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infectious diseases,⁵ but particularly in respiratory infection scenarios.^{6,7} Furthermore, previous studies have highlighted the value of using host transcriptomic markers to elucidate the prognosis of disease.^{8,9} Our meta-analysis of patients with respiratory syncytial virus¹⁰ identified a specific signature of host transcripts that is different to the gene expression pattern triggered by other respiratory viruses. The study by McClain and colleagues² represents an important step forward in this context, indicating that similar methods of diagnosis could be used before the development of symptoms or the occurrence of detectable viral shedding. Further research is needed to investigate whether transcriptomic signatures are affected by coinfections, and whether they can be used for a larger variety of infectious agents and across a range of different infection timepoints.

Although research on using host gene expression to diagnose infections is still in its infancy, this shift in focus from the identification of the microorganism to the host transcriptome might represent a promising approach that could lead to the development of new diagnostic methods. In the near future, we hope that new point-of-care devices will be available for pathogen detection based on minimal host gene expression signatures for use at different evolutionary phases of the disease course, even before the development of symptoms.

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Direct effects of pneumococcal conjugate vaccines among children in Latin America and the Caribbean

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See **Articles** page 405

In Latin America and the Caribbean, more than 70% of the 52 countries and territories have introduced pneumococcal conjugate vaccines (PCVs) into their national immunisation programmes for infants. More than 73 million children live in the region, and, as of 2018, about 82% had received at least three doses of PCV.¹ Many reports have described the benefits of PCVs in North America,^{2,3} with recent evidence showing these findings in the Latin American and Caribbean countries.^{4,5} In *The Lancet Infectious Diseases*, Clara Inés Agudelo and colleagues' observational study⁶ reports data from the Sistema Regional de Vacunas (SIREVA) network. The study is substantial in size (>12 000 isolates), territory

(ten countries, eight of which had been using a PCV), and time covered (about 12 years). This observational study provides evidence for the benefits of PCV programmes on reducing the burden of invasive pneumococcal diseases due to *Streptococcus pneumoniae* among children younger than 5 years in this region.

The authors examined the proportions of submitted isolates that were specific serotypes or groups of serotypes and also converted numbers of isolates to annual reporting rates from participating countries. They found that both annual reporting rates for disease caused by vaccine serotypes and the proportion of isolates submitted to SIREVA that were vaccine serotypes decreased following

PCV introduction for countries using the ten-valent pneumococcal conjugate vaccine (PCV10) targeting ten serotypes (Brazil, Chile, Colombia, and Paraguay) and for countries using the 13-valent vaccine (PCV13; Argentina, Dominican Republic, Mexico, and Uruguay). The magnitude of change varied across countries; given the variation found, the surveillance programme design, and differences in immunisation programmes in the participating countries, no conclusion can be made from these data on whether programmes using PCV13 provided more benefit than programmes using PCV10.

The authors also found increases in both annual reporting rates for invasive pneumococcal diseases caused by non-vaccine serotypes and in the proportion of isolates that were non-vaccine serotypes. Note that disease rates, rather than proportions of isolates, should be used to infer whether PCV programmes are associated with replacement disease (ie, an increase in disease caused by serotypes the vaccine does not target).⁷ Because effective conjugate vaccines remove vaccine serotypes from circulation and therefore from isolates available for submission to surveillance programmes, the proportion of the post-vaccine isolate pool made up of non-vaccine strains will increase, even in situations in which the amount of disease caused by non-vaccine serotypes is unchanged. The annual reporting rates through SIREVA are most likely to be an underestimate of disease burden in the participating countries, as the annual reporting rates were lower than disease rates reported elsewhere.^{2,8} The authors found modest increases in annual reporting rates for non-vaccine serotypes as a group in most but not all SIREVA countries and increases in disease caused by serotype 19A in most countries using PCV10.

The study results are important additions to the current body of evidence available in the region of Latin America and the Caribbean. A systematic review of the literature on the effect of PCVs on hospitalisation and mortality in children younger than 5 years in Latin American countries⁵ also indicated significant effect of both PCV10 and PCV13, with no evidence of superiority for one vaccine over the other. More recently, a multi-country impact assessment estimated declines in mortality due to pneumonia in ten countries in the Latin American and Caribbean region, five of which are also included in the SIREVA study.⁶ Most countries showed evidence of a decline in pneumonia mortality among children aged 2–59 months following PCV introduction.⁹

Pneumococcal disease burden remains high in adults, particularly among the elderly. As the population is ageing in several large countries in this region, the need for prevention of pneumococcal disease in older adults is increasingly important. Despite the robust evidence for direct PCV benefit among children, the available evidence remains sparse for this region on the indirect effect of PCV introduction and pneumococcal serotype distribution among the elderly. Selected countries have recently recommended PCV13 vaccination for the elderly population; nonetheless, if indirect effects are occurring to the extent seen elsewhere, the value of these policies might be limited.

Last but not least, it is essential to consider the still unknown extent of pneumococcal-attributable COVID-19 morbidity and mortality, particularly in older adults. As recently suggested,¹⁰ this information will be important for tailoring vaccination strategies in the near future, given the heavy burden imposed by COVID-19 on health systems. The COVID-19 pandemic has already resulted in disruption of ordering and administration for infant vaccines in the USA,¹¹ an indicator that sustaining high coverage for PCV and other infant vaccines and the health benefits of these programmes will be more challenging during the COVID-19 pandemic.

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



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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.¹ 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^{2,3} can occur in some cases. Among the more than 20 human enteroviruses that can cause HFMD,⁴ 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,^{5,6} 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.⁷ Additionally, even though vaccine effectiveness had been evaluated and deemed effective, in a test-negative case-control study by Wang and colleagues,⁷ 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 birth⁸ 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,⁹ 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.¹⁰ 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 colleagues¹¹ 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

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See [Articles](#) page 418