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Editorial

The Vanguard of Paediatric Protection: Innovation, Vigilance, and the Oral Frontier

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The 43rd Annual Meeting of the European Society of Paediatric Infectious Diseases (ESPID), held in the historic and vibrant city of Bucharest from May 26th to 30th, 2025, convened at a watershed moment for global child health. As the world moves further away from the acute disruptions of the COVID-19 pandemic, the landscape of paediatric infections has not simply returned to its prior state; rather, it has transformed into a complex arena defined by technological breakthroughs in vaccine delivery, the aggressive re-emergence of classic pathogens, and a deepening understanding of the host-pathogen interface at the mucosal level. This year's proceedings in Bucharest have underscored a fundamental truth: while our technological toolkit is expanding at an unprecedented rate, our success in protecting the world's most vulnerable population, its children, depends entirely on our ability to integrate high-tech precision with old-school clinical vigilance.

At the heart of the conference's scientific discourse was a profound re-evaluation of mucosal immunity, specifically the role of the oral cavity. Traditionally viewed by clinicians as a mere entry point for pathogens or a passive route for oral vaccines, the oral environment was reframed in Bucharest as a sophisticated and active battleground. The plenary symposium on "Mouth Matters" highlighted that the success of next-generation vaccination strategies may hinge on the chemical and immunological nuances of saliva. Erwan Sallard and his colleagues presented provocative data regarding adenovirus-based vaccines, which have gained global prominence through their use in various viral vector platforms. Their research demonstrated that saliva is far from a neutral medium; it possesses type-specific interactions that can either inhibit or enhance the infectivity of viral vectors. Specifically, the study noted that while certain species of adenoviruses are hindered by salivary components, others, such as Ad20, show an exceptional ability to cross mucus barriers and maintain infectivity. However, the discovery that sialic acid in saliva acts as a broad-spectrum inhibitor poses a significant hurdle for the design of oral vaccine vectors. This research compels the scientific community to move toward a more personalized understanding of vaccine efficacy. It suggests that the success of a vaccine dose may be influenced not just by a child's systemic immune status or genetics, but by the specific composition of their salivary environment. This "salivary barrier" must now be factored into the engineering of oral delivery systems, ensuring that the next generation of vaccines can navigate the host's natural defences to reach their intended immunological targets.

Complementing this mechanistic view was a powerful longitudinal study from South Africa, presented in collaboration with Radboud University Medical Centre. This research utilized saliva as a non-invasive window into the internal state of children suffering from severe respiratory tract infections. By tracking cytokines and antibodies over a two-year period, researchers discovered that severely ill children exhibit a uniquely dampened mucosal inflammatory profile, a "signature" of immune dysfunction that was detectable in saliva but notably absent in serum samples. This disconnect between systemic and mucosal immune coordination during periods of high disease burden positions saliva as a revolutionary diagnostic tool. Especially in resource-limited settings where blood draws are invasive and laboratory infrastructure is taxed, the ability to use salivary biomarkers to identify high-risk children early in the course of an illness could dramatically improve triage and survival outcomes. While salivary diagnostics offer a non-invasive and patient-friendly window into a child's health, their clinical translation requires a sophisticated understanding of the underlying physiological regulators that differ significantly from adults. A critical consideration for the paediatric infectious disease community is that salivary gland function is governed by the Autonomic Nervous System (ANS), which remains in a state of flux and maturation throughout early childhood. The parasympathetic and sympathetic branches responsible for water-rich and protein-rich secretions respectively, do not achieve adult-like coordination in neonates and young infants, leading to high inter-individual variability in flow rates and biomarker concentrations. Furthermore, many of the promising biomarkers identified at ESPID 2025, such as cortisol and various inflammatory cytokines, exhibit pronounced circadian rhythms. In paediatric patients, these diurnal variations may not be fully established at birth and can be easily disrupted by the irregular sleep-wake cycles common in hospitalized or acutely ill children. Without standardized sampling times and age-specific reference intervals that account for this "biological

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clock," there is a significant risk of diagnostic misinterpretation. Consequently, as we move toward regulatory approvals for these novel diagnostic platforms, it is imperative that developers conduct rigorous validation studies that specifically address the developmental milestones of the ANS and the chronobiological stability of salivary analytes in children. Establishing these normative "baselines" is the only way to ensure that salivary diagnostics move from a research-grade curiosity to a reliable, evidence-based tool for the frontline clinician

While we look toward the future of salivary diagnostics and personalized mucosal vaccines, the conference was also haunted by the resurgence of a familiar and formidable foe: Bordetella pertussis. Annika Van Ron and her team provided a harrowing account of the pertussis epidemic currently sweeping through the Netherlands and much of Western Europe. The data presented in Bucharest suggests that we are witnessing more than just a seasonal spike; we are seeing the consequences of an "immunity gap" created by years of reduced pathogen circulation during pandemic lockdowns. In France alone, cases surged from a few hundred to nearly 40,000 within a single year, resulting in a tragic mortality toll among infants under the age of one. The European pertussis crisis is further complicated by the alarming emergence of macrolide resistance, a development that threatens the very cornerstone of our therapeutic and prophylactic strategies. The identification of the A2047G mutation in European isolates, a resistance profile previously concentrated in Asia, signals a global shift in the evolution of this pathogen. In Finland, a strategic shift back toward bacterial culture protocols, rather than relying solely on PCR diagnostics, has been instrumental in detecting these resistant strains. This serves as a vital lesson for public health authorities: in our rush to adopt rapid molecular testing, we must not abandon the traditional culture methods that allow us to monitor antimicrobial sensitivity and genomic shifts. The resurgence of pertussis is a stark reminder that even our most established vaccine programs require constant monitoring and, perhaps, a reconsideration of booster schedules and maternal immunization uptake. The theme of regional challenges and the need for localized vigilance was further exemplified by the work of Alexander Ilic and colleagues, who focused on the implementation of the pneumococcal vaccine in Romania. As the host nation for this year's ESPID, Romania's experience provides a critical case study in the transition toward higher-valent pneumococcal conjugate vaccines. The challenge of serotype replacement, where non-vaccine strains move in to fill the ecological niche left by targeted strains remains a persistent threat. The discussion in Bucharest emphasized that maintaining high levels of community protection requires not only the introduction of new technology but also the robust infrastructure to ensure every child, regardless of their socioeconomic status, receives the full course of vaccination.

In a similar vein of regional public health urgency, Bridget Freyne from Ireland presented sobering data on the re-emergence of syphilis. This "great imitator" is no longer a historical footnote but a rising threat to neonatal health. The Irish experience mirrors a broader European trend where shifting social dynamics and gaps in prenatal care have led to an increase in congenital syphilis. The presentations in Bucharest called for a revitalized focus on universal prenatal screening and rapid intervention, reminding the paediatric community that infectious disease management is inextricably linked to the broader health of the maternal population. The complexity of neonatal care was also a major focal point in the discussions led by Cristina Marcas and her Italian colleagues regarding Congenital Cytomegalovirus (cCMV). Despite being the leading non-genetic cause of sensorineural hearing loss, cCMV remains a condition of inconsistent management. The emerging evidence discussed in Bucharest suggests a paradigm shift: we must move away from the binary classification of infants as either "symptomatic" or "asymptomatic." New longitudinal data indicates that infants traditionally labelled as asymptomatic often harbour subtle neurodevelopmental impairments, such as receptive language delays, that only manifest in later childhood. The consensus emerging from the 2025 meeting is that the time for universal neonatal screening for cCMV has arrived. Early diagnosis, followed by the timely initiation of antiviral therapy like valganciclovir, has been shown to significantly reduce the incidence of long-term disability, but only if the window of opportunity in the first weeks of life is captured.

Technology's role in refining treatment was perhaps most evident in the sessions dedicated to precision antifungal therapy. As we treat more children with complex immunodeficiencies, the incidence of invasive fungal infections has risen. However, the standard "one-size-fits-all" dosing models are increasingly seen as inadequate. Presentations on drugs like posaconazole and isavuconazole highlighted the dramatic variability in how children metabolize these medications compared to adults. In many cases, standard doses led to subtherapeutic levels that resulted in breakthrough infections and fatalities. The message from the clinical pharmacologists in Bucharest was clear, Therapeutic Drug Monitoring (TDM) is no longer a luxury for specialized centres but a clinical necessity. By utilizing real-time PK modelling and TDM, clinicians can tailor antifungal therapy to the individual child's physiology, ensuring efficacy while minimizing toxicity. The 43rd ESPID meeting has also been a platform for celebrating the success of long-acting monoclonal antibodies, particularly in the fight against Respiratory Syncytial Virus (RSV). The CLEVER trial of clesrovimab has provided a sense of optimism that we may finally be able to offer uniform protection to all infants, regardless of their gestational age or weight. By providing a single dose that offers protection throughout the entire RSV season, clesrovimab addresses many of the logistical barriers that limited the reach of earlier interventions. This move toward broad-spectrum immunoprophylaxis represents a major step forward in reducing

the seasonal burden on paediatric hospitals and protecting infants during their most vulnerable first months of life. The conference also addressed the re-emergence of pathogens in the post-COVID landscape that fall outside the traditional viral and bacterial categories. The resurgence of *Mycoplasma pneumoniae* in the Netherlands and the persistent, under-recognized burden of *Strongyloides stercoralis* in Spain remind us that the microbial world is constantly in flux. The "immunity gap" and shifting migration patterns mean that paediatricians must maintain a broad differential diagnosis, looking for atypical presentations of "old" diseases that may be presenting in new ways.

As the 43rd Annual Meeting in Bucharest concluded, the overarching sentiment was one of "Integrated Precision." We are entering an era where we can engineer vaccine vectors to bypass salivary inhibitors, use monoclonal antibodies to provide instant immunity to neonates, and use genomic tools to track resistance in real-time. However, these technological marvels are only as effective as the public health systems that deliver them and the clinicians who remain vigilant enough to spot the first signs of a resurgent epidemic. The lessons from ESPID 2025 call us to be both innovators at the bench and guardians at the bedside, ensuring that the progress of science is always translated into the protection of every child.

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