



A mother and baby at a hospital in Baganuur, Mongolia. Infant vaccination against hepatitis B could reduce the country's crippling high rate of liver cancer.

VACCINES

Taking a shot at protection

A vaccine to prevent hepatitis B, the most common cause of liver cancer, has promise — and limitations.

BY KAREN WEINTRAUB

The worldwide hepatitis B virus (HBV) epidemic frequently feels personal for Indermohan Narula, a physician in Ulaanbaatar, Mongolia. Earlier this year, he saw a young woman whose liver was so scarred by HBV infection that, were she to continue her pregnancy, she would have put her life at risk. Her liver disease was untreatable, so he did what he could: he encouraged her to protect herself by ending the pregnancy and avoiding fatty foods and alcohol. “The question now is what she can do for herself and her family,” he says.

Despite such sad encounters, Narula, who is team leader of the Global Fund to Fight AIDS, Tuberculosis and Malaria in Mongolia,

sees hope for the future. Four years earlier, he helped that same woman to deliver a healthy baby boy. The infant immediately received the HBV vaccine, greatly increasing the odds that he would not develop the same disease as his mother. Stories such as this portend a healthier future for Mongolia, which currently has the world's highest rate of liver-cancer mortality — here and elsewhere, the main cause of this disease can be eliminated by the HBV vaccine.

More than 240 million people worldwide are chronically infected with HBV, according to the World Health Organization, and the virus is responsible for just over half of the world's cases of liver cancer and about 30% of all cases of cirrhosis (scarring of the liver)¹. Public-health officials are trying to protect future generations

by vaccinating as many children as possible; they have made considerable progress, but the virus is proving to be a tricky target. Not all children are getting vaccinated, and those who are still sometimes get infected. Until those gaps can be closed, and until decades have passed and immunized children grow into adulthood, HBV will remain a major threat to public health.

Early vaccination is crucial in the fight against HBV, which is generally transmitted during childbirth or through dirty needles or sex. More than 90% of adults exposed to the virus clear the infection within six months, most with few or no symptoms. But the younger that someone is exposed, the greater the odds of a chronic infection. Younger immune systems seem to be less able to fight the infection without help, says Vinh Pham, an infectious-disease specialist at the New York University Langone Medical Center. If infants are exposed to HBV during birth, immediate vaccination can erase the virus from their systems. But an unvaccinated child who picks up the virus during the first year of life will almost certainly develop a chronic infection, and 15–25% of these children will eventually die from related liver cancer or cirrhosis.

The World Health Organization has recommended universal infant vaccinations against HBV since 1992. As of 2012, 183 nations routinely vaccinate infants, and 79% of children worldwide are protected. “That was really the first vaccine that got [widespread] uptake

in the developing world," says Paul Offit, an infectious-disease specialist at the Children's Hospital of Philadelphia in Pennsylvania.

As with most vaccines, however, implementation rates are still below where they should be, says Neal Halsey, director of the Institute for Vaccine Safety at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland. The problem is particularly acute, Halsey says, in central African countries, which have some of the highest rates of HBV infection. More vaccinations in these countries would greatly reduce rates of cirrhosis and liver cancer decades into the future.

Universal infant vaccination against HBV has proven to be hugely successful in many countries. The United States instituted such a programme in 1991; before then, about 18,000 children under the age of 10 were infected there every year. About half caught the virus from their mothers during childbirth, Offit says, and the rest were infections passed on through unprotected sex (including rape), sharing dirty needles, or casual interactions such as sharing a toothbrush or washcloth. Vaccination has now almost eliminated the infection among this age group.

INOCULATION DEFERRED

Preventive strategies are not limited to universal infant vaccination programmes — Canada and some countries in Europe vaccinate children at school, between the ages of 10 and 12. Such an approach works well in nations without a lot of mother-to-child transmission and where there is infrastructure to provide the multi-shot vaccination in adolescence. It would not, Halsey argues, be as effective in the United States, where vaccinations are not given in schools and where healthy teenagers typically see a doctor just once a year. In addition, parents in the United States have been slow to accept the idea of giving vaccines associated with sexually transmitted diseases

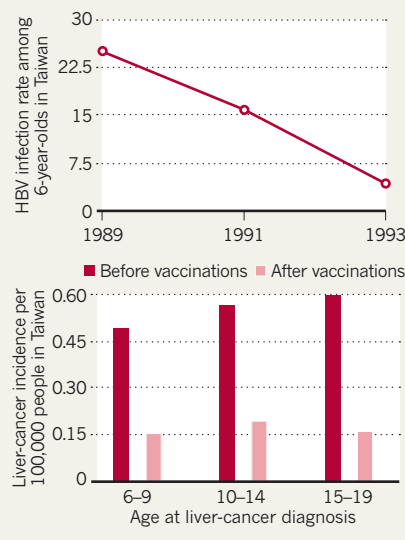
to their children. The backlash against another cancer vaccine, one typically given to young adolescents to protect against cervical cancer caused by the human papilloma virus (HPV), has led researchers to speculate that attempts to move HBV vaccination from infancy to adolescence would elicit a similar parental reaction.

Six countries with low HBV infection rates — the United Kingdom, Denmark, Finland, Iceland, Norway and Sweden — have opted to forgo universal vaccination, choosing instead to focus on screening those at highest risk. Although there is clear consensus in the United Kingdom that childhood vaccination is important, adding an HBV shot to the schedule is complicated by politics and financial constraints, says John Edmunds, a specialist

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IMMUNITY BOOST

Taiwan launched a programme of universal infant vaccination against hepatitis B virus (HBV) in 1986. Since then, rates of HBV infection in the country have tumbled, along with rates of childhood liver cancer.



in infectious-disease modelling at the London School of Hygiene and Tropical Medicine. "It's not necessarily the highest priority when compared with other changes to the vaccine programme that we could and should introduce," he says.

In many countries, however, screening programmes trying to identify those at highest risk are simply ineffective. In the 1980s and early 1990s, the United States targeted vaccination to adults at highest risk — including sex workers, intravenous drug users and men who had sex with men — and recommended universal screening of pregnant women. But that policy failed because "people didn't identify as being at high risk", Halsey says, and vulnerable mothers, including sex workers, slipped through the cracks. The rates of new HBV infections in adults barely budged. It was another reminder that human behaviour can undermine even the best vaccines, and even more reason why nationwide infant immunization programmes might — at least for some countries — be the most effective option.

THE WAY FORWARD

Taiwan, which has had universal vaccination since 1986, provides perhaps the best example of the HBV vaccine's potential benefits (see 'Immunity boost'). Between 1977 and 1980, there were 454 cases of liver cancer among young Taiwanese people aged 5 to 29, whereas between 2001 and 2004 there were just three cases². But in adults too old to have been vaccinated, Pham says, the rate of liver cancer is essentially unchanged because people who are chronically infected rarely clear the virus.

The oldest of those vaccinated are now reaching the age of 30, and protection is largely

holding. The data suggest that booster shots are not generally needed — at least so far, says Chien-Jen Chen, a liver-cancer researcher and vice president at the Genomics Research Center at Academia Sinica in Taipei. "It seems to be that the hepatitis B vaccine has very long-term protection," he says.

But vaccinations do not always guarantee complete immunity. A study first published in 2012 found low rates of infection — around 2% — in nearly 9,000 Taiwanese high-school students who had been vaccinated as children³. Infection rates were highest in teenagers whose mothers were also infected, suggesting that the viral load received during birth might have overwhelmed the vaccine.

Across the Formosa Strait, in China, a universal infant immunization programme that started in 1992 is credited with protecting 80 million children from HBV infection. When vaccinations began, nearly 10% of children under the age of five had the virus. By 2006, the infection rate had dropped below 1%. But this resounding success has a potentially troubling footnote. According to a 2013 study, many of the viruses that remain in the younger population have accrued mutations — a sign that the pathogen might be evolving under the selective pressure of vaccines⁴. Doctors are watching carefully for any sign of a new strain that is broadly resistant to vaccination.

For now, researchers see no reason why even more babies around the world cannot be vaccinated. A three-dose vaccine regimen can cost US\$30 or less and rarely triggers an allergic response or any serious complication. "It's really a very safe vaccine," says Halsey. Despite this, some parents remain uncomfortable with vaccines, not trusting them to do more good than harm. "We begged for cancer vaccines for several decades," Halsey says. "Parents should not be hesitant to protect their child against a relatively common cause of cancer."

Liver cancer is an expensive disease in terms of both human lives and treatment cost (see page S4). According to Edmunds, "in the long run, the hepatitis B vaccine will be one of the most cost-effective vaccines. But it takes a very long time to achieve those gains." Public-health systems focus their resources where they are most acutely needed. Does it make more sense to spend public money addressing a virus that will not cause liver cancer for decades or a virus such as HIV that is causing pain and suffering today? At this point, says Edmunds, that is a question each country is addressing for itself. ■

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