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

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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.[1–3]

Infections occur year-round in many different climates worldwide, with epidemics every few years.[4,5] Previously obtained data indicated an interval of 1–3 years between *M pneumoniae* epidemics in Europe and Israel.[5] 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.[6]

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.[6] 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),[6] similar to the incidence of other respiratory pathogens.[7] A further unprecedented, yet substantial, reduction in the incidence of *M pneumoniae* was observed in the second year (0·70%, 2021–22),[8] when other respiratory pathogens resurged as an indicator of community transmission.[8,9]

The first global prospective surveillance study of *M pneumoniae* (ESGMAC MAPS study)[10] 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%).[10]

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),[10] 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.[10] *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).

See Online for appendix 2

See Online for appendix 3

See Online for appendix 4

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.[11,12] 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.[6] The

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,[13] 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.[5] 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).[6] 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.[11] 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[2] and extrapulmonary manifestations[14,15] 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).

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