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Is hepatitis A virus infection under control? lessons in the application of viral sequencing for the development of vaccination schemes in emergency situations

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Despite that hepatitis A virus (HAV) affects approximately 10 million people annually and it is the most common cause of acute viral hepatitis worldwide [1], in the last decades, its study has been largely eclipsed by the interest in hepatitis B and hepatitis C viruses. Moreover, even in the presence of a highly effective vaccine against HAV introduced in 1995 [2], HAV still represents a global health concern. Since HAV infection is mostly asymptomatic in children, developing countries with high incidence rates usually have a low burden of disease [3], and studies of HAV infection in developed countries with low incidence rates are limited. Thus, HAV infection may be underestimated in multiple geographical regions and also more research on virus evolution is needed for improving preventive measures to contain the infection in emergency situations. An example of these situations was the multi-country HAV outbreaks occurred in Europe (a region of very low HAV endemicity) between 2016 and 2017 mostly affecting the men who have sex with men (MSM) population [4].

Currently, outbreak control is mostly hampered by vaccine shortages. The World Health Organization (WHO) recommends universal vaccination against HAV by including two doses in the national immunization schedules for children aged >1 year if justified based on the data of acute HAV incidence, declining endemicity from high to intermediate and cost-effectiveness [5]. However, some low-income countries are implementing a single dose as an optimal schedule [6], and this scheme also has been implemented in outbreaks. Despite that, it is essential to take into account that a deficient schedule against HAV may result in a growing number of susceptible adults as reported in the USA, where outbreaks continue to occur as result of lower hepatitis A immunization rates than other vaccines [7]. This information might be explained by Sabria and colleagues' article in *EBioMedicine* describing the deep-sequencing analysis of overlapping fragments covering the complete capsid coding region of HAV recovered from samples of the 2016–2017 HAV outbreak in Barcelona. Their analysis of HAV evolution at the quasispecies level in vaccinated and non-vaccinated individuals revealed amino acid replacements occurring in and around the epitopes. Notably, mutations were significantly higher in the quasispecies of vaccinated patients suggesting a positive selection of antigenic variants in these individuals [8].

In spite of the limited number of samples; the lack of information on the presence of neutralizing antibodies to HAV and the inclusion of immunosuppressed individuals (HIV-infected patients), a condition whose impact on the course of HAV infection cannot be ruled out, Sabria et al.'s article denotes the need of designing better strategies to prevent the emergence of vaccine-escape variants. Also, Sabria and colleagues' data enable the discussion in terms of re-evaluating if a single dose of HAV vaccine is the best alternative in outbreaks and risk groups for infection.

The global impact of outbreaks in specific geographical regions is evidenced by the report of an HAV outbreak in the Americas, specifically in Chile affecting mostly MSM in 2016. The viral sequences recovered from Chile are related to one of the main strains recovered in Europe (V16–25801 cluster) [9] opening the possibility that the V16–25801 cluster may have originated from America or Europe and subsequently propagated. In light of this possibility, data from Sabria and colleagues support that it is crucial for countries in epidemiological transition to quickly recognize and differentiate endemic outbreaks from outbreaks related to sexual transmission in MSM because different control measures and approaches may be required depending on the type of outbreak. Thus, the assiduous study of the emergence of vaccine-escape variants by using available tools is relevant in endemic, and non-endemic conditions since antigenic variants have the potential to expand into the general population.

New sequencing strategies bare the biological events that occur during an infection that is apparently under control. An example of this is the evasion of the immune response by positive viral selection [10]. Understanding the immune mechanisms by which HAV has co-evolved with the human host resulting in the selection of antigenic variants holds promises to open new avenues of investigation with the ultimate goal of virus eradication. Close monitoring of the infection, detailed guidelines for following cases in endemic and non-endemic regions, and the scrutiny of the emergence of vaccine-escape variants worldwide is recommended in the construction of predictive models of the evolution of the infection, needed to define vaccination strategies for containing the virus.

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Declaration of interest

No conflicts of interests to declare.

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