Protecting the most vulnerable from hand, foot, and mouth disease

Hand, foot, and mouth disease (HFMD) is an important public health problem in many countries, especially in the Asia-Pacific region where cyclical outbreaks occur every few years. Although the disease is a common affliction in young children and generally manifests as a self-limited mild febrile illness characterised by the appearance of maculopapular rashes or blisters on the hands, soles, and buttocks, severe disease complications such as aseptic meningitis, encephalitis, acute flaccid paralysis, or even death can occur in some cases. Among the more than 20 human enteroviruses that can cause HFMD, enterovirus A71 (EV-A71) stands out as one of the most clinically significant serotypes, being associated with severe disease outcomes more frequently than other common causes such as coxsackievirus A16. More importantly, existing epidemiological data showed increasing incidence and fatality of severe infections of EV-A71 with decreasing age, making infants and toddlers the most susceptible to infection complications.

No effective antiviral drug is available to treat and manage EV-A71 infections, and the three approved inactivated monovalent EV-A71 vaccines are only available in China. Although these vaccines are already being used in China for opt-in community vaccination programmes, they are indicated only for children older than 6 months. Additionally, even though vaccine effectiveness had been evaluated and deemed effective, in a test-negative case-control study by Wang and colleagues, vaccine effectiveness for younger children aged 6–23 months was lower than that for those aged 24–71 months. The lower effectiveness in younger children is a concern because they have the highest risk for severe disease complications from EV-A71 infection, and this effectiveness might be even lower than that when extrapolated for younger infants.

The human immune system is not fully functional at birth and having just left the sterile environment of the womb, the neonatal immune system is in a state of naivety and constantly exposed to new pathogens. The immaturity of their immune system renders neonates extremely susceptible to more severe disease outcomes from infections compared with older children. Additionally, vaccines administered to neonates tend to be suboptimal if they have not been optimised for their unique immune system, an obstacle in the quest to establish protective immunity in this most vulnerable group. Thankfully, neonates can acquire antibodies from the mother through placental transfer in the womb and might continue to receive them after birth through breastmilk. This makes perinatal vaccination of mothers, close to parturition, a feasible option for neonatal vaccination.

To protect the youngest infants (aged younger than 6 months) from infection, an effective protocol for perinatal vaccination of expectant mothers appears to be the best choice. In *The Lancet Infectious Diseases*, Xianglin Wei and colleagues report a longitudinal cohort study to assess the immunity of 1066 mother–neonate pairs in the first 36 months after birth in local hospitals in southern China during 2013–2018. The authors collected blood samples at parturition and during follow-up at specific timepoints and tested for the presence of neutralising antibodies against EV-A71 with virus neutralisation assays. The key finding from their study was the effective transfer of neutralising antibodies from mother to fetus through the placenta. However, these antibodies rapidly degraded post-parturition in both mothers and neonates, and 50% of neonates had neutralising antibody titres below the cutoff of 16 for protective immunity by age 2 months. Although no significant difference was found between breastfeeding status of mother–neonate pairs on the neutralising antibody titres, with only a single dose of vaccine administered, the decay of neutralising antibodies in mothers post-parturition is expected and might have decreased below the cutoff for protective immunity even if antibodies had indeed been transferred to the breastfeeding neonates.

Taken together, the findings of Wei and colleagues showed the transfer of protective immunity through the placenta from the mother to fetus and that antibody titres of mother and neonate are similar at birth. Even though the antibody levels declined rapidly, the findings provide an insight for the adjustment of perinatal vaccination protocols regarding the optimal level of
immunity to be attained in mothers pre-parturition and the exploration of vaccination for neonates aged 2 months followed by a booster at age 6 months to establish longer term protective immunity, as suggested by Wei and colleagues to ensure the success of the vaccination in the youngest children who are also the most at risk for severe complications arising from EV-A71 infections.

We declare no competing interests.

Yong Wah Tan, *Justin Jang Hann Chu
micqjh@nus.edu.sg

Collaborative and Translation Unit for HFMD, Institute of Molecular and Cell Biology, Agency for Science, Technology and Research, Singapore, Singapore (YWT, JJHC); Laboratory of Molecular RNA Virology and Antiviral Strategies, Department of Microbiology and Immunology, and Infectious Disease Programme, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 117597, Singapore (JJHC)