This study[5] has several other implications. First, predictive markers associated with poor outcome could help triage patients and intensify monitoring and prompt implementation of life-saving interventions, prioritising patients who might benefit from liver transplantation. Second, at a time when already fragile health-care systems are overwhelmed by an influx of patients with yellow fever, as during the Brazil outbreak in 2017–18, application of simple clinical and laboratory evaluations might help improve triage algorithms and resource allocation.

Most importantly, severe cases and fatal outcomes due to yellow fever would not occur if vaccine coverage was high in all at-risk areas. Although overall substantial increases in vaccine coverage have occurred since 1970, notable gaps remain in contemporary coverage within yellow fever risk zones, requiring between 394 million and 473 million more people to be vaccinated to achieve the 80% population coverage threshold recommended by WHO.[10] Until we achieve such high coverage, yellow fever remains a global threat[11] through rapid exportations via travellers, such as in 2016 between Angola and China.[12] The world needs to be better prepared in terms of preventive vaccination, diagnostic capabilities,[13] and improved clinical management. This study[5] is a step towards improving clinical management of patients with yellow fever.

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Novel insights into pneumococcal lineages in the vaccine era

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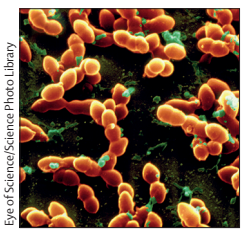
In *The Lancet Infectious Diseases*, Stephanie Lo and colleagues[1] provide an interesting description of the genetic structure of 3233 pneumococcal strains causing invasive pneumococcal disease in children younger than 3 years from six countries where pneumococcal conjugate vaccines (PCVs) had been implemented.

The implementation of PCVs has been a huge success, with a substantial decrease in the incidence of invasive pneumococcal disease and non-invasive infections, as well as a reduction in antibiotic resistance.[2] Nevertheless, two facts have emerged: we have learned from carriage studies that *Streptococcus pneumoniae* remains a major bacterial species in the nasopharyngeal microbiota of children, because they carry *S pneumoniae* as much as they did before PCV implementation,[3,4] and pneumococci remain one of the leading causes of bacterial infections.[2]

To date, the surveillance programmes that aim to assess the impact of PCVs are mainly based on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serotyping of capsular antigens—the same ones that are targeted by PCV-elicited antibodies. Besides showing a fall in the number of infections caused by almost all vaccine serotypes, these surveys have shown the emergence of non-vaccine serotypes, with variations in magnitude and diversity from country to country. With regard to magnitude, invasive pneumococcal disease caused by pneumococci expressing non-vaccine serotypes has substantially increased in incidence in several countries during the past 4 years, thereby eroding the impact of PCVs.[2] By contrast, no substantial increase in incidence of invasive pneumococcal disease caused by non-vaccine serotypes has been reported in the USA.[5]

With regard to serotype diversity, the emerging non-vaccine serotypes vary greatly: serotype 12F and 2 in Israel;[6] serotypes 8, 9N, and 12F in the UK;[7] and serotypes 24F and 12F in France.[8] We do not really understand the reason for these differences. Multi-locus sequence typing to characterising lineages has revealed the genetic diversity behind serotypes, as exemplified by serotype 19A isolates.[9] Whole-genome sequencing of 240 isolates of the same multidrug-resistant clone that was identified by the Pneumococcal Molecular Epidemiology Network (PMEN) in the pre-vaccine era,[10] namely PMEN1 (Spain23F-1), revealed the dynamics of serotypes, with five capsular switches and multiple acquisitions of antibiotic resistance into this lineage over nearly three decades.[11] Furthermore, whole-genome sequencing that was used to explore a sample of 301 serotype 3 isolates of the PMEN31 clone (Netherlands3-31) revealed the emergence of a lineage expressing a higher rate of recombination, higher prevalence of antibiotic resistance, and lower resistance to opsonophagocytic killing than expressed by its ancestor.[12]

Another milestone has been reached with the species-wide genomic study by Gladstone and colleagues[13] in *EBioMedicine*, which preceded the study by Lo and colleagues.[1] After analysing the genetic structure of nearly 20 000 pneumococcal isolates from both carriage and invasive pneumococcal disease from various geographical origins, Gladstone and colleagues proposed an international definition of clusters that makes it possible to track their evolution more efficiently than multi-locus sequence typing. Of interest, two-thirds of the 35 predominant clusters expressed vaccine serotypes along with non-vaccine serotypes, which indicates the potential for spread and serotype replacement in these lineages. Using this cluster definition, Lo and colleagues described serotype replacement in South Africa and Israel due to increased incidence of clusters predominantly expressing non-PCV13 serotypes (defined by the authors as non-vaccine type clusters) and expansion of non-vaccine serotypes within clusters predominantly expressing PCV13 serotypes (defined as vaccine-type clusters).

One of the most striking findings is the top emerging cluster, GPSC3, which in the period following PCV13 implementation expressed serotype 8 in South Africa but serotype 33F in Israel and the USA. Similarly, cluster GPSC5 was found to express serotype 35B/D in South Africa and Malawi but serotype 19A in Israel in the post-PCV13 period. Of interest, different clusters expressing the same serotype but different antibiotic-resistance profiles are evolving differently. For example, the spread of serotype 12F in Israel is related to an increase in the prevalence of the penicillin-resistant cluster GPSC55 and a decrease in that of the cluster GPSC26, which is mostly susceptible to penicillin. The authors also report an increase in antibiotic resistance among most of the emerging non-vaccine-type clusters, which probably results from the selection of ancient multidrug-resistant PMEN clones because of antibiotic use.

Lo and colleagues present a novel complex pneumococcal landscape. Such species-wide whole-genome sequencing studies will undoubtedly help us to understand how *S pneumoniae* is adapting to its environment, mechanisms of vaccine escape and serotype replacement, and changes in invasiveness, disease profile, and antibiotic susceptibility, beyond the prism of serotype. Certainly, the geographical representation needs to be increased to refine the picture, and some crucial questions remain. For more than 15 years, we have known that the disease potential and clinical presentation varies from among serotypes,[14] but will different clusters expressing the same non-vaccine serotypes cause the same disease? By taking advantage of clinically well documented collections of pneumococcal strains, further cluster association studies by age, clinical presentation, and underlying diseases could provide some answers.

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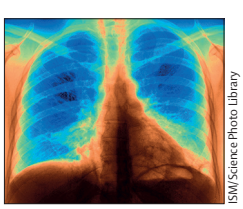
PCR-based routine diagnostics uncover hidden burden of Legionnaires' disease

In *The Lancet Infectious Diseases,* Patricia Priest and colleagues[1] report the first near-nationwide study of routine systematic PCR testing to assess the incidence of Legionnaires' disease in hospitals in New Zealand. They found that the overall incidence was 5·4 per 100 000 population, and *Legionella longbeachae*, not detected by the urine antigen test, was the cause in 150 (63%) of 238 cases.

As shown in the study by Priest and colleagues,[1] *L longbeachae* causes at least similar numbers of cases of Legionnaire's disease as *Legionella pneumophila* in New Zealand. Infection by this pathogen is commonly associated with exposure to composts and potting soils, and cases have increased in Europe over the past 10 years.[2] Most *Legionella* spp infections—in line with the study of Priest and colleagues—are sporadic but clusters can occur.

In patients admitted to hospital with community-acquired pneumonia, it is of clinical relevance to know if legionella needs to be covered empirically or not, because the mainstay of therapy, β-lactams, have no activity against legionella. But how should we decide which treatment to use?

Previous studies show that legionella usually causes severe disease but the incidence is substantially lower than that of pneumococci or *Haemophilus influenzae*.[3] Consequently, guidelines recommend mandatory coverage (β-lactam plus macrolide) in intensive care units but leave it to the discretion of the treating physician for moderately ill patients.[4,5] Discontinuation of macrolide treatment is recommended unless atypical pathogens, particularly legionella, have been detected. However, detection of legionella is difficult because it does not grow easily on standard media and culture sensitivity is estimated to be between 10% and 80%.[6] The most frequently used test is the urine antigen test, which detects *L pneumophila* serogroup 1 with a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