fibrosis, then liver cirrhosis, then death," Sven Pischke, his doctor at the University Medical Center Hamburg-Eppendorf, says matter-of-factly. “That was a shock, of course,” Stadler says.

Patients like him are a new challenge for European physicians. Until a few years ago, no one even knew they existed. Hepatitis E was seen as an exotic disease that travelers from India or Africa sometimes brought home. Now, it’s clear that there’s a silent epidemic of the virus at home, with an estimated 300,000 people infected annually in Germany alone. Most appear to catch it from eating pork, with blood and plasma transfusions playing a smaller role. The virus occurs in other developed countries as well—including the United States, Japan, and Australia—though infections appear to be much rarer there.

Scientists are still scrambling to understand the epidemiology of hepatitis E, but they know that in Europe, infection rates rival those for other major hepatitis pathogens (A, B, and C). Two questions are looming large: Should blood donations be screened for the virus? And what can be done to eliminate it from swine herds?

RESEARCHERS SUSPECTED a new form of hepatitis in 1978, when hundreds of people in Jammu and Kashmir, in northern India, got sick—and four men and six pregnant women died—from what appeared to be a waterborne hepatitis virus. Similar but larger outbreaks followed in India, Pakistan, and China, killing thousands of people, many of them pregnant women. It wasn’t until 1983 that Russian scientist Mikhail Balayan isolated the virus from his own stool after a gutsy self-experiment: He drank a cocktail of yogurt and stool samples from Soviet soldiers infected in Afghanistan. Hepatitis E became known as an important waterborne pathogen in Asia and Africa; two strains, named genotype 1 and 2, together kill an estimated 58,000 people per year.

But in 1997, scientists discovered that pigs in the U.S. Midwest carried a new strain of the virus, which they named genotype 3. It was soon identified in European pigs as well, and surveys showed that many Europeans had antibodies to it, a sign they had been infected at some point in their lives. Genotype 3 was very different from its relatives: Pork, not dirty water, appeared to be its main transmission route, and it seemed not to cause any symptoms. “Hepatitis E does not exist,” says Hans Zaaier, who heads the department of bloodborne infections at Sanquin, a nonprofit blood transfusion service in Amsterdam.

Almost immediately after Holger Stadler received a new heart, his body began to reject it. To save the 58-year-old retired plumber from northern Germany, doctors replaced his blood plasma with donated plasma lacking the antibodies that targeted the donor organ. It worked—but 3 years later, it’s clear that Stadler received something else in the bargain: the hepatitis E virus (HEV). It’s a pathogen that most people get rid of easily without even getting sick. But Stadler is taking drugs that dampen his immune system to prevent another rejection of his heart. As a result, he can’t clear the virus; it has been quietly replicating in his liver ever since. “If that is not resolved, it leads to liver

Europe’s new Hepatitis problem

Many get infected with hepatitis E, and a few get very sick. How can the virus be stopped?

By Kai Kupferschmidt

A pig liver sausage named figatellu (left) has been linked to hepatitis E infections.
"These are two completely distinct diseases." (It’s not clear whether genotype 3 might also spread in developing countries, hiding in the shadow of its more obvious relatives.)

Alas, the new strain wasn’t as innocuous as it seemed. In 2008, French researchers reported that in a group of 300 recent transplant patients, 14 had an acute hepatitis E infection. Six got rid of the virus quickly, but eight couldn't seem to shake it. At Hannover Medical School in Germany, hepatitis specialist Heiner Wedemeyer couldn’t believe it at first. "We are one of the largest transplantation centers in Europe," he remembers thinking. “We would have seen that.” But when he started screening patients he soon found some that were chronically infected with hepatitis E, as did other clinics all over Europe. Patients had one thing in common: a weakened immune system.

There’s not much doctors can do to help them. For transplant patients, one option is lowering the doses of immunosuppressive drugs to allow the immune system to regenerate, but this increases the risk of organ rejection. Doctors also use ribavirin, a drug approved for hepatitis C and several other viral infections. But there hasn’t been a controlled trial yet, and ribavirin has serious side effects.

These patients are the visible part of a much wider epidemic. Surveys have shown that 17% of adults in Germany have antibodies against the virus, meaning they became infected at some point; so do 14% in Austria, 4% in southern Italy, and 27% in the Netherlands. One Dutch study found that antibody levels in people aged 18 to 21 dropped from almost 20% in 1995 to less than 5% in 2000, then rose again to 13% in 2011, which suggests the infection is re-emerging, says Zaaijer, a co-author on the study.

Blood and blood products account for at least some of the new infections. One study suggested that 1200 blood components containing the virus are transfused each year in the United Kingdom, and roughly one in a thousand blood donors in the Netherlands carries the virus. (By contrast, a recent U.S. study found that antibody levels in people aged 18 to 21 dropped from almost 20% in 1995 to less than 5% in 2000, then rose again to 13% in 2011, which suggests the infection is re-emerging, says Zaaijer, a co-author on the study.)

A much bigger risk factor is the consumption of sausages and other pork products. Hepatitis E has been shown to be ubiquitous in swine herds in many European countries. Most animals become infected without getting sick between 3 and 6 months after birth, when antibodies inherited from their mothers start to wane. And there’s strong evidence that the virus is passed on to humans through pork. In one study, Wim van der Poel, a veterinary virologist at Wageningen University and Research Centre in the Netherlands, analyzed hepatitis E sequences found in Dutch blood donors between 2010 and 2015. “When we looked for the closest sequence ever found, [it] was always a swine sequence from the same region,” he says.

What's unclear is which pork products carry the highest risk. In one region in the south of France, infections have been linked to consumption of figatellu, a pig liver sausage that's often eaten raw. Scientists are still trying to pinpoint which other products contain the virus. It’s difficult to culture the virus from meat products, and looking directly for viral RNA is technically complicated; moreover, finding RNA does not mean the food contains intact virus that can infect a consumer. Meanwhile, some studies have also shown a risk from eating shellfish or fruit.

In the United States, in contrast, hepatis E "is very rare even in transplant patients and the immunosuppressed," says Jay Hoofnagle of the National Institute of Diabetes and Digestive and Kidney Diseases in Bethesda, Maryland. One theory is that U.S. residents eat less raw or undercooked pork. Another theory: Pigs in Europe may suffer from immune deficiencies because of some other infection. “An HIV-like agent may cause pigs or wild boar to develop chronic HEV infection,” Hoofnagle says.

**WITH SO MANY UNKNOWNS**, controlling this silent epidemic is a challenge. Ireland already screens blood products for hepatitis E, and other countries are debating doing so. Like everything else involving the blood supply, “it’s a touchy subject,” Pischke says. Screening is costly and may not make sense for the general population, which has little to fear from HEV, says Rainer Seitz, head of transfusion medicine at the Paul Ehrlich Institute in Langen, Germany, a federal institute responsible for blood safety. But he supports screening blood products before use in immunocompromised patients. The virus's apparent ubiquity in pork products and elsewhere in the environment also makes general blood screening questionable, Zaaijer says. “It’s like screening donors for flu in times of flu. The blood is safe, but the air isn’t,” he says. It’s far more important to make food and water free of hepatitis E, he adds.

One way to do that would be to vaccinate pigs. A human vaccine has already been approved in China, and scientists think a swine vaccine is feasible as well. But getting pig farmers to adopt it would be difficult, Van der Poel predicts, because their animals don’t get sick. And you’d have to be careful to vaccinate every last animal in a herd, Zaaijer adds; otherwise, the virus might just spread slowly, meaning that animals would get infected later in life, closer to slaughter, which might increase the risk in meat.

Reimar Johne, who studies hepatitis E at the Federal Institute for Risk Assessment in Berlin, is trying to find out how the virus can be inactivated in food. Twenty minutes at 70°C destroys it, but what about drying, smoking, or curing meat? To find out, Johne has started to make sausages in the lab himself. After adding a strain of hepatitis E, he can process the meat any way he wants and check whether viable virus survives. “It’s a bit artificial,” he says. “But for the moment, it’s all we have.”

*Holger Stadler’s name has been changed at his request.*
Europe's new hepatitis problem
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Editor's Summary

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