Congenital cytomegalovirus infection: Study successfully implements pooled saliva tests

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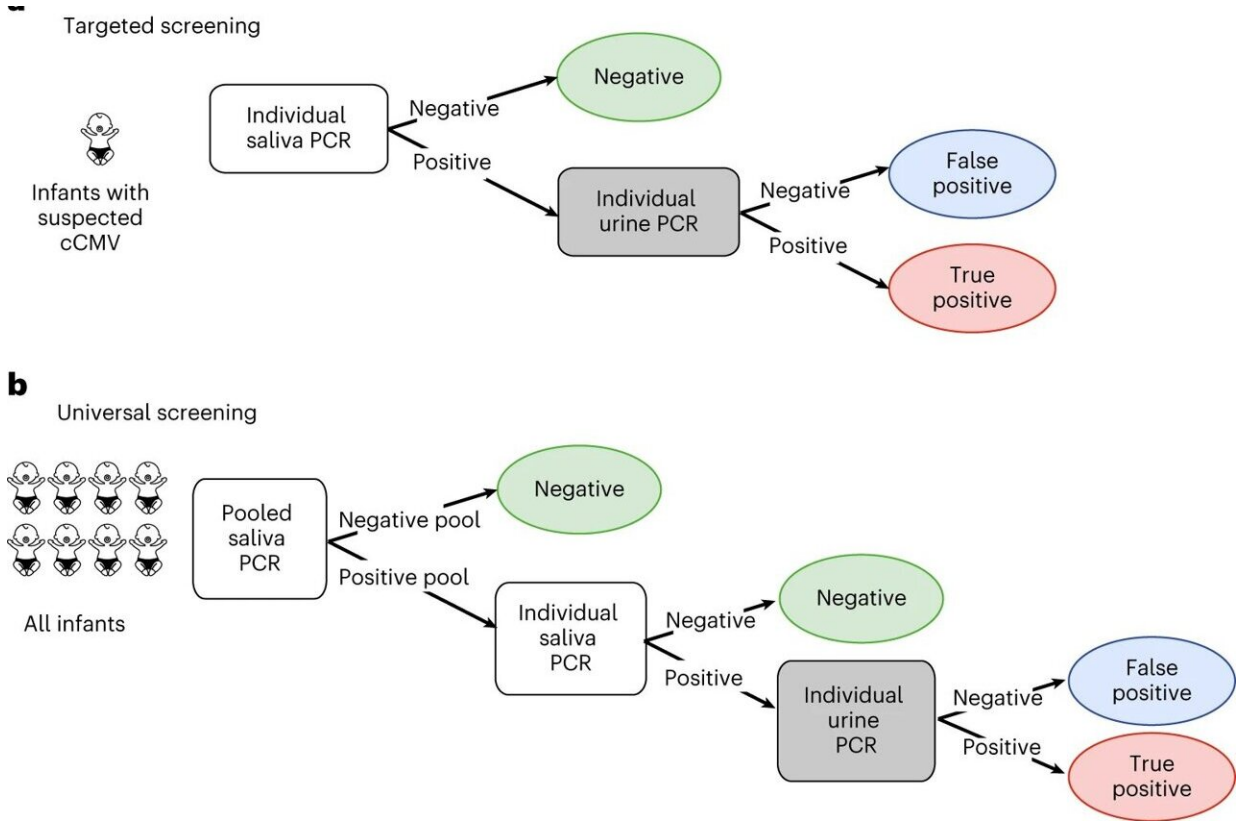

Schematic presentation of neonatal cCMV screening algorithms at the Hadassah Medical Center. **a**, Targeted screening algorithm of suspected neonates by conventional individual saliva RT–PCR with confirmatory urine testing (used in 2014–2022). **b**, Universal screening algorithm, applying the newly implemented saliva sample pooling (beginning in April 2022). Credit: *Nature Medicine* (2024). DOI: 10.1038/s41591-024-02873-3

In a recent study, researchers have successfully introduced pooled saliva polymerase chain reaction (PCR) tests for the universal screening of congenital cytomegalovirus (cCMV) infection. This new method helps detect and intervene early in the most common congenital infection, known for causing hearing loss and developmental problems.

Each year, tens of thousands of newborns are affected by cCMV infection, making it a leading cause of childhood neurologic deficits with lifelong implications. The global burden of cCMV is significant, and the absence of a universal screening method has posed challenges in promptly identifying and addressing cases. Current screening methods focus on high-risk cases, but this misses many asymptomatic infants.

With a birth prevalence of 3.4 per 1,000 in the studied population, the successful implementation of pooled saliva tests, as demonstrated by the study, signifies a crucial advancement in early detection. The challenge lies in developing a reliable and efficient testing strategy due to the absence of a high-throughput screening test that can identify all infected neonates.

This breakthrough has the potential to transform the lives of numerous infants annually, offering a more efficient and accessible means of identifying cCMV cases, particularly those that may present asymptomatically at birth and would otherwise go unnoticed.

The study, conducted in the two Hadassah Medical Center hospitals in Jerusalem from April 2022 through April 2023, involved the screening of 15,805 infants, constituting an impressive 93.6% of all live newborns. The implementation of pooled saliva tests emerged as a routine screening method during this 13-month period, showcasing its efficacy and reliability.

Researchers explored a sample pooling approach for congenital

cytomegalovirus (cCMV) detection, where a group of samples is tested together. If the pooled sample is negative, all individual samples are considered negative; if positive, they are re-tested individually. The study aimed to leverage the low birth prevalence of cCMV (average 6.4 per 1000) for efficient screening. They predicted a 99.5% sensitivity for an 8-sample pool based on viral loads.

Over 15,000 infants were screened using this method, achieving an empirical efficiency of 6, reducing required tests by 83%, with minimal sensitivity loss. cCMV was identified in 54 neonates, of whom more than half were asymptomatic at birth and would have been otherwise missed.

The research team included Professors Dana G. Wolf from Hadassah Hebrew University Medical Center and the Lautenberg Center for General and Tumor Immunology and Moran Yassour from the Hebrew University, along with their teams and the Hadassah Neonatology team headed by Professor Smadar Eventov-Friedman.

"Congenital cytomegalovirus (cCMV) is the most common intrauterine infection. We were driven by the unmet clinical need to identify all infants with cCMV, including those who are asymptomatic at birth, so that early treatment and monitoring could be delivered to a large proportion of infants who are otherwise not diagnosed," said Professor Wolf.

"This project was facilitated by the newly available pooled diagnostic approach and the interdisciplinary collaborations that we had established during the COVID-19 pandemic, which made universal screening of cCMV possible. Our findings project the wide feasibility and benefits of saliva sample pooling to enhance universal neonatal screening for cCMV. Data derived from the implemented universal screening will serve to define the true burden of cCMV and assess future vaccines."

The study supports the use of pooled saliva testing as a cost-effective and sensitive method for universal screening of congenital cytomegalovirus (CMV). The pooling setup is easily integrated into medical laboratories, and parental acceptance is high. The research emphasizes the clinical importance of universal screening for early diagnosis, monitoring, and potential treatment of cCMV.

While limited to two hospitals, the study suggests that universal screening is crucial to uncover undiagnosed cases, though prevalence estimates may vary across populations. Large-scale implementation needs consideration of potential case misses. Data from universal screening will help define cCMV burden, risk factors, and outcomes, emphasizing the need for further assessment in different subpopulations due to varying prevalence by race, ethnicity, and maternal seroprevalence.

Professor Yassour commented, "This collaboration, born during the COVID-19 pandemic, has seamlessly extended its impact to address new medical challenges. Our transformative pooled-testing approach shifts from testing around 10% of newborns to universal testing of approximately 95%. While adjusting facility infrastructure may pose challenges, it's a worthwhile, one-time investment with immense benefits for all newborns and their families worldwide."

The successful implementation of pooled saliva tests represents a significant stride in the field of universal newborn screening for cCMV, offering a promising avenue for early detection and intervention. The research team anticipates that this approach will pave the way for enhanced global efforts in combating the impact of cCMV on newborns.

More information: Lior Merav et al, Implementation of pooled saliva tests for universal screening of cCMV infection, *Nature Medicine* (2024). DOI: 10.1038/s41591-024-02873-3