

## *Mycoplasma pneumoniae*: delayed re-emergence after COVID-19 pandemic restrictions



*Mycoplasma pneumoniae* is a common cause of respiratory tract infections with community-acquired pneumonia as the major disease-related burden. Compared with other pathogens, *M pneumoniae* is atypical in many ways: it is one of the smallest self-replicating organisms, has a reduced and highly stable genome (0.8 Mbp), lacks a cell wall, grows slowly (generation time 6 h), requires close contact for transmission, and has a distinct disease presentation (atypical pneumonia), the pathogenesis of which might involve host cell-mediated immunity.<sup>1-3</sup>

Infections occur year-round in many different climates worldwide, with epidemics every few years.<sup>4,5</sup> Previously obtained data indicated an interval of 1–3 years between *M pneumoniae* epidemics in Europe and Israel.<sup>5</sup> Several factors, including waning herd immunity or introduction of new subtypes into the population, account for the periodic occurrence of epidemics. The most recent epidemic occurred in late 2019–early 2020 simultaneously across multiple nations, predominantly in Europe and Asia.<sup>6</sup>

In March, 2020, the introduction of non-pharmaceutical interventions (NPIs) against COVID-19 resulted in an abrupt ending of these epidemics and a marked decline in *M pneumoniae* detection worldwide.<sup>6</sup> Compared with the pre-pandemic incidence of *M pneumoniae* (8.61%, 2017–20), a significant reduction was observed in the first year after the implementation of NPIs (1.69%, 2020–21),<sup>6</sup> similar to the incidence of other respiratory pathogens.<sup>7</sup> A further unprecedented, yet substantial, reduction in the incidence of *M pneumoniae* was observed in the second year (0.70%, 2021–22),<sup>8</sup> when other respiratory pathogens resurged as an indicator of community transmission.<sup>8,9</sup>

The first global prospective surveillance study of *M pneumoniae* (ESGMAC MAPS study)<sup>10</sup> was initiated in April 2022 to allow for rapid notification regarding the geographical location of any substantial increase in activity via monthly website updates alerting clinicians. First data from this surveillance yielded a sustained very low incidence of *M pneumoniae* in the third year from April, 2022, to March, 2023 (0.82%).<sup>10</sup>

However, though at very low levels, an increase in case numbers was noted in some countries in the last months of the third year (January to March, 2023),<sup>10</sup> which subsequently warranted increased vigilance. Here, we report

on the further course in the fourth year after the introduction of NPIs, from April 1 to September 30, 2023 (6-month period).

Prospective surveillance data were obtained from 45 sites in 24 countries from the four UN regions: Europe, Asia, the Americas, and Oceania. Laboratory information of participating sites has been previously described.<sup>10</sup> *M pneumoniae* was detected by PCR in all four UN regions (appendix 2). The mean incidence of *M pneumoniae* as detected by PCR during the 6-month period was 4.12% (SD 7.94; appendix 2). The incidences of *M pneumoniae* as detected by PCR were significantly higher in Europe and Asia than in America and Oceania and higher than those observed in previous testing periods in the same UN regions since the start of the prospective surveillance (appendix 3). Overall, *M pneumoniae* was detected by PCR in 1067 (0.71%) of 149 980 tests during the 6-month period (appendix 2). The most frequent detections in Europe were from Denmark ( $n=436$ ), Sweden ( $n=145$ ), Switzerland ( $n=132$ ), Wales ( $n=49$ ), and Slovenia ( $n=41$ ), and in Asia from Singapore ( $n=172$ ) (appendix 4). Positive test numbers (but not the total number of tests) were also reported from Belgium by PCR ( $n=136$ ) and from Finland using combined serology and PCR with no distinction possible between the detection methods ( $n=129$ ) (appendix 2). Detections by IgM serology were 158 (6.58%) of 2403 and by IgG serology were 292 (12.35%) of 2364 (appendix 2).

These global prospective surveillance data show the re-emergence of *M pneumoniae* in Europe and Asia more than 3 years after the introduction of COVID-19 pandemic restrictions. This delayed re-emergence is striking because it occurred long after NPIs were discontinued, and because it is, to our knowledge, a phenomenon unique to this pathogen. Other respiratory pathogens with a sustained reduction in incidence but earlier resurgence than *M pneumoniae* were *Mycobacterium tuberculosis* and *Bordetella pertussis*, for which increased notifications were not reported until 2021 and 2022, respectively.<sup>11,12</sup> Why is *M pneumoniae* also atypical in this respect?

Numerous theories exist for the altered epidemiology of infections surrounding the COVID-19 pandemic. Most do not apply to *M pneumoniae* after the severe reduction in incidences long after the discontinued NPIs.<sup>6</sup> The

*Lancet Microbe* 2024;  
5: e100–101

Published Online  
November 23, 2023  
[https://doi.org/10.1016/S2666-5247\(23\)00344-0](https://doi.org/10.1016/S2666-5247(23)00344-0)

See Online for appendix 2

See Online for appendix 3

See Online for appendix 4

possibility of a viral-bacterial interaction as was observed for *Streptococcus pneumoniae*, when the temporal suppression of respiratory syncytial virus, influenza viruses, and human metapneumovirus was associated with a decline in pneumococcal disease in young children,<sup>13</sup> could be excluded given the much earlier resurgence of respiratory viruses while *M pneumoniae* was still absent. As postulated for the occurrence of *M pneumoniae* epidemics, waning herd immunity could also account for the delayed re-emergence. Transient herd immunity from the last epidemic period in several countries in late 2019–early 2020 could have led to the delayed re-emergence considering an interval of up to 3 years between *M pneumoniae* epidemics in these UN regions.<sup>5</sup> However, we have not yet observed a re-emergence in countries where the last epidemic was reported earlier (eg, Germany, Finland, and Norway; all in 2017–18).<sup>6</sup> In addition, no re-emergence was detected by PCR, but a further decline in detections of *M pneumoniae*-specific IgM and IgG antibodies indicative of waning immunity was observed at sites that reported data separately for PCR and serology (eg, Homburg, Germany; and Rotterdam, The Netherlands).

As this delayed re-emergence is atypical and probably unique for *M pneumoniae*, the atypical characteristics that distinguish *M pneumoniae* from other pathogens should be strongly considered. Among those, the slow generation time (6 h), long incubation period (1–3 weeks), and relatively low transmission rate could be factors leading to a longer time interval required for the re-establishment of *M pneumoniae* infection within a population.

In countries where *M pneumoniae* has re-emerged, case numbers are comparable to pre-pandemic (endemic) numbers. The further development of the re-emergence should be monitored to evaluate whether case numbers will escalate to epidemic levels or result in an exceptionally large wave of infections as was observed for the resurgence of other pathogens.<sup>11</sup> The progression and severity of the re-emergence are difficult to predict and whether it will lead to an increase in rare cases of severe disease<sup>2</sup> and extrapulmonary manifestations<sup>14,15</sup> because of the previously reduced exposure remains unknown. However, the global prospective surveillance will alert clinicians to the magnitude and severity of re-emerging infections, thereby allowing a prompt response with adequate management.

We declare no competing interests. All data collected and analysed in this study are included in the appendices. Monthly updates of the ESGMAC MAPS study

are published on the ESGMAC website (<https://www.escmid.org/research-projects/study-groups/study-groups-g-n/mycoplasma-and-chlamydia/esgmac-maps-study>).

Copyright © 2023 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

\*Patrick M Meyer Sauter, Michael L Beeton, on behalf of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Mycoplasma and Chlamydia Infections (ESGMAC), and the ESGMAC Mycoplasma pneumoniae Surveillance (MAPS) study group<sup>†</sup> [patrick.meyersauter@kispi.uzh.ch](mailto:patrick.meyersauter@kispi.uzh.ch)

<sup>†</sup>For the members of the ESGMAC MAPS study group, see appendix 1

Division of Infectious Diseases and Hospital Epidemiology, University Children's Hospital Zurich, Zurich CH-8032, Switzerland (PMMS); Microbiology and Infection Research Group, Department of Biomedical Sciences, Cardiff Metropolitan University, Cardiff, UK (MLB)

- 1 Reimann HA. An acute infection of the respiratory tract with atypical pneumonia: a disease entity probably caused by a filtrable virus. *JAMA* 1938; **111**: 2377–84.
- 2 Waites KB, Talkington DF. *Mycoplasma pneumoniae* and its role as a human pathogen. *Clin Microbiol Rev* 2004; **17**: 697–728.
- 3 Pánisová E, Unger WWJ, Berger C, Meyer Sauter PM. *Mycoplasma pneumoniae*-specific IFN-gamma-producing CD4(+) effector-memory T cells correlate with pulmonary disease. *Am J Respir Cell Mol Biol* 2021; **64**: 143–46.
- 4 Uldum SA, Bangsbo JM, Gahrn-Hansen B, et al. Epidemic of *Mycoplasma pneumoniae* infection in Denmark, 2010 and 2011. *Euro Surveill* 2012; **17**: 20073.
- 5 Beeton ML, Zhang XS, Uldum SA, et al. *Mycoplasma pneumoniae* infections, 11 countries in Europe and Israel, 2011 to 2016. *Euro Surveill* 2020; **25**: 1900112.
- 6 Meyer Sauter PM, Beeton ML, Uldum SA, et al. *Mycoplasma pneumoniae* detections before and during the COVID-19 pandemic: results of a global survey, 2017 to 2021. *Euro Surveill* 2022; **27**: 2100746.
- 7 Brueggemann AB, Jansen van Rensburg MJ, Shaw D, et al. Changes in the incidence of invasive disease due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis* during the COVID-19 pandemic in 26 countries and territories in the Invasive Respiratory Infection Surveillance Initiative: a prospective analysis of surveillance data. *Lancet Digit Health* 2021; **3**: e360–70.
- 8 Meyer Sauter PM, Chalker VJ, Berger C, et al. *Mycoplasma pneumoniae* beyond the COVID-19 pandemic: where is it? *Lancet Microbe* 2022; **3**: e897.
- 9 Clark SA, Campbell H, Ribeiro S, et al. Epidemiological and strain characteristics of invasive meningococcal disease prior to, during and after COVID-19 pandemic restrictions in England. *J Infect* 2023; **87**: 385–91.
- 10 Meyer Sauter PM, Beeton ML, ESGMAC and the ESGMAC MAPS study group. *Mycoplasma pneumoniae*: gone forever? *Lancet Microbe* 2023; **4**: e763.
- 11 Burrell R, Saravanos G, Britton PN. Unintended impacts of COVID-19 on the epidemiology and burden of paediatric respiratory infections. *Paediatr Respir Rev* 2023; published online Aug 3. <https://doi.org/10.1016/j.prrv.2023.07.004>.
- 12 Izu A, Nunes MC, Solomon F, et al. All-cause and pathogen-specific lower respiratory tract infection hospital admissions in children younger than 5 years during the COVID-19 pandemic (2020–22) compared with the pre-pandemic period (2015–19) in South Africa: an observational study. *Lancet Infect Dis* 2023; **23**: 1031–41.
- 13 Danino D, Ben-Shimol S, van der Beek BA, et al. Decline in pneumococcal disease in young children during the coronavirus disease 2019 (COVID-19) pandemic in Israel associated with suppression of seasonal respiratory viruses, despite persistent pneumococcal carriage: a prospective cohort study. *Clin Infect Dis* 2022; **75**: e1154–64.
- 14 Meyer Sauter PM, Theiler M, Buettcher M, Seiler M, Weibel L, Berger C. Frequency and clinical presentation of mucocutaneous disease due to *Mycoplasma pneumoniae* infection in children with community-acquired pneumonia. *JAMA Dermatol* 2020; **156**: 144–50.
- 15 Narita M. Classification of extrapulmonary manifestations due to *Mycoplasma pneumoniae* infection on the basis of possible pathogenesis. *Front Microbiol* 2016; **7**: 23.