

Hepatitis E and Maternal Deaths

[Announcer] This program is presented by the Centers for Disease Control and Prevention.

[Christina Dzikowski] Hi, I'm Christina Dzikowski and today I'm talking with Dr. Alain Labrique, Assistant professor in the Department of International Health and Department of Epidemiology at the Bloomberg School of Public Health and Director of the JHU Global mHealth Initiative. Our conversation is based on his perspective on hepatitis E and maternal deaths, which appears in CDC's journal, *Emerging Infectious Diseases*. Welcome, Dr. Labrique.

[Alain Labrique] Thank you, Christina, it is a pleasure to be here today, and I'm really excited to be able to share some of our recent findings in terms of hepatitis E work.

[Christina Dzikowski] So, Dr. Labrique, what is hepatitis E and how is it different from other more well-known forms, such as hepatitis A, B, and C?

[Alain Labrique] "Hepatitis" just means an inflammation, or swelling, of the liver so we group these different viruses together as "hepatitis viruses" because they all cause liver disease, and then keep assigning them letters of the alphabet when we discover a new one. So, hepatitis E got its official name in the 1980s, but it wasn't until the early 1990s that researchers had actually cloned and sequenced this virus. So, before that, it was generally referred to as "enteric non-A, non-B hepatitis."

So, the "enteric" part just means that it's transmitted through the digestive tract. So, if you eat or drink something that's been contaminated by feces from someone with hepatitis E, which is quite frequent, unfortunately, in places where hygiene is poor and access to clean water is low, you can get infected and sick. So the term for this is "fecal-oral transmission."

So, in fact, one important piece of the hepatitis E story is worth sharing here. In 1983, as the legend goes, a colleague of ours, a Russian virologist, Mikhail Balayan, was able to isolate and visualize this new agent using electron microscopy. But he was studying an outbreak of non-A, non-B enteric hepatitis in Afghanistan, and in the absence of a cold chain, and probably also permission from his supervisors, to transport these specimens back to his lab in Moscow, he actually filtered the stool from nine acute patients, mixed it with yoghurt and ingested the slurry. So roughly 30 days later, he developed symptoms and was able to examine his own stool with phenomenal results. So, this is not recommended by either Johns Hopkins or the CDC, I'm sure.

Hepatitis A is transmitted this way, as well. So, I like to tell my students to remember this using the mnemonic, "the vowels are in the bowels," so hepatitis A and E. They both can cause similar symptoms, like fever, anorexia, or not wanting to eat, nausea and vomiting, weakness, and other non-specific symptoms. But there's also a more distinctive symptom of hepatitis called "jaundice," which is when your skin and the whites of your eyes take on a yellowish color. And that yellowish color we see with people with jaundice comes from the substance called bilirubin; it's a pigment that your body produces as a by-product of recycling blood cells. Usually your liver processes bilirubin and then you excrete the leftovers in your feces. But as you can imagine,

if bilirubin is building up in your body so much that you start to turn yellow, it's a good sign that your liver isn't working properly.

So, we tend to focus, at Johns Hopkins, on the severe end of things, so where hepatitis E causes serious illness and death in pregnant women, and obviously those very serious cases are what we're most concerned about. In most cases, hepatitis E and hepatitis A cause a mild illness and this resolves on its own. But hepatitis E and A also don't usually cause chronic infections in healthy people. You get infected, you may feel sick for a few weeks and even have a little bit of jaundice, but then you recover.

Now, hepatitis B and C, on the other hand, they also cause some short-term illness, but they can both cause chronic infections that remain in your liver for years. And over time, those chronic hep B and hep C infections can increase your chance of getting liver cancer or needing a liver transplant. That's why you may have seen a lot of these ads on TV recently to encourage, say Baby Boomers, to get tested for hepatitis C; so many people have hepatitis C infections and don't even know it, but there are treatments out there that can really reduce the risk of liver cancer.

[Christina Dzikowski] So how do people get it?

[Alain Labrique] In most of the developing world, where hepatitis E commonly causes large outbreaks, we've found that the primary way to get infected is to drink water or eat food, as I was saying earlier, that's been contaminated with HEV from someone else's feces. And this often happens in South Asia when flooding occurs during the monsoon, and either the water supply is overwhelmed by fecal contamination, or when the water purification plants, where they exist, break down.

In the US, in Europe, in parts of China, Japan, so eastern/south-east Asia, another, zoonotic or animal-borne genotype of HEV predominates. And in these populations, hepatitis E infection can come from eating undercooked wild game, so deer, boar, and even regular undercooked pork. In the past decade, we've become increasingly aware that HEV infections are far more common in places like the US and Europe, likely due to exposures to HEV through the food system, or exposure to untested blood products.

One of our colleagues, X. J. Meng, in the US, has actually looked at the presence of live virus in commercially bought pig livers. So walking into, say, a giant grocery store and just picking out pig livers from the shelf was actually able to infect animals using the hepatitis E that was recovered from those specimens. We've seen some infections transmitted through blood transfusions or transplants -- and actually, the FDA just announced on September the 20th of 2012 that it's going to start taking a closer look at the blood supply in the US. Right now, in the US, we don't screen blood or organ donors for HEV.

Another way to get hepatitis E is through what we call vertical transmission, which is when a pregnant woman who is infected with hepatitis E passes the virus to her newborn child. And this is another big issue related to hepatitis E and pregnancy. Besides the pregnant women sometimes

getting very sick and often dying, there can be problems for the newborn, as well. It's actually something we're looking into right now.

[Christina Dzikowski] So is this a major public health problem throughout the world?

[Alain Labrique] Well, Christina, it's a huge problem, especially in countries that don't have a good infrastructure for clean water and sanitation. David Rein and his colleagues at the University of Chicago estimated that there might be around twenty million infections and about 70,000 deaths caused by HEV in a single year. We think hepatitis E is now the number one cause of acute viral hepatitis in the world.

In some situations, like in refugee camps, it can really explode into outbreaks very very easily and rapidly. I know of some outbreaks, just in the past month, going on in refugee camps in South Sudan, in Kenya, because it's often just so difficult to maintain access to clean water and sanitary conditions in these challenging humanitarian disasters. We've seen similar situations in urban slums, in places we work in Bangladesh, and in other areas where lots of people can't get clean water easily or dispose of waste in a sanitary way.

Lastly, there aren't any good treatments for hepatitis E so treatment is largely supportive, meaning we address the symptoms, maintain hydration, nutrition, etc. So even though most people don't end up in the hospital or dying from hepatitis E, that's an awful lot of people to be laid out for a whole month, missing work, losing income, and in outbreak situations, filling up what few hospitals and clinics may be available. So, it's a big problem, and we're hoping that a number of promising vaccines that have been developed could prevent hepatitis E from occurring in the first place, while we work towards improving living conditions in these resource limited settings.

[Christina Dzikowski] So, is this virus found in the United States?

[Alain Labrique] That's a fantastic question. Actually, it is and it surprised a lot of people, since we don't see a lot of people getting sick from it here in the US. My colleagues, Mark Kuniholm and Kenrad Nelson, tested blood samples from more than 18,000 people in the US and found that 20 percent of them, roughly, had antibodies to hepatitis E. So we think that in the US, and in Europe and other industrialized countries, a lot of people are probably getting exposed and infected and recovering, without any noticeable symptoms. Some of it may be through undercooked food or from working with animals. The truth is, we're not really sure yet. Another thing is that hepatitis E wasn't even on the public health radar until recently and the early tests for it weren't very good. So it's also likely that we missed a lot of cases and we just didn't recognize hepatitis, acute viral hepatitis, as being caused by hepatitis E virus. So now that we're starting to look for hep E, we'll probably detect more cases in the US.

Now one place where we really want to look is in people who are getting transplants, not just liver transplants, but any kind of organ transplants. And the reason is that these patients usually end up taking drugs that suppress their immune systems so that the transplants don't get rejected. But now as a result of this immune suppression, they also can't get rid of viruses so easily. And

in this population of patients, we do see some chronic HEV infections and complications, which is unusual in people with healthy immune systems.

Now, as for why we don't seem to have a big hepatitis E outbreaks in the US – mostly, we have pretty good sanitation and clean water supplies, which makes it harder to keep a chain of infection going. Another reason is that the genotype of HEV that's most common in the US and Europe is the kind found in pigs, and it might be a little less virulent and a little less well adapted to humans than the strains we found in South Asia and Africa, for example.

Now one of the things our group has been looking at carefully is to see how the immune system responds to hepatitis E. In places like rural Bangladesh, where we see a lot of malnutrition, under-nutrition, and other co-incident infectious diseases, it may be that people are predisposed to more severe hep E than in the US. But really, these different geographic patterns are something we're still working out and pursuing research to answer the questions.

[Christina Dzikowski] What is the relationship between pregnant women and HEV?

[Alain Labrique] That's a great question. From what we've learned so far, we suspect it has a lot to do with how a woman's immune system and hormone levels change during pregnancy to protect the fetus. These changes are really fascinating, and they affect more than just hepatitis E. When women are pregnant, they're more susceptible to some other infectious diseases as well, but at the same time, other conditions, like rheumatoid arthritis, might actually improve or go into remission. This is a really important area of research, but also a really complex one, because there are so many different changes happening in the body over those nine months.

Some of these changes, like increased progesterone levels, may make it easier for the virus to replicate. So with these shifts in the immune system messengers, which we call cytokines, that help prevent the mother's immune system from attacking the fetus by mistake, but these same shifts might also make it harder for pregnant women to fight viral infections. So another hypothesis is that the mother's immune system itself develops an extremely self-injurious response to the virus, and sets off a kind of chain reaction that ends up damaging the body, instead of saving it from attack. So the infection might cause problems in blood clotting that lead to bleeding, which is a serious problem for pregnant women. And, of course, there's other factors were that finding, like the host's nutritional status, the strain of the virus, that may also play a role in the severity of infection that we see in pregnancy. There's a lot of moving pieces in this puzzle and we've been working now for over a decade and we're still trying hard to figure it out.

I should also point out, however, that men can also die from hepatitis E, so, as well as women who aren't pregnant. And I don't want to give the wrong impression that hepatitis E only affects pregnant women. Men seem to get exposed to HEV and infected more often than women, maybe because of their daily activities in parts of the world where this is most significant. In some of these conservative communities, women's mobility is actually restricted, so to some extent that protects them the exposures to hepatitis E that men may have in disproportionate ratios. Usually, however, when men get infected, the illness is pretty mild. A small fraction of men with hep E do get liver failure and die, but there's something unusual about pregnancy that seems to really increase the chance that the disease will either be severe or fatal.

[Christina Dzikowski] Well, do we know how many women die each year from HEV?

[Alain Labrique] We don't have really solid numbers, but it's probably in the tens of thousands, and most of the deaths are in South and Central Asia and in Africa. This is why, I think, this paper was, for us, such an important contribution to the literature, is because it surprised us in Bangladesh to see how many pregnant and non-pregnant women were dying from hepatitis-related causes.

Worldwide, there may be something like 70,000 deaths each year from hepatitis E, in both men and women, according to that study from the University of Chicago I mentioned earlier. But again, these are modeled estimates so until we have a system that actually captures head counts and is able to diagnose, effectively, the true numerator, the true number of cases, it's going to be very hard for us to put an accurate estimate to the real burden of hepatitis E deaths that we see. Most countries don't have formal surveillance for hepatitis E, and a lot of hospitals don't test for it. And keep in mind, many women in developing countries can't pay for hospital care, or simply can't get to a hospital because they're too far and there's no reliable transportation or roads. So we really need to improve surveillance to get accurate counts and to be able to answer your question about how many of deaths we see annually from hepatitis E.

[Christina Dzikowski] Can you tell us about the vaccines for HEV?

[Alain Labrique] Sure. There's actually a number of vaccines, both experimental and that have been through the series of trials that demonstrate vaccine efficacy. Two different vaccines have already been developed and tested and shown to work extremely well and also to be safe. Neither of these vaccines, however, is available globally at the moment.

[Christina Dzikowski] Well, why isn't it being used?

[Alain Labrique] The first vaccine has a frustrating story attached, from the perspective of international health research. It was developed by GlaxoSmithKline and the Walter Reed Army Institute of Research and tested, in collaboration with the Nepali government and military on soldiers from the Nepali army. The idea was that Nepal, which is in South Asia, is right at the heart of the endemic part of the world for hepatitis E, so it made sense to try out the vaccine there. But the decision to test the vaccine in soldiers caused a lot of controversy, both about informed consent and the ability of a young soldier to opt out when there's a lot of pressure to participate. But also, related to the representativeness of that population to where the true burden of morbidity and mortality, so illness and death, really resided, which was in women of reproductive age and there were very few women of reproductive age in that cohort that was studied in Nepal. So after that trial ended, it took a while for the results to be published and they finally showed that the vaccine worked pretty well, but the company decided not to move ahead with it, after all the efforts. So this decision has also been part of a larger debate about whether companies that test new drugs or vaccines have the responsibility to make the drug or vaccine available to populations in which they were tested. As of today, as far as I know, the company still has no plans to produce the vaccine, although there are still researchers who are looking into that Walter Reed GlaxoSmithKline vaccine.

Now, the newer vaccine, the one made in China, that was recently published in 2010, is called Hecolin, and it was just licensed earlier this year, in 2012, for sale and distribution in China. But it will take a while to get it into mainstream production and then the company will have to demonstrate that the vaccine meets safety and efficacy requirements in other countries so that it can be used elsewhere.

But even after all this, there will still be many obstacles, including willingness to pay, how and when to distribute the vaccine to people who need it. And the issues of who will pay for the vaccine, who will organize and monitor the distribution, and so on, are sometimes just as challenging as the science behind developing the vaccines themselves.

[Christina Dzikowski] If pregnant women are unable or unwilling to be vaccinated, would it help if men in the communities were vaccinated?

[Alain Labrique] It probably wouldn't hurt, but it might not help as much as we'd hope. We talk a lot about "herd immunity," which is what happens when you vaccinate a really high proportion of the population for some disease, like measles, and that high vaccination rate helps protect the few who aren't immune or who weren't able to be vaccinated. Now the reason herd immunity works is because a virus can't infect people who are technically already immune, and if there aren't enough people to infect, it can't go anywhere within that population, so the spread is really restricted. So when a major part of the population is vaccinated and subsequently immune, then it's really tough for the virus to keep circulating, and the chances of coming into contact with a sick person are really small. —So this is the ideal scenario that we hope for when we emphasize the importance of vaccination for everyone.

But with hepatitis E, and most diseases, vaccinating only half the population probably isn't enough to get a herd immunity effect to kick in. It's true that if men are immune, and at least if they're less likely to be sick, then they won't be shedding so much virus in their stool, so the water sources may be less contaminated, which sounds pretty good. But there will still be other women who are infected and shedding virus, and since this is a waterborne virus, maybe men and women in a village upstream who are shedding virus into the water source may be resulting in infections downstream, so it's not clear that this strategy would really have the effects we'd want to see in terms of preventing disease in pregnant women.

So what we really hope that it may be possible to vaccinate pregnant women themselves, or women in late adolescence or just after marriage, when they're at highest risk of becoming pregnant and they need that protection from the infections as they go into pregnancy. So that way we won't have to count on herd immunity to protect them. Now, that said, so far, neither of the two HEV vaccines has been tested specifically in pregnant women. There were a few women in the Chinese vaccine trial who were pregnant and inadvertently vaccinated who ended up not having problems as a result of the vaccine, but we do really need some dedicated studies to make sure that it's safe and effective to use a vaccination of pregnant women strategy. We also need to find out how early we'd need to vaccinate to ensure that women are protected by the time they reach the second or third trimester, which is when we tend to see the most severe hepatitis E and the most elevated rates of mortality.

[Christina Dzikowski] Are there any other public health interventions that could be used to control HEV in pregnant women, and are they being used?

[Alain Labrique] So, this is a struggle that's as old as public health itself. I think the initiative that communities have taken around the world to improve access to clean and safe water and to improve overall sanitation are really the best interventions that would help curtail the risks of hepatitis E. Probably, because these interventions end up controlling a lot more, in terms of the spread of infectious disease, than just hepatitis E, and they have benefits on the entire population, from newborns to children to pregnant women. Smaller, community-level efforts, like educating communities about home water purification methods, sanitary waste disposal, building latrines, providing soap, and so on – these are also good. Water is a shared resource that's so central to people's lives. So it's really the vaccines and these large-scale infrastructural interventions that will make the most substantial difference.

At the end of the day, we need to invest resources to put this emerging infection on the map. We often say that hepatitis E is so neglected, it's left off the lists of neglected tropical diseases. So we need better assays, and surveillance to better quantify the global burden, so this virus is given the attention it deserves from the public health community.

[Christina Dzikowski] Thanks, Dr. Labrique. I've been talking with Dr. Alain Labrique about his perspective, *Hepatitis E, a Vaccine-Preventable Cause of Maternal Deaths*, which appears in the September 2012 issue of CDC's journal, *Emerging Infectious Diseases*. You can see the entire article online at www.cdc.gov/eid.

If you'd like to comment on this podcast, send an email to eideditor@cdc.gov. That's e-i-d-editor - one word - at c-d-c-dot-gov. I'm Christina Dzikowski, for *Emerging Infectious Diseases*.

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