INTRODUCTION

A smouldering public-health crisis

Long overshadowed by HIV, the hepatitis C virus is starting to take its toll. And the heat is on to find and treat those affected.

BY LAUREN GRAVITZ

In the early 1980s, when AIDS was still unexplained and HIV was spreading unchecked, another blood-borne virus was also on the move. Like HIV, this unknown infectious agent struck intravenous drug users and blood transfusion recipients. But it was stealthier than HIV, often causing its victims no discomfort as it multiplied undetected for many years, even decades. The virus manifested itself slowly, starting with flu-like symptoms, such as fever and fatigue, and gradually working up to a fully fledged attack on the liver, where it could cause cirrhosis or cancer[1].

That culprit, identified in 1989, was hepatitis C virus (HCV). Some 130–200 million people are now estimated to be infected worldwide. Rates of transmission in the United States, Europe and Japan have plummeted since the virus was identified, however, thanks to disposable medical instruments and a screened blood supply. But the virus continues to thrive in developing nations, which lack the resources to treat people who do not appear ill. Treatment is expensive, lengthy and causes numerous side effects — and, for all that, it works only about half the time. The upshot is that more than 350,000 people worldwide die from HCV-related liver disease every year[2].

Hepatitis C is just as deadly as HIV — both kill about 10,000–15,000 people per year in the United States, according to David Thomas, an infectious diseases specialist at Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland. But HIV gets about 30 times more research funding in the United States than HCV, he says. And as increasing numbers of chronic hepatitis C cases manifest their most serious symptoms, the smouldering problem is turning into a burning public-health issue that threatens to stretch researchers, patients, and the health-care system to their limits.

THE QUIET EPIDEMIC

Two other viruses that target the liver were discovered before HCV: hepatitis A, which causes an acute infection with symptoms that fade within months, and hepatitis B, which commonly becomes chronic in children and in up to 10% of adults. HCV remained undetected for far longer because it replicates slowly and causes symptoms similar to other diseases. It was only when researchers at the National Institutes of Health (NIH) in Bethesda, Maryland, began to tease apart the causes of liver disease in the 1970s that they discovered that another infectious agent was involved.

HCV is transmitted through the blood, mainly via transfusions, shared needles and reused medical supplies. Sexual and mother-to-child transmission is much less likely than for HIV. In developed nations, most new infections occur in injection-drug users. An estimated 1.6% of the US population carries HCV, as many as three-quarters of whom don't know they have it[3]. In poorer countries, the reuse of medical supplies is still common and — in combination with a lack of screening of blood donations — is fuelling the virus's spread. Complicating the picture, HCV exists in at least eleven variations or at lest six genotypes, and treatment success varies by genotype. (see 'Spread of HCV').

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Different countries confront distinct challenges when dealing with the HCV epidemic. The Egyptian healthcare system, for instance, has to cope with the highest rate of transmission in the world, at least 14% of Egypt's citizens infected — three times the global infection rate (see 'A uniquely Egyptian epidemic', page S12). Elsewhere, severity of the HCV epidemic is obscured by other, more immediately severe public health concerns. Throughout much of Africa, HCV 'hides behind' widespread HIV and hepatitis B virus infections, says virologist Jean-Michel Pawlotsky, director of the French National Reference Center for Hepatitis B, C and delta. On a recent visit to a country in southern Africa, Pawlotsky noticed that they screen blood for HIV and hepatitis B but that "they don't have the resources" to screen for HCV.

"All countries share a few common challenges with hepatitis C," says John Ward, director of the viral hepatitis program at the US Centers for Disease Control and Prevention. "One is a very low level of awareness of the severity of the problem — clinician knowledge of HCV seems to be inadequate no matter what country you're in."

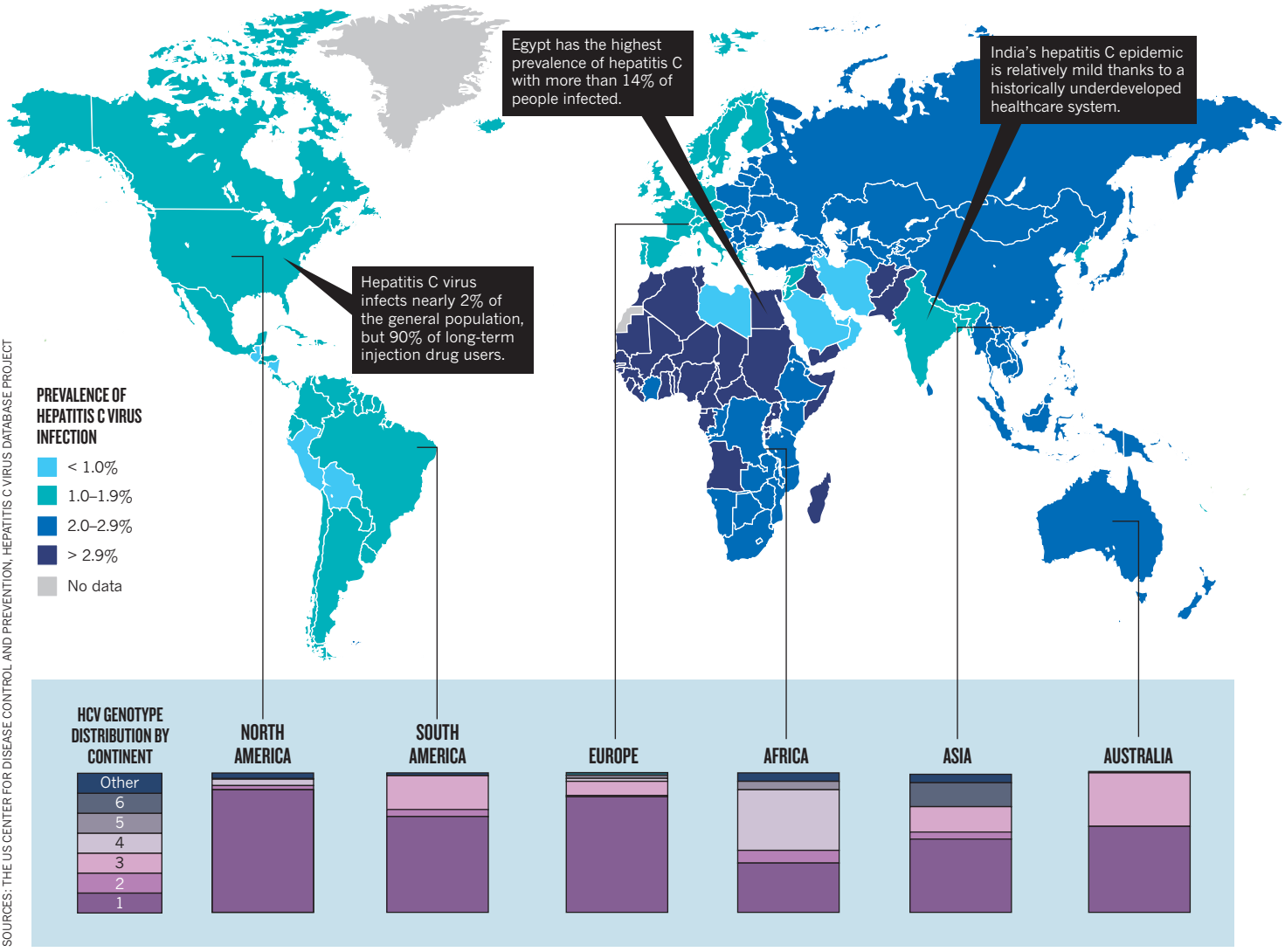
Even when a country is acutely aware of its HCV problem, the best available options are barely adequate to the task. In France, where politicians were found guilty of distributing HIV-contaminated blood in the mid-1980s, officials are now trying to prevent a repeat with HCV. French public-health workers have been screening the populace intensively for HCV, and the French government estimates that it has identified 60% of the country's infected citizens, Pawlotsky says. "Half of those have been treated, and half of those treated have been cured." Which, he says, means that "with the heaviest campaign worldwide and the largest proportion of screened patients, we have only cured twelve to fifteen percent" of those infected nationwide.

Pawlotsky and others note that there has been progress towards preventing HCV infection. This success has come in part because the rise in HCV infections coincided with that of HIV, and the HIV-related public-health campaign targeted practices (such as sharing needles) that also contributed to HCV transmission. Combined with introducing thorough screening of blood donations, health officials in the United States were able to lower the infection rate from as high institution listed, as several hundred thousand per year to about 20,000 per year now. Still, "20,000 a year is not a small number," says Brian Edlin, an epidemiologist and infectious diseases specialist at the State University of New York Downstate College of Medicine in Brooklyn, New York. "It's still a fire that's spreading — not as quickly as in the past, but it's spreading."

According to Ward, HCV infections are on the rise in older teenagers and young adults. Of those already infected, the groups most at risk of becoming symptomatic in the United States are veterans, who have an infection rate at least three times that of the general population, and

THE SPREAD OF HCV

The hepatitis C virus reaches across the globe with highest prevalence in north Africa and south Asia. A major challenge is tailoring treatments and vaccines to the various viral genotypes which affect treatment response.



SOURCES: THE US CENTER FOR DISEASE CONTROL AND PREVENTION, HEPATITIS C VIRUS DATABASE PROJECT

baby boomers (those born between 1946 and 1964). In fact, baby boomers, who make up about 30% of the US population, account for two-thirds of the people in the United States with HCV.

The potential healthcare burden these numbers represent is alarming. Over the past five years, the number of veterans with HCV who have liver cancer has tripled[4]. Some Veterans Affairs hospitals now report more cases of liver cancer than colon cancer, says Janet Durfee, who directs nationwide public-health programmes for the Department of Veterans Affairs. By contrast, in the general population, colon cancer is about four times more prevalent.

HOPE FOR NEW DRUGS

Much about HCV remains to be fully understood. It remains a mystery, for instance, why some people inflected with HCV never develop symptoms. About 15–20% of those infected with HCV can clear the virus without pharmaceutical help, and among teenagers and young adults, the proportion can climb as high as 50% (ref. 5). Of those who can't fend off the virus on their own, most remain stable for decades, without any major symptoms. In the 10–15% of people who have symptoms, however, the virus causes cirrhosis: the liver becomes fibrotic and scarred, resulting in jaundice and a swollen abdomen, as well as a dangerous build-up of toxins in the blood and other serious complications. In some patients with cirrhosis, the disease advances slowly, but one in four — 2–4% of all HCV cases — develops liver cancer or liver failure.

"The majority of people will not go on to develop cirrhosis if they don't have other viruses or co-morbidities such as alcoholism," says Harvey Alter, an NIH virologist whose research led to the discovery of HCV. "Seventy to eighty percent do well without treatment. But we can only say that for the first 30 years or so, because that's all we have data for."

The standard treatment for HCV infection is two daily doses of ribavirin, a nonspecific antiviral agent, combined with a weekly injection of interferon-α, which activates the immune system and impedes viral replication. Not only is the treatment prolonged, lasting either 24 weeks or 48 weeks depending on the virus genotype, but it can cause serious side effects, ranging from fatigue and flu-like symptoms to anaemia and severe depression. Patients, and their healthcare providers, would welcome anything that might shorten treatment, reduce its side effects and increase its efficacy. "Getting away from interferon is everbody's goal," says Alan Perelson, a mathematical and theoretical biologist who specializes in HCV at Los Alamos National Laboratory in New Mexico. "It comes with side effects, cost,

inconvenience, injections, and the fact that not everybody responds to it."

Changes are afoot. Two new antivirals are speeding their way to market. Boceprevir, made by drug giant Merck, headquartered in Whitehouse Station, New Jersey, and telaprevir, made by Vertex Pharmaceuticals, based in Cambridge, Massachusetts, are both inhibitors of an important viral protein, the NS3/4A protease. The drugs are designed specifically to attack HCV genotype 1, which is the most prevalent genotype, accounting for about 60% of global infections, and the least responsive to current treatment. They will supplement, but not replace, the standard interferon plus ribavirin therapy. Thus, they won't eliminate the cocktail's difficult side effects and may introduce new ones. The good news is that in phase III trials, each drug, in combination with the standard treatment, increased the cure rate of people with HCV genotype 1 from under half to 70%, while cutting treatment time in half for some.

"Just one new antiviral added to the standard of care will make a huge difference," says Charles Rice, executive and scientific director of the Center for the Study of Hepatitis C in New York. "But the game's not over. We'd really like to eliminate the current standard of care and replace it with something that works better and has fewer side effects." There are several promising therapies at various points in the pharmaceutical pipeline (see 'New drugs hit the target', page S5). But there is a built-in delay in development: every new drug must be tested against the current, year-long, treatment regimen.

And drug developers are facing an elusive foe. The virus replicates so rapidly and is so error-prone when it does, that many genetic variations — including those that confer drug resistance — exist inside someone before he or she is diagnosed. The best strategy is therefore to throw multiple drugs at the virus at once, enough such that the pathogen would be unable to mutate to resist them all. Statisticians calculate such a feat would take two or three antivirals, all of which must target different components of the virus (a strategy similar to the drug cocktails used to fight HIV). The number of drugs needed "will depend on how hard it is for the virus to generate the number of mutations required to gain resistance," Perelson says.

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Further complicating the problem, because the risk factors for infection with HCV and HIV are similar, many people who are HIV-infected are also infected with HCV (up to 30% in the United States). For reasons that are not yet understood, this co-infected group has a lower cure rate and suffers from more side effects. Moreover, many of the antiretroviral drugs used against HIV can build up in the liver, poisoning the organ that the HCV drugs are working to save. And the new protease-inhibitor drugs have not yet been vetted in more than a few dozen co-infected patients. "The amount of information we have on those who are dually infected is abysmal," says Thomas. "We're going to have these treatments available this year and not have any idea on how to use them in combination with antiretrovirals."

Most researchers and public health experts concur that, in addition to better treatments, the ultimate solution is a hepatitis C vaccine. "Otherwise, we'll have infection from other parts of the world where therapies are not available," Pawlotsky says. But vaccine development is challenging, and the virus has kept researchers guessing for decades already (see 'A moving target', page S16).

OUT OF HIV'S SHADOW

When discussing HCV, comparisons with HIV are nearly unavoidable — both appeared on the communicable disease radar around the same time and both have similar modes of transmission. But the HCV problem cannot be solved by repurposing the agents developed to fight HIV, given the marked differences in the biology of these viruses. "Their differences are greater than their similarities," says Miriam Alter, an epidemiologist at the University of Texas Medical Branch in Galveston. She notes that HCV has been endemic to human populations for centuries, and it is biologically much different from HIV.

The differences also stretch beyond biology and into public-health initiatives. The discovery of HIV led to a huge amount of funding for antiviral research and development around the world. "With hepatitis C," says Thomas, "we haven't even had widespread adoption of treatment here in the US."

Even diagnosis of HCV infection (see 'A testing journey', page S20) has lagged far behind HIV. The CDC estimates that about 80% of HIV-infected people in the United States know they have the disease, but the figure for HCV awareness is about 30%. And worldwide, that number shrinks to an abysmal 5%. "We're looking at an epidemic that is five times the size of the HIV epidemic, that spreads more quickly, that is treatable and ultimately curable. And yet, as a nation, we've got our heads in the sand," says Edlin.

At the same time, it's hard to deny that the field has made great strides in a short time. As Rice says: "In 1975, there was this agent causing all this disease, and nobody knew what it was. And here we are today and we can effectively treat a majority of people who are infected." The research is headed in the right direction — but disease awareness still lags far behind. It will take a concerted effort and a huge national and international collaboration among public-health officials, doctors and governments to stop the raging epidemic before it burns through the limited resources of healthcare systems around the world. ■

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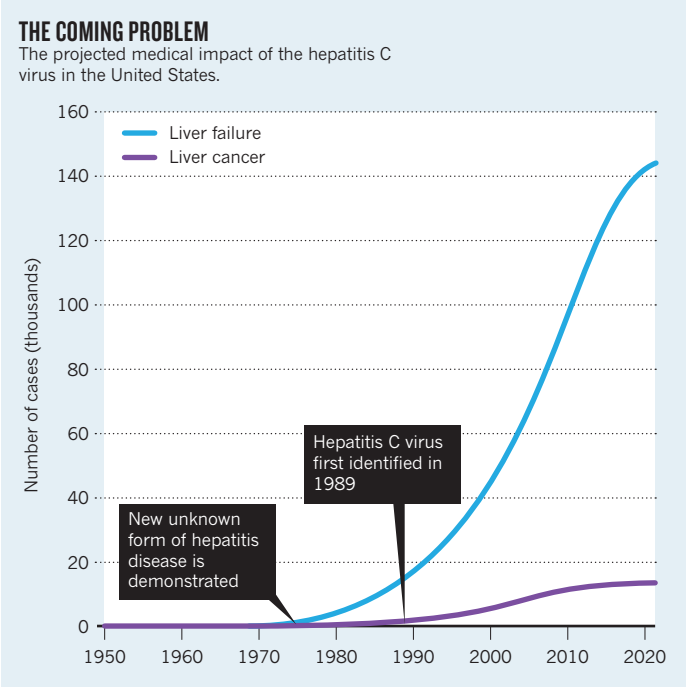

SOURCE: DAVIS GL ET AL. GASTROENTEROLOGY 138, 513–521 (2010).

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