May 8th 2025

To,

Dr Paul Sax,

Editor-in-chief

Clinical Infectious Diseases

We are pleased to submit our manuscript entitled **“Clinical and Genomic Features of Post-Early-Onset Disease Invasive Group B Streptococcal Infections in Infants: A 15-Year Retrospective Study”** for consideration as an Original Article in *Clinical Infectious Diseases*.

This study presents a comprehensive 15-year analysis of infant invasive GBS disease beyond early-onset disease (EOD) at Boston Children’s Hospital, a large, freestanding pediatric referral hospital in the United States of America. We integrate clinical data with genomic sequencing of *Streptococcus agalactiae* isolates to examine pathogen diversity, antimicrobial resistance patterns, and associations with severe clinical outcomes such as ICU admission and meningitis.

Our dataset provides comprehensive clinical information on infant GBS invasive disease beyond the early-onset period, including both late-onset (LOD) and very late-onset disease (VLOD). Using whole-genome sequencing, we characterize the genetic diversity of GBS isolates, estimate the potential coverage of current vaccine candidates, and assess antimicrobial resistance profiles. We compare genomic features between LOD and VLOD isolates and present a case study of a twin pair to explore possible transmission pathways for VLOD. Additionally, we describe the clinical manifestations of severe disease—defined by ICU admission and meningitis presentation. Finally, we examine associations between molecular determinants and key clinical outcomes, including ICU admission, meningitis, and abnormal laboratory indicators.

Our findings underscore the role of host responses in driving clinical severity, as we found no consistent bacterial genomic predictors of poor outcomes. Notably, all isolates encoded targets of current maternal vaccine candidates, and our data suggest that both late-onset disease (LOD) and very late-onset disease (VLOD) share similar clinical and genomic profiles—highlighting the arbitrary nature of current temporal disease definitions. These insights have important implications for diagnostics, vaccine implementation, and public health surveillance.

We believe this work will be of interest to your readership given the journal’s focus on translational infectious disease research and its commitment to advancing clinical and genomic understanding of bacterial pathogens. This manuscript has not been published or submitted elsewhere, and all authors have read and approved the final version.

Thank you for considering our work and we hope that these findings can be disseminated through the pages of your journal.

Sincerely

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