VACCIREVIEW

Incidence, risk factors, and costs of neonatal enterovirus hospitalizations in Denmark

Bibliography

Norris RS, Egeskov-Cavling AM, Franck KT, Nygaard U, Fischer TK, Johannesen CK. Incidence, risk factors, and costs of neonatal enterovirus hospitalizations in Denmark. Int J Infect Dis. 2026; 164:108417.

Summary

This nationwide, register-based case-control study from Denmark quantifies how often neonatal enterovirus (EV) infections lead to hospitalization, which infants are at highest risk, and what these episodes cost the health system. Over nine years (2015–2023), the authors included the complete national birth cohort of 544,168 neonates and linked multiple high-quality registries using unique personal identifiers. Neonatal EV hospitalizations were defined by either a laboratory-confirmed positive EV test with a temporally related admission or an EV-related ICD-10 diagnosis, with overlap carefully handled to avoid double counting.

A total of 181 neonates met the EV case definition, corresponding to an **incidence of 34 hospitalizations per 100,000 live births**. There was considerable year-to-year variation, with peaks in 2018 and 2023, and the highest annual incidence reaching 60 per 100,000 live births in 2023. The clinical picture was frequently severe: **nearly half of the infants (48%) had central nervous system** (CNS) involvement, and **20% had sepsis**; **9% had both CNS disease and sepsis**. Median length of stay was 3.5 days overall, but longer for CNS and sepsis categories, particularly CNS infection with or without sepsis.

Seasonality emerged as a key determinant. Eighty-two percent of admissions occurred between **June and November**, with prominent peaks in September, October, and November, and very low case numbers during winter and early spring. The authors also found that neonates who were not first-born had more than twice the odds of EV hospitalization compared with first-born infants, even after adjustment for other covariates. This is consistent with the hypothesis that older siblings, especially those in daycare or school, introduce EV into the household, with subsequent transmission to vulnerable neonates. Gestational age and major perinatal indicators (including Apgar scores and mode of delivery) were not strong drivers of risk, and congenital anomalies were uncommon among cases, suggesting that severe neonatal EV infection can occur in otherwise healthy term infants. The authors emphasize that EV testing in neonates is usually reserved for more severe presentations, particularly suspected meningitis, encephalitis, or sepsis-like illness, so their cohort is likely enriched for severe disease;

milder EV infections are presumably underdiagnosed and managed in outpatient settings or not recognized at all.

The economic analysis used diagnosis-related group tariffs (2024 values) to estimate direct hospital costs. Across the study period, total neonatal EV hospitalization costs were approximately €5.3 million, with an average of €29,213 per patient. CNS infections without sepsis were the most expensive category, with mean costs around €41,977 per patient, while combined CNS infection and sepsis had the highest per-patient cost, exceeding €60,000 on average, despite smaller case numbers. Cost peaks in 2018 and 2023 reflected higher case counts and longer lengths of stay, whereas in 2020, during COVID-19, fewer but more severe cases resulted in the highest cost per patient.

The authors acknowledge several limitations, including potential under-ascertainment of mild cases, residual confounding due to limited data on household composition and behaviors, and cost estimates restricted to direct hospitalization costs without long-term sequelae or societal costs. Nonetheless, the use of national data, linkage of clinical and laboratory records, and a matched control group provide robust estimates of incidence, risk factors, and direct costs. The study concludes that **while neonatal EV hospitalizations are rare events at the population level, they are clinically significant, seasonally patterned, and economically burdensome, especially when CNS is involved.** This, the authors argue, justifies heightened clinical vigilance in late summer and autumn, particularly for neonates with older siblings, and supports consideration of targeted preventive strategies, including the exploration of EV vaccines and antiviral therapies.

Comment

This study delivers precisely what clinicians and policymakers need for neonatal enterovirus: hard numbers. It confirms that severe neonatal EV disease is uncommon in a high-income setting—on average 34 hospitalizations per 100,000 live births—but when it happens, it is often serious and expensive, dominated by meningitis and sepsis with substantial per-case costs. For bedside practice, the message is straightforward: in late summer and autumn, especially in later-born neonates with older siblings, EV should sit high on the differential for fever, sepsis-like presentations, and neurologic symptoms.

The more provocative question is whether such a rare condition justifies vaccine development. On incidence alone, the answer might appear no: even a perfectly effective neonatal EV vaccine would prevent relatively few hospitalizations per birth cohort in Denmark. However, the picture is more nuanced. First, these data represent only one country; global burden, particularly in low- and middle-income settings with higher

transmission and less intensive supportive care, may be substantially greater. Second, the authors rightly highlight that current cost estimates exclude long-term neurologic sequelae after neonatal EV meningitis or encephalitis, as well as indirect societal costs. If future studies demonstrate a meaningful rate of neurodevelopmental impairment, the cost–benefit calculus could shift.

That said, broad-spectrum EV vaccines face formidable technical and programmatic hurdles: antigenic diversity, the need for early-life or even maternal immunization, and competition for resources with pathogens of higher and more clearly quantified burden. The most realistic near-term implication of this work is not a stand-alone EV vaccine, but a stronger case for targeted surveillance, improved diagnostics, and possibly inclusion of EV in multivalent platforms if such technologies emerge. For now, the rarity of clinically recognized neonatal EV in high-income countries argues for cautious prioritization: vigilance and better data first, vaccines only if global burden and preventability are convincingly demonstrated.

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