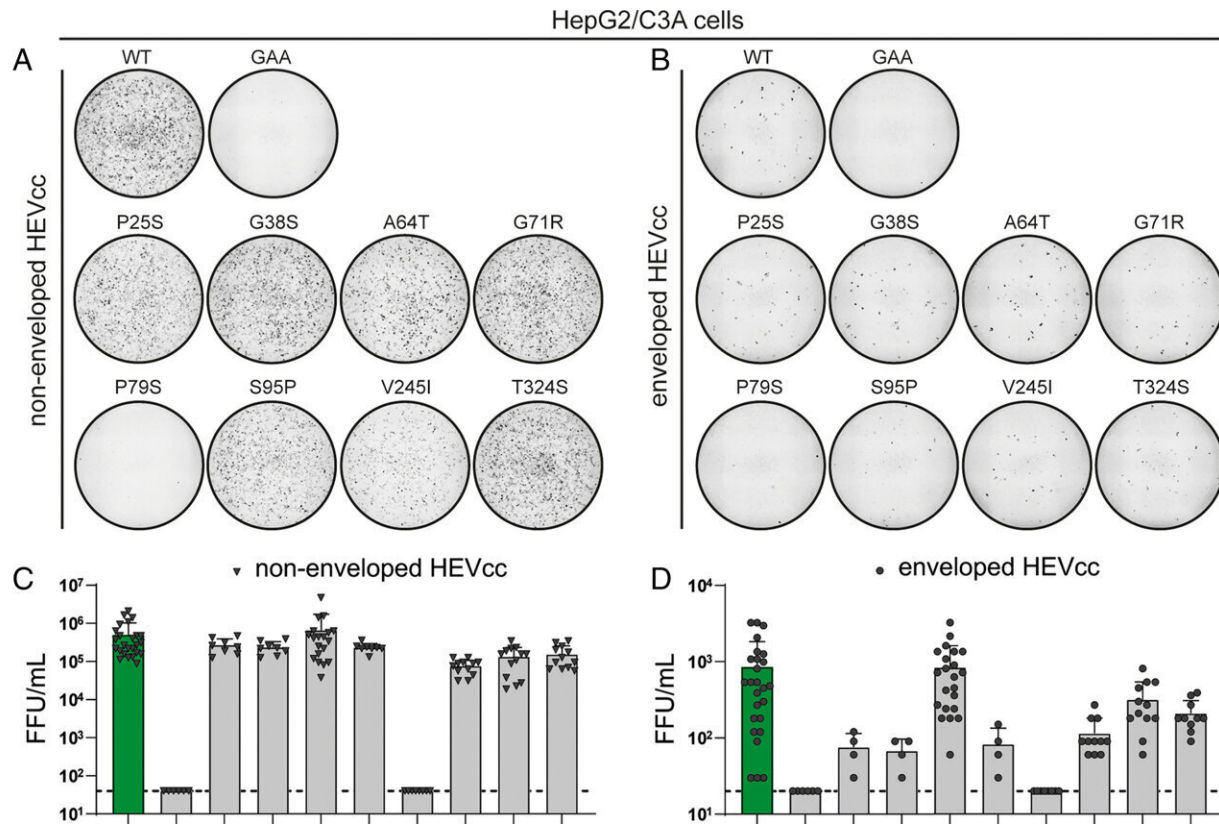


# How hepatitis E tricks the immune system

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Determination of production of infectious viral particles of ORF2 variants. Representative images of whole 96 wells of non-enveloped (A) or enveloped (B) HEVcc infected HepG2/C3A cells stained for ORF2 protein (black). Images were taken using a Keyence microscope with 4× magnification and processed using CellProfiler. Viral titers were determined by serial dilution of non-enveloped (C) and enveloped (D) HEVCC. Dashed line indicates lower limit of quantification (LLOQ) (titers below LLOQ set to LLOQ);  $n \geq 4 \pm \text{SD}$ . PHHs were infected with non-enveloped HEVcc (multiplicity of infection of 2) overnight and were incubated for 3 d. RNA was harvested from the cells (E) and the supernatant (F) to determine RNA copy numbers by RT-qPCR ( $n \geq 3 \pm \text{SD}$ ).

(G) Representative fluorescence images of infected PHH stained for ORF2 protein. (H) The number of ORF2 protein-positive cells were determined by immunofluorescence staining using CellProfiler and normalized to WT ( $n \geq 3 \pm \text{SD}$ ). Dashed line indicates LLOQ. Credit: *Proceedings of the National Academy of Sciences* (2022). DOI: 10.1073/pnas.2202653119

Over 3 million people are infected with the hepatitis E virus every year. So far, no effective treatment is available. An international team has investigated which factors are important for the virus in the course of its replication cycle and how it manages to maintain the infection.

The researchers analyzed various mutations of the [virus](#) and found changes that may allow the virus to trick the immune system. The team from the Department for Molecular and Medical Virology at Ruhr-Universität Bochum led by Dr. Toni Luise Meister, Dr. Daniel Todt and Professor Eike Steinmann reported their results in the *Proceedings of the National Academy of Sciences* on August 15, 2022.

## Advantages and disadvantages of mutations

Antibodies are an important defense mechanism against [viral infections](#) in our body. They specifically bind mostly to surface proteins of viruses to render it harmless. But, viruses have developed strategies to evade this neutralization. During an infection with the hepatitis E virus, [random mutations](#) often give rise to virus variants that can coexist within an infected person. The antiviral agent Ribavirin, which many chronically infected patients receive, can even increase the formation of such variants.

The research team took a closer look at eight [capsid protein](#) variants from samples of chronically infected patients treated with ribavirin in

the laboratory. The team wanted to know: Do the genetic changes bring advantages or disadvantages for the virus? Do they influence the virus' ability to replicate or its infectivity?

"While seven of the investigated mutations behaved exactly like the wild type virus, we found differences in one mutant," says Toni Luise Meister. This mutation affects the capsid protein, which is essential for packaging the [viral particles](#).

"The viruses with this mutation are assembled incorrectly, are probably smaller than the wild type virus, and the capsid protein does not accumulate in the cell," says Daniel Todt. These particles are not infectious, but are correctly recognized and bound by antibodies of the immune system.

"This could be an advantage for the virus. These defective particles could potentially catch antibodies, so that there are no longer enough to neutralize correctly assembled, [infectious virus particles](#)," adds Eike Steinmann.

## Hepatitis E

The hepatitis E virus (HEV) is the main cause of acute viral hepatitis. About 70,000 people die from the disease every year. After the first documented epidemic outbreak in 1955 to 1956, more than 50 years passed before researchers took a closer look at the issue.

Acute infections usually heal on their own in individuals with an intact [immune system](#). In patients with reduced or suppressed immune systems, such as organ transplant recipients or HIV-infected patients, HEV can become chronic. HEV is also particularly threatening for pregnant women.

**More information:** Toni Luise Meister et al, A ribavirin-induced ORF2 single-nucleotide variant produces defective hepatitis E virus particles with immune decoy function, *Proceedings of the National Academy of Sciences* (2022). DOI: [10.1073/pnas.2202653119](https://doi.org/10.1073/pnas.2202653119)

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