VACCIREVIEW

Real-World Safety of Herpes Zoster Vaccines: Shingrix vs Zostavax in VAERS, 2006–2024

Bibliography

Cai H, Jia B, Song Z, Wang L, Zhao S. Real-world safety of herpes zoster vaccines: A pharmacovigilance study based on the Vaccine Adverse Event Reporting System (May 2006–December 2024). Vaccine. 2025;63:127628. doi:10.1016/j.vaccine.2025.127628

Conclusion

In VAERS database, recombinant zoster vaccine (**RZV, Shingrix**) shows a lower proportion of reported serious and fatal adverse events than live attenuated zoster vaccine (**ZVL, Zostavax**), with mainly transient local and systemic reactogenicity. No consistent signal emerged for anaphylaxis or syncope for either vaccine, while Guillain–Barré syndrome (GBS) signals for RZV were method-dependent and remain hypothesis-generating.

Summary

This pharmacovigilance study compared real-world safety profiles of ZVL and RZV using US VAERS data from May 2006 to December 2024. The authors extracted individual case safety reports (ICSRs) where zoster vaccines were reported alone or co-administered, and focused their main analyses on monotherapy ICSRs (>90% of all reports) to minimize confounding by other vaccines. They performed descriptive analyses, time-to-onset (TTO) analyses, and disproportionality analyses with special emphasis on designated/important medical events and three adverse events of special interest: anaphylaxis, GBS, and syncope.

Overall, 39,007 ZVL-alone and 69,195 RZV-alone ICSRs were identified. Among these, serious AEFIs were reported in 11.2% of ZVL vs 4.6% of RZV reports, and fatal outcomes in 0.5% vs 0.3%, respectively, acknowledging that these are proportions within reported events and not incidence rates. Most reports came from the US, and the majority of ICSRs for ZVL were pre-2017, consistent with subsequent preference for RZV and ZVL discontinuation in several countries. Females and individuals aged 60–69 years predominated among ICSRs for both vaccines, whereas serious AEFIs were more often reported in older patients and proportionally more often in males.

More than 80% of AEFIs occurred within 7 days of vaccination (notably 92.0% for RZV alone and 82.9% for ZVL alone), with a peak in the first 0–2 days; serious AEFIs tended to have longer TTO than non-serious events. For ZVL, median TTO was 6 days for serious vs 1 day for non-serious AEFIs; for RZV, 2 vs 1 day, respectively. RZV-related reports were

dominated by systemic reactogenicity (pyrexia, pain, chills, headache, injection-site pain, fatigue, myalgia, nausea), whereas ZVL had strong signals for herpes zoster (including reactivation), vesicular rashes, and ocular/otologic complications.

At SOC and HLT levels, ZVL generated more positive disproportionality signals than RZV, including infections, skin disorders, and herpes viral complications, while RZV signals clustered around reactogenicity and non-serious neurologic symptoms (e.g., "feelings and sensations NEC," "administration site reactions NEC," "dyssomnias"). At PT level, RZV's top events were non-serious systemic and local reactions; for ZVL, "herpes zoster" and related cutaneous and ophthalmic manifestations had very high EBGM values. Using EMA DME/IME lists, ZVL – but not RZV – showed signals for blindness, unilateral blindness, deafness, neurosensory deafness, necrotizing retinitis, varicella zoster pneumonia, and polymyalgia rheumatica; RZV had one unique IME signal, injection-site necrosis.

For **adverse events of special interest**, no disproportionality signals were found for anaphylaxis or syncope for either vaccine, at PT or SMQ level. For GBS, ZVL showed no signal by any method, whereas RZV showed positive signals by ROR and BCPNN (both for PT and SMQ) but not by PRR or MGPS, highlighting inconsistency across methods and the hypothesis-generating nature of these findings. The authors emphasize that VAERS lacks denominator data and is subject to under- and stimulated reporting, so these data cannot provide incidence rates or establish causality; they conclude that RZV's overall safety profile in routine use is reassuring and consistent with its preferential recommendation.

Comment

The study's main strengths are its very large sample size, long observation window (nearly two decades), and systematic use of multiple disproportionality methods with harmonized **MedDRA** coding, providing a granular, side-by-side view of RZV and ZVL across seriousness, timing, and clinically prioritized event categories. Focusing on monotherapy ICSRs, separating serious from non-serious events, and applying EMA DME/IME lists are good methodological choices that increase clinical interpretability, clearly differentiating expected, short-lived reactogenicity (predominant for RZV) from rare but more serious neurological and ophthalmic signals (more prominent for ZVL). The handling of GBS as an AESI, with explicit reporting of method-dependent signal detection, is also intellectually honest and aligns with ongoing regulatory surveillance, rather than over- or under-stating risk.

However, as with all spontaneous-report analyses, the results are constrained by well-known VAERS limitations: absence of denominator data and background rates, under-reporting of mild events, variable data quality, and potential stimulated reporting that may differ between vaccines and over time. The complicates poral separation between the ZVL and RZV eras, differences in indications (especially for immunocompromised adults), and evolving awareness around specific events such as GBS complicate direct comparative interpretation, as do unmeasured confounders like concurrent infections or comorbidities. In practice, these findings should be integrated with controlled epidemiologic data and clinical trial/meta-analytic evidence; viewed in that combined context, they support current policy that RZV is both more efficacious and, from a serious-AE perspective, at least as safe—and likely safer—than the legacy live vaccine, while reinforcing the need for continued, methodologically robust monitoring of rare events such as GBS.

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