



Hepatitis E vaccination: Questions and answers

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What is Hepatitis E and what is the global burden of disease?

Hepatitis E is caused by hepatitis E virus (HEV), a small ribonucleic acid virus which is relatively stable in the environment. It is sensitive to heat, chlorination and ultraviolet light. There is one recognized serotype of HEV with 4 known genotypes (genotype 1, 2, 3 and 4). HEV genotypes 1 and 2 primarily infect humans, whereas genotypes 3 and 4 mainly infect mammals and are a zoonotic disease for humans. Genotype 1 is the most prevalent HEV genotype and is widely distributed in several countries in Asia and Africa. Most cases of hepatitis due to genotype 4 have been reported in mainland China. Every year, there are an estimated 20 million HEV infections worldwide, leading to an estimated 3.3 million symptomatic cases of acute hepatitis E. WHO estimated that HEV caused approximately 44 000 deaths in 2015.¹

What are the signs and symptoms and who is at particular risk?

Clinical features of HEV disease (all genotypes) are similar to those of acute viral hepatitis caused by other hepatotropic viruses. Genotype 1 and 2 is mainly faecal-orally transmitted, in particular faecal contamination of drinking water. The transmission of genotypes 3 and 4 is mainly zoonotic, through consumption of uncooked or undercooked meat, with the environment also a likely source of infection.

In immunocompetent persons, acute illness is infrequent and often mild. The case-fatality in immunocompetent is generally low. Pregnant women, persons with pre-existing liver disease and immunosuppressed persons are at high risk of fatal disease, with case-fatality ratios in pregnant women of 10 to 25%.² Outbreaks of the disease are of particular concern when they occur in overcrowded settings with inadequate clean water supply and waste management services. Treatment for acute hepatitis E is generally supportive. Outbreak response measures include surveillance, health promotion and water, sanitation and hygiene (WASH) interventions such as water chlorination.

What kind of vaccine is available?

To date, only one vaccine against HEV (HEV 239 vaccine, Hecolin®), based on a genotype 1 HEV strain, has been licensed in China in December 2011 for use in healthy adults aged ≥ 16 years. The

¹ GLOBAL HEPATITIS REPORT, 2017.

<https://apps.who.int/iris/handle/10665/255016> accessed August 2019 ² Kamar N, Bendall R, Legrand-Abravanel F, Xia NS, Ijaz S, Izopet J DH. Hepatitis E. Lancet. 2012;379(9835):2477–88

vaccine consists of viral protein produced in bacterial cells, which is purified and formulated with Alum as adjuvant. The vaccine is administered using a 3 dose schedule at 0, 1 and 6 months.

What are the storage requirements?

HEV 239 is currently available as single pre-filled, non-auto-disabled syringe without vaccine vial monitor. It should be stored at 2–8 °C and has an approved shelf life of 36 months under appropriate storage conditions.

Where is the vaccine used? Is the vaccine prequalified?

To date, the vaccine has been licensed in China a country with a well-functioning National Regulatory Authority and is in programmatic use there. HEV 239 vaccine has not been used outside of China with the exception of vaccine use within the ongoing clinical trial in Bangladesh³ and in an ongoing Phase I trial in the USA. Registration processes are ongoing in Pakistan and USA. HEV 239 is currently not WHO prequalified though prequalification is not a prerequisite for use at the country level. The respective national regulatory authorities decide on use of the vaccine.

Is the vaccine immunogenic and efficacious?

The vaccine has proven to be immunogenic and highly efficacious among healthy adults aged 16–65 years old. In a large Phase III randomized trial with more than 100 000 participants, the primary (per protocol) analysis revealed 100% vaccine efficacy (95% CI: 72.1%–100%; $p < 0.0001$) during the 12 months after the third dose.

Vaccine efficacy after 2 doses revealed 5 cases of hepatitis E among 54 973 placebo recipients (and none among the 54 986 vaccine recipients with efficacy of 100.0% (95% CI: 9.1%–100.0%).

Recent data show that 96.7% of vaccinated elderly aged >65 years seroconverted at one month after the final dose.⁴

What is the duration of protection?

The Phase III trial was extended 4.5 years to assess the long-term efficacy of the vaccine. It did not significantly decrease during the extended follow-up period and was 93% (95% CI: 78.6%–97.9%) among participants having received all three doses, and 85% (95% CI: 67.1%–93.3%) among those with at least one dose.

Does the vaccine confer cross-protection?

HEV strains that infect humans belong to one currently identifiable serotype, with marked serological cross-reactivity as well as evidence for cross-protection in non-human primates and in

³ Effectiveness Trial to Evaluate Protection of Pregnant Women by Hepatitis E Vaccine in Bangladesh. ClinicalTrials.gov Identifier: NCT02759991.

⁴ Yu XY et al. Safety and immunogenicity of hepatitis E vaccine in elderly people older than 65 years. Vaccine. 2019 Jul 26;37(32):4581–4586

humans.^{5,6,7} Therefore, HEV vaccine with recombinant pORF2s, such as Hecolin®, derived from a given genotype is expected to provide cross-genotype protection against all four genotypes.⁵

In the Phase III trial, of 23 persons who developed HEV infection (22 in the placebo group and 1 in the vaccine group), viral genotype could be studied in 13 patients. Of these 13 isolates (all in the placebo group), 12 were genotype 4 and one was genotype 1. This indicates that protection provided by the HEV 239 vaccine in this trial was mainly against infection with HEV genotype 4. Efficacy and effectiveness data on specific protection afforded by the HEV 239 vaccine against genotype 2 or 3 HEV infection.

How do we know the vaccine is safe?

In 2014, the Global Advisory Committee on Vaccine Safety (GACVS) assessed overall HEV 239 vaccine safety derived from the clinical trial data.⁸ These data suggest that the vaccine is well tolerated. Short-term local and systemic solicited adverse event data show more frequent local adverse events in the Hecolin® group compared to the control group. The solicited systemic adverse events and unsolicited adverse events occur at similar rates between study groups. There appear to be no difference in serious adverse events or death identified in the Hecolin® group compared to the control group. In summary, available safety data in healthy subjects are reassuring. The vaccine also appears to be safe elderly >65 years⁴ as well as in chronic hepatitis B surface antigen carriers.⁹

Is HEV vaccination efficacious and safe to be administered during pregnancy?

In general, the theoretical risk of serious complications conferred by inactivated vaccines during pregnancy is low. In 2014, GACVS evaluated data on the safety of immunization of pregnant women for several inactivated and live attenuated vaccines. There was no evidence of adverse pregnancy outcomes from the vaccination of pregnant women with inactivated viruses, bacterial vaccines, or toxoids. GACVS concluded pregnancy should not preclude women from immunization with these vaccines, if medically indicated.¹⁰

Regarding the safety of Hepatitis E vaccine in pregnant women, limited data show (37 pregnant women inadvertently vaccinated during the Phase III trial) that the vaccine was well tolerated in pregnant women with rates of adverse events similar to those observed in matched non-pregnant

⁵ Recommendations to assure the quality, safety and efficacy of recombinant hepatitis E vaccines. https://www.who.int/biologicals/expert_committee/POST_ECBS_2018_Recommendations_HEP_E_vaccines.pdf?ua=1

⁶ Zhang J et al. Development of the hepatitis E vaccine: from bench to field. *Semin Liver Dis.* 2013;33:79–88.

⁷ Purcell et al. Pre-clinical immunogenicity and efficacy trial of a recombinant hepatitis E vaccine. *Vaccine* 21 (2003) 2607–2615

⁸ Weekly epidemiological record. Global Advisory Committee on Vaccine Safety, 11–12 June 2014. No. 29, 2014, 89, 321–336.

⁹ Wu T, Huang SJ, Zhu FC, et al. Immunogenicity and safety of hepatitis E vaccine in healthy hepatitis B surface antigen positive adults. *Hum Vaccin Immunother* 2013;9:2474–2479.

¹⁰ Global Advisory Committee on Vaccine Safety. Safety of Immunization during Pregnancy. A review of the evidence. World Health Organization, 2014. Available at: http://www.who.int/vaccine_safety/publications/safety_pregnancy_nov2014.pdf, accessed December 2017.

women.¹¹ Hepatitis E vaccine was further used as comparator vaccine in HPV trial, about 1000 women in the Hepatitis E group became pregnant in the course of the trial. No serious adverse events were reported.¹² There are no data on vaccine immunogenicity in pregnant women and data on whether HEV 239 vaccine prevents the severe hepatitis E seen during pregnancy is also pending wider use in this population.

No interim data are yet available from an ongoing clinical trial in Bangladesh in women of childbearing age, though to date no serious adverse events have been registered (Personal Communication with the Principal Investigator).

In 2015 WHO recommended that the vaccine should be considered in special situations to mitigate consequences in pregnant women.

According to the manufacturer, Hecolin® is not contraindicated during pregnancy, though the package insert states that *“No relevant research data is available for these persons, and full consideration of the pros and cons should be taken to decide whether to use this product.”*

Who should be vaccinated?

In special situations such as outbreaks where the risk of hepatitis E or of its complications or mortality is particularly high, **WHO recommends using the vaccine.**¹³ In particular, the use of the vaccine to mitigate or prevent outbreaks of hepatitis E should be considered as well as the use of the vaccine to **mitigate consequences in high risk groups such as pregnant women** as outlined above.

To date, WHO does not make a recommendation on the introduction of the vaccine for routine use in national programmes due to absence of sufficient information, in particular on vaccination of recipients <16 years of age, immunosuppressed patients, and on the degree of cross-protection the vaccine may confer. However, national authorities may decide to use the vaccine based on the local epidemiology.

Where are the knowledge gaps?

To date, few data have been generated following the Phase III clinical trial data leading to licensure of the vaccine.

Data gaps remain on the epidemiology of hepatitis E, in particular: the incidence and mortality of the disease in the general population as well as in special populations; the efficacy of the hepatitis E vaccine against disease caused by HEV of genotypes 1, 2 and 3; the efficacy of schedules of hepatitis E vaccination with <3 doses; the duration of protection following hepatitis E vaccination and the possible need for booster doses; and co-administration.

¹¹ Safety of the Hepatitis E Vaccine for Pregnant Women: A Preliminary Analysis. HEPATOLOGY, Vol. 55, No. 6, 2012

¹² Qiao YL, Wu, T, Li RC, et al. Efficacy, Safety, and Immunogenicity of an Escherichia coli-Produced Bivalent Human Papillomavirus Vaccine: An Interim Analysis of a Randomized Clinical Trial. JNCI J Natl Cancer Inst (2020) 112(2): djz074

¹³ Hepatitis E vaccine: WHO position paper, May 2015. Weekly epidemiological record. No. 18, 2015, 90, 185–200

The added benefit of implementing a vaccination intervention on top or instead of WASH remains to be assessed.

In 2015, WHO acknowledged the need for more comprehensive data on the use of the hepatitis E vaccine. In all situations where it is deployed, experience with the use of the HEV 239 vaccine, including the occurrence of any adverse events, should be documented. Analysis of vaccination in outbreak situations could provide valuable data on safety and effectiveness of the vaccine as well as the age-specific attack rates.

Considerations for implementation of vaccination in an outbreak setting.

The use of HEV 239 vaccine in an outbreak setting should be guided by an in-depth epidemiological analysis.

Countries may consider using the vaccine within a trial setting for which regulatory and ethical approval by the respective entities is indispensable. Any vaccine trial should be implemented according to good clinical practice, which entails informed consent processes. Tailored communication and social mobilization are important elements to address. The use of the vaccine in a trial setting requires regulatory approval but may proceed without licensure of the vaccine in the country. Licensure of the vaccine may be sought in parallel to the envisaged vaccine trial.

Hepatitis E vaccination may further be used outside of trial settings to mitigate the consequences of outbreaks. In this case, the respective national regulatory authorities will need to advise on regulatory matters. In general, licensure will need to occur in a timely manner to avoid the outbreak being over and to maximise the number of deaths averted.

Thorough documentation and generation of data are of great value to guide future outbreak responses.

Further information:

- Hepatitis E vaccine. WHO position paper:
<https://apps.who.int/iris/handle/10665/242352>
- Hepatitis E Vaccine: Composition, Safety, Immunogenicity and Efficacy:
https://cdn-auth-cms.who.int/media/docs/default-source/immunization/hepatitis/2_hepevaccsafety_immunogenicity_efficacy_final_1oct2014.pdf?sfvrsn=f8f7f2c8_8/2_HepEvaccsafety_immunogenicity_efficacy_final_1Oct2014.pdf
- Recommendations to assure the quality, safety and efficacy of recombinant hepatitis E vaccines.
https://cdn-auth-cms.who.int/media/docs/default-source/immunization/hepatitis/post_ecbs_2018_recommendations_hep_e_vaccines.pdf?sfvrsn=6d1bbe97_8/POST_ECBS_2018_Recommendations_HEP_E_vaccines.pdf