EDITORIAL

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Hidden benefits beyond herpes zoster: a potential preventive strategy against hepatobiliary diseases

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Herpes zoster (HZ) vaccination has long been recognized for its efficacy in preventing shingles and its related complications, particularly in aging populations [1]. However, in a compelling nationwide cohort study, Kim et al. [2] present evidence suggesting that the benefits of live-attenuated HZ vaccination may extend beyond cutaneous protection in the realm of hepatobiliary and pancreatic disease prevention. This observation aligns with previous evidence suggesting that varicella-zoster virus (VZV) infection can impair hepatobiliary function, thereby supporting the notion that HZ vaccination may help reduce the risk of these diseases. Although rare, cases of acute pancreatitis associated with VZV infection have primarily been reported in immunocompromised individuals [3]. VZV-related hepatitis has also been documented, particularly in individuals with impaired immune function [4]. Notably, liver cirrhosis is associated with an increased risk of HZ infection, further emphasizing the importance of zoster prevention in patients with underlying hepatobiliary disease [5].

The protective effect of vaccination was most prominent during the 1–4-year period after inoculation and gradually declined. This time-dependent pattern is consistent with the waning immunity observed with live-attenuated zoster vaccines. Significantly, the effect persisted for up to 8 years, although the degree of protection diminished beyond that period. This trajectory aligns with previous findings. For example, an extensive cohort study reported that the efficacy of the live zoster vaccine was 67.2% in the first year after vaccination but declined to 14.9% after 10–12 years [6]. These observations highlight the time-limited nature of vaccine-induced immunity and raise essential considerations regarding the potential need for booster vaccination strategies, particularly in high-risk populations.

In subgroup analyses, the protective association was more pronounced in men, individuals aged < 60 years, and smokers. These patterns raise essential questions regarding differential vaccine responsiveness and immune modulation across demographic and behavioral groups. Host factors, such as age-related immune senescence, sex-based immunologic variation, and the pro-inflammatory state associated with smoking, may influence vaccine efficacy. Further investigations are warranted to clarify these mechanisms and optimize vaccine strategies for targeted populations.

The authors suggest several biologically plausible mechanisms to explain these associations. VZV reactivation has been implicated in systemic inflammation, hepatic microvascular injury, and stress-induced autonomic dysfunction, all of which may contribute to hepatobiliary pathology. In contrast, HZ vaccination enhances T-cell-mediated immunity. It induces transient elevations of cytokines such as interleukin-6 and interferon-gamma, potentially promoting an anti-inflammatory environment that protects hepatic and biliary systems from immune-mediated injury. In addition to the mechanistic insights, the implications of this study are clinically meaningful. Vaccination may not only prevent viral reactivation but also modulate the trajectory of chronic diseases. This concept is in line with emerging evidence linking zoster vaccination to reduced risk of conditions such as dementia, suggesting a broader systemic benefit and highlighting the evolving role of immunization in aging populations [7].

One of the key strengths of this study is the use of a large nationwide cohort derived from Korea's National Health Insurance Database. This comprehensive data source enabled

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the authors to conduct a robust longitudinal analysis to examine the association between HZ vaccination and the risk of hepatobiliary diseases. Notably, this topic remains understudied. In addition, the application of rigorous 1:1 propensity score matching helped reduce confounding factors and improved the internal validity of the findings.

However, this study has several limitations. As with all observational studies, residual confounding factors remain a concern. In particular, unmeasured variables such as dietary patterns, alcohol use, and health-seeking behaviors may have influenced the observed associations. The possibility of "healthy vaccinee bias," where individuals who receive vaccinations are generally healthier or more engaged with healthcare, may lead to an overestimation of the protective effect. Another limitation is the study's exclusive focus on the live-attenuated zoster vaccine. Although this vaccine was widely used during the study period, it does not reflect the newer recombinant zoster vaccine, which has only recently become available in Korea. Given the higher and more sustained immunogenicity of the recombinant vaccine, future prospective studies are required to assess whether similar hepatobiliary benefits can be observed with this formulation.

In conclusion, this study offers novel insights into the broader clinical impact of live-attenuated HZ vaccination, suggesting that its benefits may extend beyond cutaneous protection to include meaningful reductions in the risk of severe hepatobiliary conditions such as hepatic failure and cirrhosis. These findings support the hypothesis that zoster vaccination exerts systemic anti-inflammatory and immunomodulatory effects, reinforcing its potential role in promoting liver health, particularly in aging populations where such diseases are increasingly prevalent. Nonetheless, uncertainties remain regarding the generalizability of these findings to immunocompromised populations, such as liver transplant recipients or individuals with advanced hepatic dysfunction in whom live vaccines are typically contraindicated [4,8]. Additional research is required to determine whether the observed protective associations apply to the entire spectrum of liver diseases. Much like an umbrella that not only shields against rain, but also provides stability in the midst of a storm, HZ vaccination may offer unexpected protection beyond its original purpose. Continued investigation of the "hidden benefits" of vaccination could inform future immunization strategies aimed at reducing the burden of chronic hepatobiliary diseases in vulnerable populations.

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