

## Hepatitis E vaccine: why wait?

In *The Lancet* today, Buddha Basnyat asks why are hepatitis E and the conjugate typhoid vaccines not available, despite their proven efficacy and safety. In 2007, Mrigendra Prasad Shrestha and colleagues assessed the safety and efficacy of a recombinant protein hepatitis E virus (HEV) vaccine that was produced in insect cells by the US Army working with GlaxoSmithKline. This vaccine showed 95.5% efficacy after administration of three doses (20 µg per dose) at months 0, 1, and 6 in a phase 2 randomised controlled trial of 2000 healthy, mostly young men in Nepal. Although GlaxoSmithKline retains the intellectual property rights to this vaccine, it reportedly has no plans for development. The results of Feng-Cai Zhu and colleagues' phase 3 trial, reported in *The Lancet* today, using a recombinant HEV vaccine (HEV 239), which was produced in bacterial cells, lend support to the efficacy and safety of such a vaccine. HEV 239 was assessed in a general population of healthy men and women (aged 16–65 years) living in Jiangsu province, China. Three doses (30 µg of purified recombinant hepatitis E antigen per dose) of HEV 239 administered at months 0, 1, and 6 resulted in 100% efficacy in 48 693 individuals, whereas 15 of 48 663 people given the placebo (hepatitis B vaccine) developed hepatitis E.

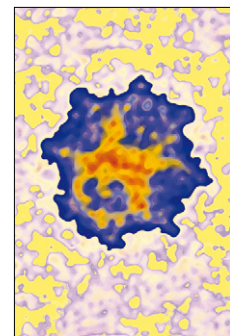
HEV is a single-strand, positive-sense RNA virus that was first recognised in India in the 1980s. This virus is transmitted enterically from individual to individual through contaminated water and uncooked food, resulting in hepatitis epidemics or sporadic cases. The highest incidence of sporadic cases in developing countries is in the age group 15–35 years; in developed countries, individuals older than 45 years have the highest incidence. A third of the world's population, mostly in developing countries, is infected with HEV. Genotypes 1, 2, and 4 are prevalent in developing countries, whereas genotype 3 is prevalent in Europe and the USA. At least 50% of acute viral hepatitis in endemic countries is caused by HEV. Because HEV infection is self-limiting, the hepatitis is usually acute. Hepatitis E cannot be clinically distinguished from the other acute viral hepatitises; therefore, diagnosis is by use of enzyme immunoassay for the detection of specific IgM or viral RNA with reverse transcriptase polymerase chain reaction.

HEV vaccines should also be assessed in pregnant women (particularly those in the second and third trimesters), immunosuppressed individuals, and infants (<2 years). Efficacy and safety should first be assessed in pregnant women with HEV infection, in whom fulminant hepatitis can arise. The mortality rate is 5–25% in pregnant women compared with 1% in the general population infected with the virus—eg, in one hospital in Kathmandu, Nepal, 20–30% of pregnant women with hepatitis E die. HEV can be vertically transmitted during pregnancy, and increases the risk of abortions, stillbirths, deaths in newborn babies, and neonatal hypoglycaemia and liver injury.

HEV infection in people with chronic liver disease can increase the mortality rate—eg, 1-year mortality in Indian individuals with these comorbidities was 70%. Hence, individuals with underlying chronic hepatic disease might benefit most from an HEV vaccine. The period of protection afforded with vaccination against HEV should also be established.

Precautions for prevention of the spread of HEV include improvements in sanitation, education about handwashing, and storage, handling, and preparation of uncooked pork. Because no treatment exists for HEV infection, development of a vaccine is the best way forward in developing and developed countries. However, developing countries are unlikely to have the resources needed to develop and test vaccines. So why have companies invested their resources in creating vaccines such as those for HEV that are safe and seem effective, and then not developed them when they are urgently needed?

The answer might be that pharmaceutical companies do not think an HEV vaccine is commercially viable. Hopefully, this situation will change after the International Symposium on Hepatitis E in Seoul, South Korea, on Sept 15–16. This symposium has been organised by the International Vaccine Institute in collaboration with WHO. Experts from around the world will gather to share data about hepatitis E epidemiology, disease burden, diagnostic methods, and vaccines. One of the planned outcomes of this symposium is the generation of strategies for the rapid development and delivery of HEV vaccines, which is not a moment too soon. ■ *The Lancet*



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For **Shrestha and colleagues' paper** see *N Engl J Med* 2007; **356**: 895–903

For a **review of hepatitis E** see *Lancet Infect Dis* 2008; **8**: 698–709

For more on **hepatitis E and pregnancy** see Aggarwal R. *Indian J Gastroenterol* 2007; **26**: 3–5