*Emmanuelle Varon, Robert Cohen
Centre National de Référence des Pneumocoques and Centre de Recherche Clinique et Biologique (EV), Centre Hospitalier Intercommunal de Créteil (EV, RC), Créteil 94000, France; Université Paris-Est, IMRB-GRC GEMINI, Créteil, France (RC); and Association Clinique et Thérapeutique Infantile du Val de Marne, Saint-Maur-des-Fossés, France (RC)
emmanuelle.varon@chicreteil.fr

EV reports grants from the French Public Health Agency and Pfizer and personal fees from Pfizer, outside of the submitted work. RC reports research grants to ACTIV from Pfizer, GlaxoSmithKline, MSD, and Sanofi-Pasteur and personal fees from Pfizer, GlaxoSmithKline, MSD, Sanofi-Pasteur, and Astra-Zeneca, outside of the submitted work.

1 Lo SW, Gladstone RA, van Tonder AJ, et al. Pneumococcal lineages associated with serotype replacement and antibiotic resistance in childhood invasive pneumococcal disease in the post-PCV13 era: an international whole genome sequencing study. *Lancet Infect Dis* 2019; published online June 10. http://dx.doi.org/10.1016/S1473-3099(19)30297-X.
2 Balsells E, Guillot L, Nair H, Kyaw MH. Serotype distribution of *Streptococcus pneumoniae* causing invasive disease in children in the post-PCV era: A systematic review and metaanalysis. *PLoS One* 2017; **12:** e0177113.
3 Cohen R, Varon E, Doit C, et al. A 13-year survey of pneumococcal nasopharyngeal carriage in children with acute otitis media following PCV7 and PCV13 implementation. *Vaccine* 2015; **33:** 5118–26.
4 Danino D, Givon-Lavi N, Ben-Shimol S, Greenberg D, Dagan R. Understanding the evolution of antibiotic-nonsusceptible pneumococcal nasopharyngeal colonization following pneumococcal conjugate vaccines implementation in young children. *Clin Infect Dis* 2018; published online Oct 29. DOI:10.1093/cid/ciy926.
5 Lewnard JA, Hanage WP. Making sense of differences in pneumococcal serotype replacement. *Lancet Infect Dis* 2019; **19:** e213–20.
6 Rokney A, Ben-Shimol S, Korenman Z, et al. Emergence of *Streptococcus pneumoniae* serotype 12F after sequential introduction of 7- and 13-valent vaccines, Israel. *Emerg Infect Dis* 2018; **24:** 453–61.
7 Ladhani SN, Collins S, Djennad A, et al. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000–17: a prospective national observational cohort study. *Lancet Infect Dis* 2018; **18:** 441–451.
8 Ouldali N, Levy C, Varon E, et al. Incidence of paediatric pneumococcal meningitis and emergence of new serotypes: a time-series analysis of a 16-year French national survey. *Lancet Infect Dis* 2018; **18:** 983–91.
9 Hanage WP, Bishop CJ, Lee GM, et al. Clonal replacement among 19A *Streptococcus pneumoniae* in Massachusetts, prior to 13 valent conjugate vaccination. *Vaccine* 2011; **29:** 8877–81.
10 McGee L, McDougal L, Zhou J, et al. Nomenclature of major antimicrobial-resistant clones of *Streptococcus pneumoniae* defined by the pneumococcal molecular epidemiology network. *J Clin Microbiol* 2001; **39:** 2565–71.
11 Croucher NJ, Harris SR, Fraser C, et al. Rapid pneumococcal evolution in response to clinical interventions. *Science* 2011; **331:** 430–34.
12 Azarian T, Mitchell PK, Georgieva M, et al. Global emergence and population dynamics of divergent serotype 3 CC180 pneumococci. *PLoS Pathog* 2018; **14:** e1007438.
13 Gladstone RA, Lo SW, Lees JA, et al. International genomic definition of pneumococcal lineages, to contextualise disease, antibiotic resistance and vaccine impact. *EBioMedicine* 2019; published online April 16. https://doi.org/10.1016/j.ebiom.2019.04.021.
14 Levy C, Varon E, Ouldali N, Béchet S, Bonacorsi S, Cohen R. Changes in invasive pneumococcal disease spectrum after 13 valent pneumococcal conjugate vaccine implementation. *Clin Infect Dis* 2019; published online March 14. DOI:10.1093/cid/ciz221.

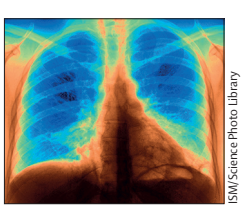
PCR-based routine diagnostics uncover hidden burden of Legionnaires' disease

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


ISM/Science Photo Library

Published **Online**
June 10, 2019
http://dx.doi.org/10.1016/S1473-3099(19)30171-9

See **Articles** page 770

high specificity (95–100%); however, sensitivity is only 70–90%. Serogroup 1 is the most common cause of human disease, but urine antigen testing is unable to detect all other potentially pathogenic non-pneumophila species of legionella. As a consequence, it is estimated that the antigen test does not identify about 10% of legionella infections.[7] Moreover, a negative result does not exclude *Legionella* spp as the pathogen.

The study by Priest and colleagues is one of several PCR-based studies that have reshaped our understanding of infectious diseases. Because culture-based testing has been the main approach in microbiological diagnostics for decades, non-growing or hard to grow organisms are often undetected in routine clinical settings. *Legionella* spp do not grow well on standard media and buffered charcoal yeast extract agar is required.[8]

PCR-based studies have shown that, for example, respiratory viruses cause more severe cases of community-acquired pneumonia than expected, that influenza pneumonia is more more common than pneumococcal pneumonia,[9] and that *Coxiella burnetti* is a relevant pneumonia pathogen outside the influenza season.[10] PCR could also help to correct an overestimated burden in some cases (eg, due to the insufficient specificity of antibody detection, as shown for *Chlamydophila pneumoniae*).[11]

The increasing availability of PCR as a routine method also generates concerns about the clinical relevance of the detected microorganism. This concern applies particularly to the genus *Legionella* but also to other aerosol transmitted genera with many species (some of them pathogenic and others not), which can be a challenge for PCR diagnostics. Although the virulence of *L pneumophila* and *L longbeachae* is evident, the virulence is not as clear for other *Legionella* species. Infections other than *L pneumophila* or *L longbeachae* have rarely been reported, mainly in patients who are immunocompromised. The current study had an epidemiological focus and did not provide large amounts of clinical data—particularly data for concomitant pathogens are absent. It is reassuring, however, that all patients had radiographically confirmed pneumonia, that most had positive results by other tests (including half who were culture-confirmed), that serology did not have a major role in this study, and that the non-pneumophila species detected were mainly *L longbeachae*.

Another concern is the relative low mortality of 2·9% (95% CI 1·2–6·0). A possible explanation might be that most studies reporting a high mortality of legionella pneumonia relied mainly on a positive urine antigen test. A higher bacterial load corresponding to a higher disease severity is likely to be required for this test to be positive, whereas PCR might detect cases with lower bacterial loads and less severe disease. Similar results were reported in the German CAPNETZ study;[7] patients with only a positive PCR result were less often admitted to hospital, had a lower mortality (4%), and less hypernatraemia than did patients with a positive urine antigen. In the German study,[7] legionella was equally common in inpatients and outpatients (3·7% *vs* 3·8%), whereas in the New Zealand study only patients who were admitted to hospital were tested.

The study by Priest and colleagues shows that the real burden of Legionnaires' disease seems to have been underestimated. This finding might have implications for community-acquired pneumonia treatment guidelines. Most studies on the causes of community-acquired pneumonia do not detect the underlying pathogen in 30–70% of individuals, despite comprehensive microbiological testing. In a relevant proportion of these cases, *Legionella* spp could be the cause.

PCR-based methods can detect very low numbers of pathogens or microorganisms of questionable virulence and the challenge is to distinguish carriage from true infection. This can result in harming patients and selecting resistance by unnecessary administration of anti-infectives or by misleading treatment selection, when the pathogen detected by PCR is the less relevant partner in a mixed (eg, viral-bacterial) infection and the main pathogen is overlooked and not addressed.Therefore, results of PCR-based testing should be interpreted with caution and always judged in the clinical context.

*Mathias W Pletz, Santiago Ewig, Tobias Welte
Institute for Infectious Diseases and Infection Control, Jena University Hospital, Jena 07740, Germany (MWP); Thoraxzentrum Ruhrgebiet, Kliniken für Pneumologie und Infektiologie, Herne und Bochum, Germany (SE); and Department of Pneumology and German Center for Lung Research, Hannover Medical School, Germany (TW)
mathias.pletz@med.uni-jena.de

We declare no competing interests.

1 Priest PC, Slow S, Chambers ST, et al. The burden of Legionnaires' disease in New Zealand (LegiNZ): a national surveillance study. *Lancet Infect Dis* 2019; published online June 10. http://dx.doi.org/10.1016/S1473-3099(19)30113-6.

2 Currie SL, Beattie TK. Compost and *Legionella longbeachae*: an emerging infection? *Perspect Public Health* 2015; **135:** 309–15.
3 Pletz MW, Rohde GG, Welte T, Kolditz M, Ott S. Advances in the prevention, management, and treatment of community-acquired pneumonia. *F1000Res* 2016; **5:** 10.12688/f1000research.7657.1
4 Ewig S, Höffken G, Kern WV, et al. Management of adult community-acquired pneumonia and prevention - Update 2016. *Pneumologie* 2016; **70:** 151–200.
5 Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections--full version. *Clin Microbiol Infect* 2011; **17** (suppl 6): e1–59.
6 Mercante JW, Winchell JM. Current and emerging legionella diagnostics for laboratory and outbreak investigations. *Clin Microbiol Rev* 2015; **28:** 95–133.
7 Baum H von, Ewig S, Marre R, et al. Community-acquired legionella pneumonia: new insights from the German competence network for community acquired pneumonia. *Clin Infect Dis* 2008; **46:** 1356–64.
8 Brady MF, Sundareshan V. Legionnaires' disease (legionella infection). In: StatPearls. Treasure Island, FL: StatPearls Publishing, 2019.
9 Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among US adults. *N Engl J Med* 2015; **373:** 415–27.
10 Schack M, Sachse S, Rödel J, et al. *Coxiella burnetii* (Q fever) as a cause of community-acquired pneumonia during the warm season in Germany. *Epidemiol Infect* 2014; **142:** 1905–10.
11 Wellinghausen N, Straube E, Freidank H, von Baum H, Marre R, Essig A. Low prevalence of *Chlamydia pneumoniae* in adults with community-acquired pneumonia. *Int J Med Microbiol* 2006; **296:** 485–91.

All for one and one for all: the true potential of whole-genome sequencing

Published **Online** May 24, 2019 http://dx.doi.org/10.1016/S1473-3099(19)30172-0

See **Articles** page 778

Global genomic databases of foodborne pathogens are important to create, maintain, and expand because we live in an integrated world in which international travel and trade of globally sourced products are extensive. The effects of contaminated products from international trade require responsible food safety bodies to take efforts to reduce these risks for public health. Monitoring and linking foodborne contamination events over time and space is crucial, and must be communicated rapidly to reduce the effects on public health. The speed at which regulators can interrupt the epidemiological curve through interventions, preventive controls, recalls, and notices is facilitated by the strong and predictive whole-genome sequencing (WGS) signals provided by globally shared genomes of the pathogens found in foods, the environment, and patients.[1]

In *The Lancet Infectious Diseases*, Roan Pijnacker and colleagues[2] report on a multi-country European outbreak of *Salmonella enterica* serotype Enteritidis linked to eggs from Poland. The evidence presented in this investigation showcased the usefulness and efficiency of coordinated WGS data collection during a regional outbreak in 2015–18. The rapid exchange of information between public health authorities and the traceability of information shared by food safety authorities can be essential in finding the vehicles of infection and coordinating risk management actions. The US Food and Drug Administration (FDA) has previously documented similar successes using WGS in the USA for understanding contamination events of *S* Enteritidis in shell eggs[3] and in many other commodities.[4] The improvements brought by WGS for outbreak response are particularly important for the most genetically homogeneous of foodborne pathogens, which is why *S* Enteritidis was a crucial case study for the FDA in adopting WGS for routine molecular epidemiology and as a regulatory tool in 2013.[1] To date, WGS has supported the FDA in more than 370 outbreak investigation and compliance cases.

The authors report that a crucial step for the success of their outbreak investigation was the strong triggering signal from the WGS data that enabled prioritisation of epidemiological follow-up of signals. The FDA has also observed this power of prediction using WGS,[5] which prompted the building of the GenomeTrakr network. Pathogen Detection web tools provide genomic linkages and phylogenetic trees daily for all 325 000 publicly released foodborne pathogen genomes. Additionally, PulseNet (managed by the US Centers for Disease Control and Prevention [CDC]) uploads to these projects at the National Center for Biotechnology Information (NCBI),[6] as does the US Department of Agriculture's Food Safety and Inspection Service. Together, the genomes in these projects are combined analytically to discover novel linkages among foodborne pathogens with roughly 4000 clusters monitored daily. These genomic data are globally available with free access to anyone who wishes to upload and compare bacterial genomes and corresponding descriptive metadata in real time. Importantly, in addition to the public NCBI database, each of the participating US agencies retains

For the **National Center for Biotechnology Information's Pathogen Detection web tools** see https://www.ncbi.nlm.nih.gov/pathogens/