


**EDITORIAL**
**Acute viral hepatitis: What we do know and still do not know about hepatitis A and E in Argentina**
**Hepatitis virales agudas: lo que sabemos y lo que aún no sobre las hepatitis A y E en Argentina**
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Acute viral hepatitis still represents a significant public health concern worldwide. The frequency of hepatitis A virus (HAV) and hepatitis E virus (HEV) infections in different countries is closely related to their socio-economic conditions. Endemicity is low in high-income countries and high in low and middle-income countries, where access to clean water, proper sanitation and hygiene practices is scarce. While both infections share a common transmission route, each has its own epidemiological characteristics. Here is a short update on these infections in Argentina.

In Argentina, HAV infection had an intermediate endemicity rate with most people becoming infected during early childhood in the pre-vaccination period. A nationwide outbreak occurred during 2003-2004, where the incidence of infection almost doubled from 66.5 cases per 100,000 inhabitants on average during 2000-2002 to 107.5 and 113.3 cases per 100,000 inhabitants in 2003 and 2004, respectively. During that time, HAV was one of the leading causes of fulminant hepatic failure and, consequently, of liver transplantation in the pediatric population. For this reason, a single-dose vaccination scheme was implemented for children at 12 months of age in this country in June 2005. Thanks to this intervention, clinical case notifications of hepatitis A decreased dramatically (88%) by the year 2007, and no liver transplants

related to infection by this virus have been recorded since then<sup>5</sup>. Argentina was the first country in the Americas to incorporate a single-dose HAV inactivated vaccine into the national immunization schedule in 12-month-old children, assuming that, in the context of an outbreak, the circulation of the wild virus would act as a natural booster. Moreover, a single-dose vaccination reduced costs, resulting in a program with a good cost-effectiveness ratio, which allowed its sustainability over time<sup>5</sup>.

The success of this strategy was evidenced by a sharp decline in the incidence of infection in all age groups and geographic regions of Argentina. Consequently, the World Health Organization Strategic Advisory Group of Experts on Immunization recommended the administration of the inactivated hepatitis A vaccine either in a single-dose or a two-dose vaccination schedule in children<sup>6</sup>. Since then, several countries in Latin America, such as Brazil, Colombia, Paraguay, and Chile have implemented the single-dose vaccination schedule. In all these scenarios, the implementation of these vaccination programs had the same impact: a decrease in the incidence of HAV infection by 80-99%. Furthermore, various studies were conducted to evaluate the immunity induced by a single-dose HAV vaccination. The results showed that these schedules promote a specific humoral and cellular immune memory response that persists up to 12 years after vaccination<sup>3</sup>. As a result of this vaccination program, Argentina is currently a country with low

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endemicity for hepatitis A. In this context, it becomes essential to continue conducting long-term studies to evaluate the effectiveness of the protective immune memory response induced by single-dose vaccination over time. Constant monitoring will be necessary to intervene promptly in the event that a two-dose schedule needs to be implemented.

To date, no cases of hepatitis A have been observed in vaccinated individuals in Argentina. However, HAV continues to circulate in our environment, resulting in a potential risk for susceptible unvaccinated adults. Several environmental surveillance studies, based on the search for HAV RNA in sewage samples, have demonstrated the presence of the virus in different regions of Argentina. Indeed, there has been a change in the epidemiological pattern. An increase in HAV incidence rate was observed among unvaccinated adults (mainly men) in 2014 and 2018. Noteworthy, the 2018 outbreak showed that most cases involved men who have sex with men <sup>2</sup>. A similar epidemiological pattern was reported in several hepatitis A outbreaks in Europe and the United States between 2016-2018, which highlights the fact that at-risk groups for HAV infection are currently susceptible unvaccinated adults.

When it comes to HEV infections in Argentina, there are more questions than certainties. The *Hepeviridae* family exhibits a great genetic diversity. Among the genotypes from *Paslahepevirus balayani* species, HEV-1 and HEV-2 infect humans exclusively, while HEV-3 and HEV-4 can also infect other animal species such as pigs, wild boars, deer, and rabbits.

HEV has a global distribution; however, two distinct epidemiological scenarios are described:

- 1) low income-countries with limited access to safe drinking water and sanitation services, where the transmission occurs through the fecal-oral route, causing large outbreaks by genotypes HEV-1 and, to a lesser extent, by HEV-2;
- 2) high income-countries with improved safe drinking water supply and sanitation, where transmission is mainly zoonotic, through consumption of uncooked or undercooked meat from infected animals or contaminated food products, resulting in sporadic cases mainly associated with HEV-3 and rarely with HEV-4. The latter scenario corresponds to the epidemiological situation in Argentina, where reported cases of hepatitis E are associated with genotype HEV-3, as observed in different regions of America and Europe.

HEV infections are underdiagnosed in Argentina as well as in the rest of the region. Accordingly, the actual incidence rate of HEV infection in our country is unknown, as the number of case notifications is very low. Various factors contribute to the underdiagnosis of this infection, but the most important are:

- 1) unawareness or lack of information among the healthcare personnel;
- 2) lack of access to diagnostic tools. It is common for healthcare professionals to consider screening for HEV after ruling out other hepatotropic viruses. A new sample taken after the symptomatic phase of illness can yield negative results for HEV RNA, as viremia and fecal shed-

ding become undetectable after 4-8 or 10 weeks from the onset of symptoms.

HEV infections can have extrahepatic manifestations—especially neurological and renal disorders— which further contribute to underdiagnosis. Healthcare professionals should consider testing for HEV in patients with neurological manifestations, even when liver function is normal.

It is worth mentioning that HEV-3 infections can progress to chronicity in immunosuppressed patients; therefore, it is necessary to study the impact of HEV infections on this risk group in Argentina. Since there is a potential risk of chronic infections, it is necessary to discuss the need for screening HEV in blood donors, as implemented in several European countries.

Although we still do not know the exact epidemiological aspects of hepatitis E in Argentina, several environmental virology studies have shown the presence of the virus in wastewater, river and dam samples. Other studies have demonstrated the high circulation of the virus in pigs, but not in derived food products such as pork meat and sausages <sup>1</sup>. Despite the evidence of viral circulation, it is still necessary to evaluate the clinical impact of these findings on the Argentinean population.

## Challenges

Viral hepatitis remains an important cause of morbidity and mortality worldwide <sup>4</sup>.

Understanding the epidemiology of HAV and HEV infections in Argentina is essential to achieve control and prevention of these infections.

With regard to HAV, it is essential to continue monitoring the long-term protective immune memory response induced by a single-dose vaccine schedule, to ascertain whether this approach remains effective in a low endemicity setting. Conducting surveillance for HAV infection in susceptible adults and promoting their vaccination with a two-dose regimen is also imperative.

The story of HEV in our country is still being written. We lack the understanding of key aspects of its epidemiology. It is necessary to promote and increase its diagnosis and notification. Moreover, testing for HEV not only in patients with hepatitis, but also in those with extrahepatic manifestations needs to be considered. By increasing surveillance of HEV infection, we will understand its true impact in Argentina.

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