Nationwide Evidence on Rotavirus Vaccination and Celiac Disease: Strengths and Remaining Gaps

To the Editor:

We read with great interest the nationwide study by Ostman et al evaluating the risk of early-onset celiac disease (CD) before and after the introduction of rotavirus vaccination in Norway. The authors should be commended for leveraging high-quality national registries (n = 740 744), and an interrupted time-series design in a setting with high vaccine coverage, all of which strengthen internal validity.[1] Their findings provide important reassurance regarding the absence of an association between rotavirus vaccination and early CD risk, consistent with large cohorts and meta-analytic data showing no overall increase in CD after rotavirus vaccination.[2]

We would highlight a few considerations relevant for interpretation and future research.

First, only Rotarix was used in the Norwegian program. Although all World Health Organization–prequalified rotavirus vaccines are live oral formulations, they differ in valency, strain origin, and immunogenicity profiles, potentially influencing intestinal immune responses and microbiome interactions.[3] Extrapolation to settings using alternative vaccines should therefore be cautious.

Second, undetected CD remains a concern. The reported cumulative incidence (1.13%) is broadly consistent with population estimates (0.7%–2.9%)[4] but lower than the 1.47% detected in Norwegian adult screening studies, where 75% of cases were previously undiagnosed.[4] Population-screening and case-finding studies show that most CD remains undiagnosed without proactive serologic testing,[5] and under-ascertainment, especially of mild or asymptomatic disease, may attenuate detection of modest vaccine-associated effects.

Third, follow-up was limited primarily to age 5 years, with sensitivity analyses to 7 years. CD often develops beyond early childhood, and incidence rises through later childhood and adolescence.[5] Several cohorts and a meta-analysis suggest that short follow-up may underestimate absolute CD incidence and potential long-latency effects of early-life exposures.

Fourth, no information was available on timing and frequency of natural rotavirus infections. Prospective studies suggest frequent infections are associated with increased risk of CD autoimmunity in susceptible children.[5] In TEDDY, gastrointestinal infections increased short-term risk, and rotavirus vaccination appeared to attenuate risk in subgroups.[6] Without infection-level data, disentangling vaccine effects from infection dynamics and herd immunity remains difficult.

In conclusion, this study provides valuable evidence supporting rotavirus vaccine safety regarding early-onset CD and aligns with broader data showing no increased CD risk. Nonetheless, vaccine-type generalizability, underdiagnosis, limited follow-up, lack of infection data, and residual confounding support the need for further large studies with extended follow-up and harmonized CD definitions.

CRediT authorship contribution statement

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Declaration of competing interest

No conflict of interest to disclose.

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