, Wong S, Cook D et al. The population level cascade of care for hepatitis C in British Columbia, Canada: the BC Hepatitis Testers Cohort (BC-HTC). EBioMedicine. 2016;12:189–95. doi: 10.1016/j.ebiom.2016.08.035.

139. Bourgi K, Brar I, Baker-Genaw K. Health disparities in hepatitis C screening and linkage to care at an integrated health system in southeast Michigan. PLoS One. 2016;11(8):e0161241.

140. Hawks L, Norton BL, Cunningham CO, Fox AD. The hepatitis C virus treatment cascade at an urban postincarceration transitions clinic. J Viral Hepat. 2016;23:473–8.

141. Wade AJ, Macdonald DM, Doyle JS, Gordon A, Roberts SK, Thompson AJ et al. The cascade of care for an Australian community-based hepatitis C treatment service. PLoS One. 2015;10(11):e0142770. doi: 10.1371/journal.pone.0142770. eCollection 2015.

142. McMahon BJ Townshend-Bulson L, Gounder P. Cascade of care for Alaska native people with chronic hepatitis C virus infection. Poster presented at the 2016 meeting of the American Association for the Study of the Liver Diseases (http://liverlearning.aasld.org/aasld/2016/thelivermeeting/144636/brian.mcmahon.cascade.of.care.for.alaska.native.people.with.chronic.hepatitis.html, accessed 24 March 2017).

143. Arora S, Thornton K, Jenkusky SM, Parish B, Scaletti JV. Project ECHO: linking university specialists with rural and prison-based clinicians to improve care for people with chronic hepatitis C in New Mexico. Public Health Rep. 2007;122 (Suppl 2):74–7.

144. Komaromy M, Duhigg D, Metcalf A, Carlson C, Kalishman S, Hayes L et al. Project ECHO (Extension for Community Healthcare Outcomes): a new model for educating primary care providers about treatment of substance use disorders. Subst Abus. 2016;37:20–4.

145. Arora S, Thornton K, Murata G, Deming P, Kalishman S, Dion D et al. Outcomes of treatment for hepatitis C virus infection by primary care providers. N Engl J Med. 2011;364:2199–207.

146. The Kirby Institute. Monitoring hepatitis C treatment uptake in Australia (Issue 6). Sydney, Australia: The Kirby Institute, UNSW Sydney; February 2017 (http://kirby.unsw.edu.au/research-programs/vhcrp-newsletters, accessed 20 March 2017).

147. ANRS, CNS. Ministère des affaires sociales et de la santé. Prise en charge thérapeutique et suivi de l'ensemble des personnes infectées par le virus de l'hépatite C. Rapport de recommandations 2016. Montroux Cedex, France: EDP Sciences; 2016 (http://social-sante.gouv.fr/IMG/pdf/rapport_.pdf, accessed 20 March 2017).

148. UNITAID. HIV/HCV co-infection strategic narrative (http://www.unitaid.eu/images/eb23/Strategic_narrative_HIV_HCV_co-infection.pdf, accessed 2 April 2017).

149. Zeshan Foundation. International roundtable summit on funding for elimination of viral hepatitis. Meeting report. Hong Kong, China SAR; June 2016 (www.endhep2030.org, accessed 18 March 2017).

150. Viral Hepatitis Strategic Information and Modelling Reference Group. Meeting report. Geneva, Switzerland; June 2016 (www.who.int/hepatitis/publications/strategic-information-modelling-meeting/en/).

151. Norheim OF, Baltussen R, Johri M, Chisholm D, Nord E, Brock D et al. Guidance on priority setting in health care (GPS-Health): the inclusion of equity criteria not captured by cost-effectiveness analysis. Cost Eff Resour Alloc. 2014;12–18.

152. Toy M, Hutton DW, So SK. Cost-effectiveness and cost thresholds of generic and brand drugs in a national chronic hepatitis B treatment program in China. PLoS One. 2015;10:e0139876.

153. Iyengar S, Tay-Teo K, Vogler S, Beyer P, Wiktor S, de Joncheere K et al. Prices, costs, and affordability of new medicines for hepatitis C in 30 countries: an economic analysis. PLoS Med. 2016;13(5):e1002032.

154. Stevens GA, Alkema L, Black RE, Boerma JT, Collins GS, Ezzati M et al. Guidelines for Accurate and Transparent Health Estimates Reporting: the GATHER statement. Lancet. 2016;388 (10062):e19–e23

155. Stanaway JD, Flaxman AD, Naghavi M, Fitzmaurice C, Vos T, Abubaker I et al. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. Lancet. 2016;388 (10049):1081–8.

156. WHO–UNICEF estimates of DPT3 coverage. Geneva: World Health Organization; 2017. (http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tswucoveragedtp3.html, accessed 10 March 2017).

157. Global policy report on the prevention and control of viral hepatitis in WHO Member States. Geneva: World Health Organization; 2013 (http://apps.who.int/iris/bitstream/10665/85397/1/9789241564632_eng.pdf, accessed 16 December 2016).

158. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology 2013; 57:1333–42.

159. Gower E, Estes C, Blach S , Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol. 2014; 61(1 Suppl):S45–57.

160. United Nations. Sustainable Development Goals. New York: United Nations; 2015 (https://sustainabledevelopment.un.org/sdgs, accessed 10 March 2017).

161. Revised injection safety assessment tool (Tool C –revised). Geneva: World Health Organization; 2008. (http://www.who.int/injection_safety/Injection_safety_final-web.pdf, accessed 10 March 2017).

162. Global AIDS response progress reporting 2016. Construction of core indicators for monitoring the 2011 United Nations Political Declaration on HIV and AIDS. Geneva: UNAIDS; 2016 (https://aidsreportingtool.unaids.org/static/docs/GARPR_Guidelines_2016_EN.pdf, accessed 30 December 2016).

163. Maheshwari A, Ray S, Thuluvath PJ. Acute hepatitis C. Lancet. 2008;372(9635):321–32.

164. Centers for Disease Control and Prevention. Testing for HCV infection: an update of guidance for clinicians and laboratorians. MMWR Morbid Mortal Wkly Rep. 2013;62 (18):362–5.

165. Service Availability and Readiness Assessment (SARA): an annual monitoring system for service delivery. Reference Manual, Version 2.2. Geneva: World Health Organization; 2015. (http://apps.who.int/iris/bitstream/10665/149025/1/WHO_HIS_HSI_2014.5_eng.pdf?ua=1, accessed 10 March 2017).

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