SVEN TORFINN/PANOS

AFRICA'S SILENT EPIDEMIC

Hepatitis now kills more people worldwide than HIV, tuberculosis or malaria. Tackling the hepatitis B virus in Africa is key to fighting back.

BY IAN GRABER-STIEHL

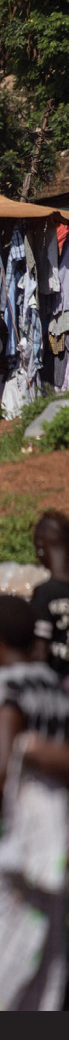
Nuru was prepared for the worst when she went to get screened for HIV eight years ago. After caring for her mother in Uganda, who died as a result of the virus, Nuru moved to the United Kingdom to study, and decided to take her health into her own hands. "I was ready to be told I had HIV," she says. "I felt, 'That's okay. I've looked up to my mother.'"

What she didn't expect was to be diagnosed with a different viral infection altogether: hepatitis B. "The way the health worker delivered it to me, it was like, 'It's worse than HIV'. I was confused, I was suicidal," says Nuru (who asked that her real name not be used for this article). "I just didn't understand what it was because no one ever talks about hep B — they talk about HIV. That's well researched, it's well talked about, well documented. It's all over the television. But hep B is not."

The hepatitis B virus (HBV), which spreads through blood and bodily fluids and invades liver cells, is thought to kill just under 1 million people every year around the world, mostly from cancer or scarring (cirrhosis) of the liver. HBV is less likely to be fatal than HIV, and many people who carry the virus don't have symptoms. But because more than 250 million people live with chronic HBV infections, more than 7 times the number with HIV, its global death toll now rivals that of the more-feared virus.

Hepatitis — or liver inflammation — is caused by a number of viruses, but types B and C are associated with the most deaths. In 2016, the most recent year for which estimates are available, the number of deaths worldwide from viral hepatitis rose to 1.4 million, outstripping those from tuberculosis, HIV or malaria individually (see 'The burden of hepatitis B').

This is despite the fact that HBV infection can be prevented by vaccination early in childhood and treated with the same antiretroviral drugs used to combat HIV. "HIV has been an acute pandemic with resources thrown at it. That's a completely different picture than hep B, which has travelled with humankind for tens of thousands of years — and by dint of that invisible carriage, has never had that injection of political advocacy, funding, energy and education that's gone into HIV," says Philippa Matthews, an immunologist at the University of Oxford,



A market in Uganda — a nation where 6% of people carry hepatitis B.

UK, who studies viral infections such as HBV.

Researchers and health workers are now hoping to change that. Two years ago, the World Health Assembly endorsed a World Health Organization (WHO) strategy to eliminate hepatitis as a public-health threat by 2030, which the WHO defined as reducing new infections by 90% and deaths by 65%.

A major focus is to combat the growing HBV crisis in sub-Saharan Africa. Other high-risk regions, such as the Western Pacific (which stretches from China to New Zealand), have long inoculated children against the virus, following a 1992 WHO decision to include HBV in routine vaccination protocols. As a result, although around 6% of people in the region are still living with HBV, most children and teenagers there are protected. But in sub-Saharan Africa, where it's also estimated that about 6% of the population are currently infected, fewer than one-tenth of children receive the necessary inoculations. The region also ranks last in every other intervention, including screening and diagnosis, and in treating those living with the virus.

"Hepatitis B has been, to a large extent, neglected," says Ponsiano Ocama, a hepatologist at Makerere University in Kampala, Uganda. Health-care workers, he says, are generally under-educated and ill-equipped to treat the virus. Matthews adds that priority for antiretroviral drugs is weighted so heavily in favour of people with HIV that some health-care workers think those with HBV stand a better chance of receiving adequate care if they contract HIV as well, even though having both infections increases the chance of early death.

With little routine screening, there are also many gaps in researchers' understanding of the prevalence and outcomes of hepatitis in vulnerable populations. While the fight against hepatitis is buoyed by progress in Western Pacific nations, the crisis in sub-Saharan Africa is flying under the radar. "It's a critical time for the region," says Matthews.

KNOWLEDGE GAP

Nuru left her UK screening appointment dejected, and feeling that she knew little about her infection. She turned to the Internet to answer questions she felt had been glossed over by the health-care professionals she saw. Public ignorance about transmission, but awareness that HBV can be passed on during unprotected sex, has given the infection a stigma that, says Nuru, smacks of the whispers that emerged around HIV when that virus first came to light in sub-Saharan Africa. Nuru's body is suppressing the virus well enough that she does not need treatment, but she doesn't talk openly about it. If news that she has HBV spreads back to Uganda, she says, then she worries people will regard her family there with suspicion. "They will be segregated, isolated — they won't get jobs," she says.

Kenneth Kabagambe, who founded Uganda's National Organization for People Living with Hepatitis B (NOPLHB) in 2011, after a friend died with the infection, says he had a similar experience when he himself was diagnosed in 2012. His doctor, he said, left him wondering whether the disease might even be comparable to Ebola.

As Kabagambe and Nuru would learn, hepatitis is sometimes referred to as the silent epidemic, because its carriers do not initially show symptoms. In some cases, the virus responsible can sabotage the liver's function over years without causing noticeable problems, until eventually a viral takeover causes cirrhosis or liver cancer.

Hepatitis C virus (HCV) is an RNA virus that is spread largely through blood — usually through unscreened blood donations, drug use, reuse of unsterilized equipment in hospitals and, to a lesser extent, unprotected sex. There is no vaccine against it, but antiviral medications can cure a chronic infection in most people. By contrast, HBV, a DNA virus, is less malignant — in that fewer adults develop chronic infections — but more widespread. It affects almost four times as many people as HCV, and is more likely than HCV to be spread from mother to baby during pregnancy or birth. HBV infection is also divided more along economic lines: it is, says Ocama, largely "a disease of the poor".

In contrast to people with HIV, adults who don't already have HBV are unlikely to become infected — and, if they do, there is only a small chance of developing a chronic infection or passing it on to other adults. The group at highest risk of becoming infected and transmitting HBV is infants, who have weaker immune systems. Compared with adults with HBV, toddlers "teem with the virus", says Mark Sonderup, a hepatitis researcher at the University of Cape Town, South Africa. So, screening and treating infected mothers, and vaccinating babies, is key to cracking down on HBV. Yet, myths still circulate among health-workers in Africa about how HBV is transmitted, including that adults with the virus should be isolated. This perpetuates the infection's stigma, says Ocama.

There are some subtleties to this picture. In Western Pacific nations, the main transmission route for strains of HBV tends to be from mother to baby, according to research[1] that dovetailed with the vaccination campaigns there in the 1990s. In sub-Saharan Africa, however — which has different HBV strains — mothers with the infection tend to have lower viral loads, making it slightly less likely that they will infect their babies during pregnancy or birth. Viral transmission from child to child, through the usual scratches of rough play and the lacklustre hygiene of youth, seems to be a more prominent infection route.

VACCINE PUSH

For many years, policymakers thought that rolling out vaccinations would be enough to halt HBV, says Maud Lemoine, a hepatologist at Imperial College London. That's true in principle, but the vaccine's design makes it difficult to administer. It is generally given in three parts. The first is a 'birth dose', which is most effective if given within 24 hours of birth. The other two doses are given later and several weeks apart. From 1990 to 2015, the proportion of children getting three HBV inoculations skyrocketed from 1% to 84%, with the Western Pacific leading the way at more than 90% coverage, just above that in the Americas; Africa lags behind at 70%[2].

But in practice, the first dose is not always given at birth — coverage of this dose is only 39% globally — and its timing is not always reported. In Africa, coverage at birth is just 10%. Administering a birth dose within 24 hours, and follow-up vaccinations on schedule, poses a monumental challenge in a region where many births are not supervised by medical professionals.

The challenge of accessing mothers in time has been compounded by a reliance on Gavi, the Vaccine Alliance, an international organization that connects public and private sectors to roll out vaccines. Gavi has been a driving force in expanding HBV vaccination in sub-Saharan Africa. But it does this through a compound inoculation that immunizes against diphtheria, pertussis, tetanus, HBV and influenza, but which isn't given until 6–8 weeks of age. A spokesperson says that the organization has not focused on providing the birth-dose vaccine, in part because it had not seen evidence that distribution systems could get the inoculations to infants within 24 hours of birth, and because it felt the more expensive 5-fold vaccine was a better target for subsidy.

On 29 November, however, Gavi's board voted to prioritize investment in HBV birth-dose vaccines, as part of a strategy targeting six new vaccine programmes from 2021 to 2025. And success in other vaccination campaigns show that it should be possible to overcome distribution challenges. In the 1990s, researchers in Indonesia gave pre-packaged single-use hepatitis B vaccines to local midwives so that they could administer an inoculation after home births, an approach now used more widely[3]. And two years ago, researchers in Laos demonstrated that providing mobile phones to vigilant health workers and local volunteers helped keep track of births and ensure more infants were vaccinated[4].

SCREENING RESEARCH

Another key to tackling HBV is screening and diagnosing adults. Mothers are among the most crucial people to check because of their propensity to pass the virus on to their babies. "If you find infected antenatal women, you can also screen their partners. You can vaccinate any household contacts who aren't infected. You can identify any other household contacts who are infected and treat them," says Matthews. "It gives you a route into more population-level interventions."

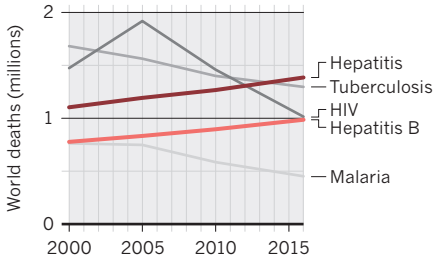
But mothers are not routinely checked before giving birth. Add to that a paucity of cancer registries with accurate data on liver cancer, and a

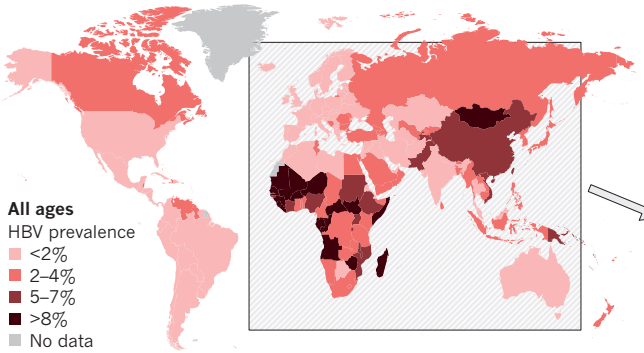
THE BURDEN OF HEPATITIS B

More than 250 million people live with the virus; few of them are diagnosed and not enough children are vaccinated against it.

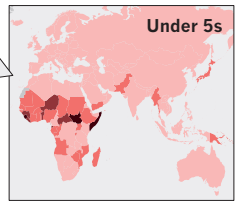
SOURCE: WHO

Rising death toll
Hepatitis infections are now associated with more deaths globally than are tuberculosis, HIV or malaria.

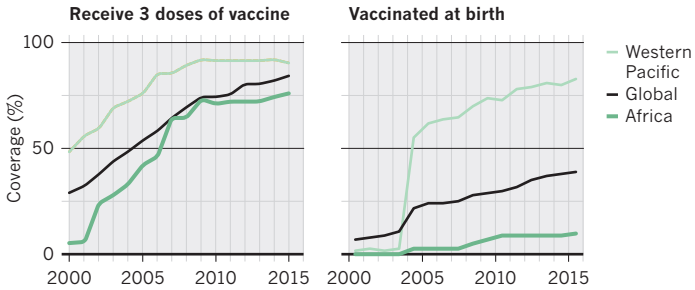




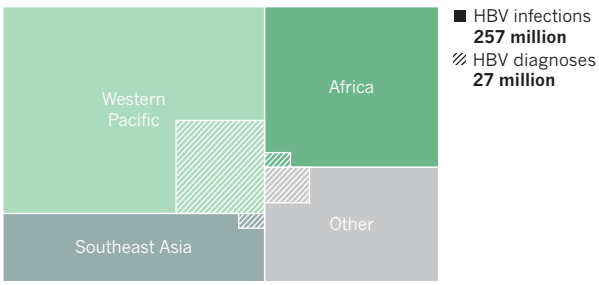
An unequal burden
The hepatitis B virus (HBV) is most prevalent in Africa and the Western Pacific, but in infants (inset), it is found mainly in Africa.



Vaccination lag
Africa is the least-vaccinated region against hepatitis B; the Western Pacific, the most. Only one in ten infants in Africa are vaccinated at birth.



Diagnosis gap
The World Health Organization wants to diagnose 90% of hepatitis B infections by 2030. The rate is currently 10%.



generally low regional turnout for testing, and it's of little surprise that researchers' picture of the prevalence and dynamics of hepatitis viruses are plagued with gaps.

Instead, the populations that are screened most reliably are those who donate blood and people such as Nuru and Kabagambe, who saw first-hand how HIV ravaged their communities, and decided to get tested. Many health professionals have criticized initiatives such as Gavi and the US President's Emergency Plan for AIDS Relief for not doing more to leverage HIV-testing networks to also provide screening for hepatitis. Lemoine points out that one negative HBV test is probably all that an adult needs, because it is so unlikely that they will be infected, whereas people might need to be retested for HIV many times.

Initial screens cost only a few dollars: health workers simply check the person's blood for evidence that their immune system has developed antibodies against the hepatitis viruses. But these checks, says Matthews, test only whether you've been exposed to the viruses, not whether you're currently infected. To get a definitive diagnosis, people need more-expensive nucleic-acid tests that detect the viral DNA of HBV (or, for HCV, viral RNA). The cost can be as high as US$200 — something that few people in sub-Saharan Africa can afford, says Olufunmilayo Lesi, a member of the WHO's advisory group on viral hepatitis. Fewer than 1% of those in the region with HBV, and 6% of those with HCV, are diagnosed, according to a WHO estimate[2].

DRIVING FORWARD

Several countries in sub-Saharan Africa are now expanding their screening efforts, including Uganda, which hopes to tie its effort to a vaccination drive aimed at mothers and infants, says Ocama. And researchers have been working on more convenient diagnostic tests. In 2017, the WHO approved a test that detects HCV RNA and runs on equipment found in most hospitals in sub-Saharan Africa — the GeneXpert nucleic-acid system. Made by Cepheid, a company in Sunnyvale, California, it is already used to diagnose HIV and tuberculosis. A test for HBV that could be run on the GeneXpert machine is in beta testing, says Sonderup, but has yet to be formally released. (Cepheid did not reply to requests for comment.)

As the world has focused on combating HIV, billions of dollars have been poured into developing antiretrovirals — drugs that people with HIV take indefinitely to inhibit the replication of the viruse. In low-income countries, the cost of these drugs is heavily subsidized, and in many cases, the same drugs can treat both HIV and HBV.

But when it comes to access to drugs, people with HBV in many resource-limited regions find themselves overlooked in favour of those with HIV. Ocama says he has known hospital administrators who have allowed physicians to administer drugs reserved for people with HIV to those with HBV — but overall, an abysmally small fraction of people in sub-Saharan Africa with HBV receive treatment.

Some countries are increasingly aware that antiretroviral drugs need to also reach people with hepatitis. In 2012, Uganda became the first sub-Saharan African country to produce a generic form of the antiretroviral tenofovir, through the company Quality Chemicals, and the drug is offered for free at some treatment centres, says Ocama. And in 2017, after years of using HIV programmes to secure drugs for people with HBV, the Senegalese Society of Gastroenterology convinced the government to make tenofovir available to them at a price similar to that offered to those with HIV.

Still, the stigma of having HBV can be as problematic as drug scarcity. Patient groups in Africa, Ocama says, are too few and far between. "For many people, I think it is a lonely journey. It is a place of isolation," says Nuru. But she and Kabagambe are determined to change this. After Nuru was diagnosed, she convinced her siblings to get tested. Three out of six tested positive for HBV. Since then, leveraging her sisters in Uganda as part of a 'whisper network', she has convinced 13 other people to be tested, and paid for the procedure.

Meanwhile, the patient network that Kabagambe founded is dedicated to educating the public about HBV and establishing a community in which people who have the virus can talk about it. "Being diagnosed with hepatitis B does not define your end," he says. "You can still prosper." ■

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CORRECTION

The News Feature 'Africa's silent epidemic' (*Nature* **564**, 24–26; 2018) erroneously referred to HIV as a DNA virus. It is, in fact, a retrovirus.