Neonatology

Commentary

Neonatology
DOI: 10.1159/000518658

Received: July 19, 2021
Accepted: July 19, 2021
Published online: September 2, 2021

COVID-19 Pandemic and Its Effects on the Development of Immunity in Infancy

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In the light of the SARS-CoV-2 pandemic with globally more than 4.3 million deaths (up to 16 August 2021) related to COVID-19, the idea of controlling infections culminated in a "zero COVID strategy" that was controversially debated in the community. Although it was not sure if this would be achievable or not, for the group of infants and young children, a rigorous infection control strategy as such might also have its hazards.

Hygiene measures and social distancing in lockdown phases throughout the pandemic have dramatically reduced influenza cases worldwide [1]. In line with that, hospital admissions for respiratory and gastrointestinal infections in children have remarkably declined. If this tip of the iceberg has disappeared, then subclinical infections which represent the vast majority in infancy will have supposingly diminished in a similar fashion. This may significantly affect immunological maturation of newborns and young infants ("immune debt") and potentially enhance the severity of childhood infections in the post-COVID era, specifically if infections are shifted to later age. As young children are often perceived in public as a major source of transmission (which is not verified for SARS-CoV-2), the above-stated epidemiological findings are used as arguments for maintaining restricted hygiene measures in the future. However, long-term consequences for infants born and growing up during lockdown are still completely unknown. A balanced view is needed between different public health goals, that is, infection control, promotion of healthy immune development in infants and early prevention of non-communicable diseases such as asthma, diabetes, obesity, and neuropsychiatric disorders.

Nature has designed a mutually favorable system for co-development of immunity and microbiome assembly early in life. The newborn is already equipped with a highly plastic armamentarium of regulatory host factors which can avoid overshooting inflammatory responses after first-time microbial exposure. This is ideally complemented by protective patterns obtained through mother-to-child transmission of maternal IgG antibodies [2] and breastfeeding [3]. The early, stepwise confrontation with a diverse range of non-pathogenic ("the good") commensal microbes is critical for the education of the infant's immune responses. Infants continue amassing environmental microbiota in every contact with family members, by mixing households, playing outside, sharing toys with same-age children or living with pets. Beyond adaptive programming of host defense against harmful

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pathogens ("the bad"), the dynamic fashion of microbiome establishment in infancy is important for network communication between organ systems and metabolic fitness, but is also vulnerable to disturbance, for example, mediated by antibiotics. Lockdown precautions significantly decrease the chance for a physiological load of exposure to environmental bacteria and viruses. Romano-Keeler et al. [4] comprehensively illustrated the impact of the COVID-19 pandemic on the infant's microbiome development and subsequent disease risk.

Recent data indicate that colonization with viruses starts with temperate bacteriophages induced from pioneer bacteria, followed by viruses that replicate in human cells which are first detectable at 4 months of age [3]. Effective defense against highly pathogenic viruses such as Enterovirus A71 infections requires educational training of the infant's immune system with constant and repetitive exposure to nonpathogenic variants in genetically diverse viruses like rhinoviruses, enteroviruses, and adenoviruses. Pretending that we would at least have an idea of how pathogenic and non-pathogenic genetically diverse viruses might displace each other, we need to admit that we are only beginning to understand how commensal viruses contribute to immunological imprinting in early infancy.

First reports show that central immunomodulatory effects such as FOXP3 expression in regulatory T cells and Th1- and Th17-related cytokine patterns are differentially controlled in infants after episodes of rhinovirus or enterovirus infections [5]. Beyond that, reduced diversity of the infant's virome and the abundance of enterovirus are potential risk factors for the development of autoimmunity in children at risk for type 1 diabetes [6, 7].

The evidence-guided communication between scientists, stakeholders and policy makers is of utmost importance. We now have a unique opportunity to incorporate the "lockdown"-based socio-environmental alterations as potential determinants of child health into research designs of ongoing population-based studies, particularly in birth cohorts. This will encourage an urgently needed open discussion on whether the reduced circulation of microbes during lockdown makes a difference to the required fine-tuning of infants' immunity in balancing infection control, allergy and autoimmunity.

The access to SARS-CoV-2 vaccines steadily increases in the industrialized world and will allow every adult to get vaccinated at least in autumn 2021. With that, the ultimate argument of excess SARS-CoV-2 mortality in patients at risk and the elderly will fade, allowing to reset the coordinates for children with their different demands and perspectives.

Conflict of Interest Statement

Both authors have no conflicts of interest to declare.

Funding Sources

There is no particular funding to this manuscript.

Author Contributions

Both authors have contributed equally to this manuscript.

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