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Recognising the asymptomatic enemy

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Respiratory infections are the leading cause of hospital admission, particularly in patients with chronic conditions, patients who are immunocompromised, and in adults older than 70 years and paediatric patients. These infections cause considerable morbidity and mortality, and subsequently result in high direct and indirect costs, particularly during epidemics and disease outbreaks.[1] The early diagnosis of infectious diseases is essential in clinical practice to better manage patients and their close contacts to avoid the spread of disease causing microorganisms. However, detection and diagnosis of the causal pathogen in the early stages of disease present difficulties.

In an index-cluster cohort study in *The Lancet Infectious Diseases*, Micah McClain and colleagues[2] report that respiratory infections can be detected before development of symptoms using transcriptomic biomarkers. McClain and colleagues identified 555 close contacts of 264 students at Duke University (Durham, NC, USA) with suspected respiratory infection and monitored them for 5 consecutive days for development of symptoms, viral shedding, and expression levels of 36 genes. Gene expression patterns differed between symptomatic individuals without microbiological confirmation, symptomatic individuals with a confirmed viral cause, and asymptomatic individuals with a pathogen detected. Using a 36-gene RT-PCR assay, McClain and colleagues could identify differential transcription patterns in infected patients up to 3 days before the development of clinical signs, with an area under the receiver operating characteristic curve of 0·77. This finding increases the time available to prevent the spread of a virus and has implications for detection of asymptomatic patients in the setting of endemic and pandemic infectious diseases, such as the ongoing severe acute respiratory syndrome coronavirus 2 pandemic. Early detection of infection and asymptomatic carriers is key to controlling the spread of viruses and consequently reducing the associated morbidity and mortality.

The use of host transcriptomic markers to diagnose infection could be particularly relevant in the context of respiratory diseases because their symptoms are usually common and diffuse, and uncertainty often exists with regard to identifying the microbial cause. Antibiotics are often administered empirically to patients presenting with infections; however, the bacterial cause is not confirmed in most cases, which can lead to inappropriate use and overuse of antibiotics.[3] The techniques commonly used to characterise an infection range from culture of the suspected microorganism, to measuring the host immune response (eg, IgG or IgM), and to molecular-based viral identification using PCR. These popular diagnostic approaches have some limitations. First, only the microorganisms included in the testing panel can be detected; therefore, the causal microorganism could remain unidentified. Second, they are unable to detect infection of inaccessible anatomical sites. Third, detecting a particular microorganism does not imply disease causality; another undetected microorganism might be the cause of symptoms.

Consistent with the findings reported by McClain and colleagues,[2] our experience is that transcriptomic responses in the host are specific to the infecting microorganism.[4] More specifically, we found that viruses and bacteria induce different patterns of host gene expression. These molecular signatures could be used to develop diagnostic tools that use a small volume of blood from the patient and that enable viral infections to be distinguished from life-threatening bacterial infections and inflammatory diseases that often cause similar febrile symptoms. This approach has been investigated in patients with various

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 virus[10] 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 colleagues[2] 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.

We declare no competing interests.

*Miriam Cebey-López, Antonio Salas
miriam.cebey.lopez@sergas.es

Genetics, Vaccines and Infections Research Group (GENVIP), Instituto de Investigación Sanitaria de Santiago, Galicia 15706, Spain (MC-L); Unidade de Xenética, Instituto de Ciencias Forenses, Facultade de Medicina, Universidade de Santiago de Compostela, Galicia, Spain (AS); and GenPoB Research Group, Instituto de Investigaciones Sanitarias (IDIS), Hospital Clínico Universitario de Santiago (SERGAS), Galicia, Spain (AS)

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

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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 study[6] 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