Global spatiotemporal dynamics of *Mycoplasma pneumoniae* re-emergence after COVID-19 pandemic restrictions: an epidemiological and transmission modelling study

*ESGMAC MAPS study group**

Summary

Background ***Mycoplasma pneumoniae*** **is a major cause of respiratory tract infections. We aimed to investigate the spatiotemporal dynamics, antimicrobial resistance, and severity of the delayed re-emergence of infections with *M pneumoniae* after the implementation of non-pharmaceutical interventions (NPIs) against COVID-19.**

Methods **Epidemiological data (positive and total test numbers, and macrolide-resistant *M pneumoniae* detections) and clinical data (hospitalisations, intensive care unit [ICU] admissions, and deaths) were collected through our global surveillance from April 1, 2017 to March 31, 2024. The moving epidemic method (MEM) was used to establish epidemic periods, and the time-series susceptible–infected–recovered (TSIR) model to investigate the delayed re-emergence.**

Findings **The dataset included 65 sites in 29 countries from four UN regions: Europe, Asia, the Americas, and Oceania. A global re-emergence of *M pneumoniae* cases by PCR detection was noted from the second half of 2023. The mean global detection rate was 11·47% (SD 15·82) during the re-emergence (April, 2023–March, 2024). By use of MEM, the re-emergence was identified as epidemic in all four UN regions, simultaneously in ten countries at calendar week 40 (early October, 2023). Macrolide-resistant *M pneumoniae* rates from Europe and Asia were 2·02% and 71·22%, respectively, and did not differ between the re-emergence and pre-COVID-19 pandemic periods. During the re-emergence, some countries reported increased hospitalisations (in adults, two of ten countries; and in children, two of 14 countries) and ICU admissions (in adults, one of nine countries; and in children, two of 14 countries). Overall, 65 (0·11%) deaths were reported, without statistical difference between pre-COVID-19 pandemic and re-emergence. The TSIR model accurately predicted, considering a 3-week generation time of *M pneumoniae* and a 90% reduction in transmission through NPIs, the observed delayed re-emergence.**

Interpretation **This large global dataset for *M pneumoniae* detections shows that although there was an unprecedented high number of detections across many countries in late 2023, the severity and number of deaths remained low. Our results suggest that the delayed re-emergence was related to the long incubation period of *M pneumoniae* infection.**

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Introduction

Mycoplasma pneumoniae is a major cause of respiratory tract infections in children and adults.[1] Although most infections are mild and self-limiting,[2] *M pneumoniae* can also cause severe pneumonia or extrapulmonary manifestations that require hospitalisation.[1,2] *M pneumoniae* is transmitted by aerosol particles and respiratory droplets through close contact.[3] Clusters and outbreaks of infections have been described in hospitals, schools, military bases, and among closed communities and institutions.[1] Epidemics occur every few years and the interval between epidemics has been found to be 1–3 years.[4,5] The long incubation period of up to 3 weeks and the relatively low transmission rate have been implicated in the prolonged duration of epidemics of *M pneumoniae* infections.[1] The cyclical epidemics were believed to be due to waning of herd immunity or the introduction of new subtypes into the population.[1,4,5]

In March, 2020, the implementation of non-pharmaceutical interventions (NPIs) against COVID-19 markedly reduced the global detection rate of *M pneumoniae* from 8·61% pre-pandemic (April, 2017–March, 2020) to 1·69% in the first year after the implementation of NPIs (April, 2020–March, 2021),[3] 0·70% in the second year (April, 2021–March, 2022),[6] and 0·82% in the third year (April, 2022–March, 2023).[7] Other respiratory pathogens, such as respiratory syncytial virus, have re-emerged since the lifting of NPIs as of 2021.[7] The sustained very low incidence of *M pneumoniae* more than three years after the initial implementation of NPIs led to major concerns regarding the risk of disproportionally high disease outbreaks due to waning herd immunity.[7]

Indeed, numerous pneumonia outbreaks were observed globally in many countries in late 2023, the fourth year after the initial implementation of NPIs.[8] The outbreaks were

Research in context

Evidence before this study

Mycoplasma pneumoniae is a major cause of respiratory tract infection in children and adults and results in epidemics every 1–3 years. The implementation of non-pharmaceutical interventions (NPIs) to control the spread of SARS-CoV-2 during the COVID-19 pandemic had a substantial effect on *M pneumoniae* detections globally. We searched PubMed without language restrictions from database inception to April 30, 2024, for studies published with the terms "*Mycoplasma pneumoniae*", "*Mycoplasma pneumoniae* re-emergence", "*Mycoplasma pneumoniae* outbreaks", "*Mycoplasma pneumoniae* epidemics", and "*Mycoplasma pneumoniae* macrolide resistance". We found evidence of epidemic cycles for *M pneumoniae* reported in isolation at a country level, with partial reports from multiple countries. Data about antimicrobial resistance of *M pneumoniae* against macrolides were sporadic. There is a scarcity of unified global reporting data for *M pneumoniae* with detailed information on patient outcomes, macrolide resistance, and the effect of NPIs on *M pneumoniae* detections.

Added value of this study

Our study reports the global spatiotemporal dynamics of the substantial *M pneumoniae* re-emergence in late 2023 with data from 29 countries. To our knowledge, this study represents the largest combined dataset for *M pneumoniae* detections. Additionally, this work provides detail of patient outcomes for several sites, information on macrolide resistance across the globe, and answers to why a substantial delay was seen in the re-emergence of *M pneumoniae* compared with the re-emergence of other respiratory pathogens.

Implications of all the available evidence

Our findings show that the re-emergence of *M pneumoniae* in late 2023 was substantial in terms of the number of detections, or even historic at most sites since the introduction of testing for this pathogen, and that it occurred across many geographical locations. This work highlights the need for continued international monitoring of *M pneumoniae* detections and antimicrobial resistance to keep clinicians informed about the emergence of future epidemics and the likelihood of no response to treatment.

attributed to *M pneumoniae* infections on the basis of our global prospective surveillance. This surveillance was initiated by the European Society of Clinical Microbiology and Infectious Diseases Study Group for *Mycoplasma* and *Chlamydia* Infections [ESGMAC] in February, 2021 and led to the ESGMAC *Mycoplasma pneumoniae* Surveillance [MAPS] study in April, 2022; hereafter referred to as the ESGMAC MAPS study.[8,9] This surveillance observed the re-emergence of *M pneumoniae* infections (global detection rate 4·12%; April–September, 2023) before the occurrence of these outbreaks, and alerted clinicians in a time-sensitive manner via monthly website updates.

For **ESGMAC MAPS** see https://www.escmid.org/science-research/study-group-collaborations/

Numerous theories exist for the altered epidemiology of infections surrounding the COVID-19 pandemic, most of which do not apply to *M pneumoniae* after the strong reduction in incidence long after discontinued NPIs.[3] Instead, the atypical characteristics that distinguish *M pneumoniae* from many other respiratory pathogens—such as its slow growth, prolonged incubation period, and low transmission rate[1]—have been hypothesised as reasons for the delayed re-emergence of *M pneumoniae*.[9]

In this study, we further expanded the global prospective surveillance study to additional sites and countries with the aim of contextualising the spatiotemporal dynamics, antimicrobial resistance, and severity of re-emerging *M pneumoniae* infections. Our objective was to develop a transmission model to understand underlying reasons for the delayed re-emergence.

Methods

Study design and population

Epidemiological and clinical data on *M pneumoniae* were obtained as part of the ESGMAC MAPS study.[7] Previously, epidemiological data were collected retrospectively by this study group for April, 2017–March, 2021 (21 countries, 37 sites)[3] and April, 2021–March, 2022 (20 countries, 34 sites)[6] to assess the effect of NPIs against COVID-19 on the transmission of *M pneumoniae*. Since April, 2022, the ESGMAC MAPS study collated data prospectively on a monthly basis (24 countries, 45 sites).[7,9] We included data on *M pneumoniae* detections from four UN regions: Europe, Asia, the Americas, and Oceania. A site was defined as an institution (ie, hospital–clinical laboratory, national–regional surveillance, or national reference laboratory) that collected laboratory-confirmed documented detections of *M pneumoniae*.

The ESGMAC MAPS study collected exclusively aggregated and anonymised epidemiological and clinical data from April 1, 2017 to March 31, 2024 that was extracted from local electronic record systems of participating sites, without accessing individual medical records. Individual patient data were neither collected at participating sites nor entered into the database, unless there was local ethics approval available that explicitly allowed this. The collaborators from participating sites confirmed that ethical review and approval was not required for this collection of aggregated and anonymised epidemiological or clinical data according to local regulations, or if it was, that the relevant approval had been obtained by the local ethics committee.

Procedures

Epidemiological data were collected that were aggregated by month for each participating site including total and positive test numbers. As previously described, because of local variations in the definition of *M pneumoniae* infection,

the absence of individual clinical information, and the difficulty of differentiating between *M pneumoniae* infection and carriage, this study collated information on *M pneumoniae* detections and not infections.[3] A case was defined as *M pneumoniae* detection in respiratory specimens (eg, at least one of nasopharyngeal or oropharyngeal swab, sputum, tracheal aspirate, or bronchoalveolar lavage) in an individual on the basis of the site's available test methods (appendix pp 6–87). Detailed information about microbiological detection methods including technique, product, and company or references to in-house test methods is listed in table 1. A positive IgM or IgG serological test was defined as antibody concentration above the cutoff of the test, as indicated by the manufacturer (appendix pp 6–87). The participating sites also indicated whether a positive serological test was confirmed by a four-fold increase over baseline IgG concentration (as serological gold standard for *M pneumoniae* infection; table 1).[3,10] Information on co-detections with other pathogens was not requested from participating sites. The study also collected retrospective epidemiological data back to April, 2017, from sites that were not involved from the beginning,[3] and on macrolide-resistant *M pneumoniae,* where available.

Macrolide-resistant *M pneumoniae* was established by the detection of point mutations (genotype) in the 23S rRNA gene, including A2063G/C/T, A2064G/C, A2067G, and C2617G/A in the *M pneumoniae* numbering system.[10] Detailed information including references about macrolide-resistant *M pneumoniae* determination methods is given in the appendix (pp 6–87) for each site that reported on macrolide-resistant *M pneumoniae* (table 1). Since macrolide-resistant *M pneumoniae* is associated with more severe disease and extrapulmonary manifestations,[8,11] we established macrolide-resistant *M pneumoniae* rates also to better evaluate the severity and outcome of the re-emergence.

Duplicates were removed in each month if not otherwise indicated (appendix pp 6–87). The epidemiological data might differ from previously published data from earlier time periods[3,6,7,9] owing to databases that have been updated and adjusted.

Clinical data were collected retrospectively for PCR-positive cases aggregated by year back to April, 2017 including hospitalisations and intensive care unit (ICU) admissions (clinical severity), and deaths (clinical outcome) separately for children and adults. Children were defined as younger than 18 years according to the UN, if not otherwise indicated.

Data on NPIs over time were collected by use of open data on country response measures to COVID-19 from the European Centre for Disease Prevention and Control,[12] the Joint Research Centre of the European Commission,[13] the global Oxford COVID-19 Government Response Tracker,[14] governmental data, previous publications,[15] or by collaborators of participating sites. Accordingly, the following NPIs were included in this study:[13,14] physical distancing; face masks indoors only; face masks outdoors; limiting the size of public gatherings (inside and outside); teleworking; closure of non-essential businesses; closure of preschools, primary schools, secondary schools, and universities (treated as separate NPIs); complete lockdown; private gathering restrictions; international border closure; and mobile app tracking. The NPI implementation and lifting periods varied quantitatively and qualitatively between countries and can be found for each participating country in the appendix (pp 88–118). Therefore, it is difficult to define a specific NPI for statistical analyses given its heterogenous and non-uniform definition, and sub-national or regional differences. Given the mode of transmission of *M pneumoniae* by aerosol particles and respiratory droplets through close contact, and for data quality and consistency against other NPIs, we have considered for our global surveillance study the duration of NPIs on the basis of the presence of wearing face masks outdoors or indoors only (whichever took longer; appendix pp 88–118).[16]

See Online for appendix

Statistical analysis

Detection rate was defined as the proportion of the number of new positive tests to the total number of tests over a specified period of time within a community. Epidemiological and clinical data were compared between different regions and time periods, respectively. Categorical and continuous variables were compared with the Fisher exact test and Mann–Whitney test, respectively. Spearman rank correlation coefficient (R; serology *vs* PCR) and the square (R^2; latitude *vs* epidemic onset[5]) were used for analyses of correlation.

To establish the start and characteristics of the re-emergence (April, 2023–March, 2024) across UN regions on the basis of *M pneumoniae* detections by PCR, the moving epidemic method (MEM) was used.[17] As previously defined,[5,17] an epidemic slope threshold of 2% was used to establish the pre-epidemic period, epidemic period, and post-epidemic period for the re-emergence. The monthly data were transformed into weekly data for MEM, as described in the appendix (pp 119–20). The week number in which the epidemic period began was used to correlate the onset of the re-emergence with the geographical location of each country.

We used a time-series model to investigate the potential reasons for the delayed re-emergence of *M pneumoniae* after lifting of NPIs. The interrupted time-series analysis has previously been used to evaluate the effects of NPIs on the overall burden of infectious diseases,[15] but it cannot help in disentangling the underlying reasons for the pathogen's delayed re-emergence once NPIs were released. We therefore chose the time-series susceptible–infected–recovered (TSIR) model as an alternative to explore the potential reasons.[18–20] The TSIR model is a discrete time adaptation of the susceptible–infected–recovered model, and it describes the number of infected and susceptible individuals as a set of difference equations, as detailed in the appendix (pp 121–22). The TSIR model was used to investigate whether the delayed re-emergence of *M pneumoniae* can be explained by epidemiological characteristics and a possible percentage reduction in transmission rate during the NPI period. Only

	Test method* (technique; in-house or product)	Patient cohort	Setting	Testing strategy	MRMp determination*	Clinical information
Europe (western)						
France						
Bordeaux						
Hospital–clinical laboratory (tertiary)	PCR (single, real-time; in-house)	Children and adults	Inpatients and outpatients	Targeted	Yes	Yes
Switzerland						
Geneva						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, real-time; BioGX Sample-Ready BD MAX System, BioGX, Birmingham, AL, USA)	Children and adults	Inpatients and outpatients	Targeted	No	Yes
Lausanne (A)						
Hospital–clinical laboratory (secondary)	PCR (multiplex, microarray; FilmArray Respiratory Panel, bioMérieux–BioFire Diagnostics, Salt Lake City, UT, USA)	Children and adults	Inpatients and outpatients	NA	No	No
Lausanne (B)						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, real-time; in-house)	Children and adults	Inpatients and outpatients	Targeted	No	Yes
Fribourg						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, real-time; Allplex PneumoBacter Assay, Seegene, Seoul, Republic of Korea and single, real-time; in-house)	Children	Inpatients and outpatients	Targeted	No	No
Bern						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, real-time; Anyplex II RB5 Detection, Seegene, Seoul, Republic of Korea)	Children	Inpatients and outpatients	Targeted	No	Yes
Lucerne						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, microarray; FilmArray Respiratory Panel, bioMérieux–BioFire Diagnostics, Salt Lake City, UT, USA)	Children	Inpatients and outpatients	Targeted	No	Yes
Bellinzona						
Hospital–clinical laboratory (regional; 0·4 million population)	PCR (multiplex, microarray; FilmArray Respiratory Panel, bioMérieux–BioFire Diagnostics, Salt Lake City, UT, USA and single, real-time; in-house)	Children and adults	Inpatients and outpatients	Targeted	No	Yes
Zurich (A)						
Hospital–clinical laboratory (tertiary)	PCR (single, real-time; in-house)	Children and adults	Inpatients and outpatients	Targeted	Yes	Yes
Zurich (B)						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, microarray; FilmArray Respiratory Panel, bioMérieux–BioFire Diagnostics, Salt Lake City, UT, USA)	Children	Inpatients and outpatients	Targeted	Yes	Yes
Zurich (C)						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, microarray; FilmArray Respiratory Panel, bioMérieux–BioFire Diagnostics, Salt Lake City, UT, USA)	Children and adults	Inpatients and outpatients	Targeted	No	No
Zurich (D)						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, real-time; ePlex respiratory pathogen panel, GenMark Diagnostics Inc., Carlsbad, CA, USA)	Adults	Inpatients and outpatients	Variable	No	Yes
St Gallen						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, real-time; Allplex Respiratory Panel, Seegene, Seoul, Republic of Korea)	Children	Inpatients and outpatients	Targeted	No	Yes
Aarau						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, microarray; FilmArray Respiratory Panel, bioMérieux–BioFire Diagnostics, Salt Lake City, UT, USA)	Children and adults	Inpatients and outpatients	Targeted	No	Yes
Hospital–clinical laboratory (tertiary)	ELISA (single-sample IgM and IgG)†	Children and adults	Inpatients and outpatients	Targeted	..	..
Basel (A)						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, microarray; FilmArray Respiratory Panel and Pneumonia Panel plus, bioMérieux–BioFire Diagnostics, Salt Lake City, UT, USA and RespiFinder, PathoFinder, Maastricht, Netherlands)	Adults	Inpatients and outpatients	Targeted	No	Yes
Hospital–clinical laboratory (tertiary)	ELISA (single-sample IgM and IgG)†	Adults	Inpatients and outpatients	Targeted	..	..

(Table 1 continues on next page)

	Test method* (technique; in-house or product)	Patient cohort	Setting	Testing strategy	MRM*p* determination*	Clinical information
(Continued from previous page)						
Basel (B)						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, microarray; FilmArray Respiratory Panel and Pneumonia Panel plus, bioMérieux–BioFire Diagnostics, Salt Lake City, UT, USA and RespiFinder, PathoFinder, Maastricht, Netherlands)	Children	Inpatients and outpatients	Targeted	No	Yes
Hospital–clinical laboratory (tertiary)	ELISA (single-sample IgM and IgG)†	Children	Inpatients and outpatients	Targeted	..	..
Germany						
Homburg						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, followed by DNA hybridization; AID CAP Bac PCR Kit, Autoimmun Diagnostika, Strassberg, Germany)	Children and adults	Inpatients and outpatients	Targeted	No	No
Hospital–clinical laboratory (tertiary)	CLIA (single-sample IgM and IgG)†	Children and adults	Inpatients and outpatients	Targeted	..	..
Würzburg						
Hospital–clinical laboratory (tertiary)	PCR (single, real-time; PCR, real-time; GeneProof *Mycoplasma pneumoniae*, GeneProof, Brno, Czech Republic)	Children and adults	Inpatients and outpatients	Targeted	No	No
Hospital–clinical laboratory (tertiary)	ELISA (single-sample IgM and IgG)†	Children and adults	Inpatients and outpatients	Targeted	..	..
Düsseldorf						
Hospital–clinical laboratory (tertiary)	PCR (single real-time; in-house)	Children and adults	Inpatients and outpatients	Targeted	No	No
Hospital–clinical laboratory (tertiary)	ELISA (single-sample IgM and IgG)†	Children and adults	Inpatients and outpatients	Targeted	..	..
Datteln–Witten–Herdecke						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, real-time; Allplex Respiratory Panel, Seegene, Seoul, Republic of Korea)	Children	Inpatients	Targeted	No	Yes
Saxony						
Surveillance (regional; 4·1 million population)	Combination of direct and indirect test methods (different techniques), but predominantly serology‡	Children and adults	Inpatients and outpatients	NA	No	No
Belgium						
National surveillance						
Surveillance (national; 60% of all Belgian microbiology laboratories)	PCR (diverse assays)‡	Children and adults	Inpatients and outpatients	NA	No	No
Antwerp						
Hospital–clinical laboratory (tertiary) and national reference laboratory	PCR (single, real-time; in-house)	Children and adults	Inpatients and outpatients	Targeted	Yes	Yes
Netherlands						
Rotterdam						
Hospital–clinical laboratory (tertiary)	PCR (single, real-time; in-house)	Children and adults	Inpatients and outpatients	Targeted	No	Yes
Hospital–clinical laboratory (tertiary)	CLIA (single-sample IgM and IgG)†	Children and adults	Inpatients and outpatients	Targeted	..	..
Haarlem						
Hospital–clinical laboratory (secondary)	PCR (multiplex, ligation-dependent probe amplification; RespiFinder Smart22, PathoFinder, Maastricht, Netherlands)	Children and adults	Inpatients and outpatients	Targeted	No	Yes
Europe (northern)						
England						
National surveillance						
National reference laboratory	PCR (multiplex, real-time; in-house)	Children and adults	Inpatient and outpatients	NA	Yes	No
Wales						
National surveillance						
Surveillance (national; 3·1 million population)	PCR (different techniques)	Children and adults	Inpatients and outpatients	NA	No	No
Denmark§						
National surveillance						
Surveillance (national; 5·8 million population)	PCR (different techniques)	Children and adults	Inpatients and outpatients	Targeted	Yes	Yes

(Table 1 continues on next page)

	Test method* (technique; in-house or product)	Patient cohort	Setting	Testing strategy	MRMp determination*	Clinical information
(Continued from previous page)						
Sweden						
National surveillance						
Surveillance (national; 10·5 million population)	PCR (different techniques)	Children and adults	Inpatients and outpatients	NA	No	No
Finland						
National surveillance						
Surveillance (national; 5·5 million population)	Combination of direct and indirect test methods (different techniques), but predominantly serology‡	Children and adults	Inpatients and outpatients	NA	No	No
Turku						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, real-time; Allplex Respiratory Panel, Seegene, Seoul, Republic of Korea)	Children and adults	Inpatients and outpatients	Targeted	No	No
Hospital–clinical laboratory (tertiary)	ELISA (single-sample IgM and paired-sample IgG)†	Children and adults	Inpatients and outpatients	Targeted	..	..
Norway						
Trondheim						
Hospital–clinical laboratory (tertiary)	PCR (multiplex PCR, real-time; in-house)	Children and adults	Inpatients and outpatients	Targeted	No	Yes
Europe (southern)						
Italy						
Rome						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, microarray; FilmArray Respiratory Panel, bioMérieux–BioFire Diagnostics, Salt Lake City, UT, USA)	Children	Inpatients and outpatients	Targeted	No	No
Padua						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, microarray; FilmArray Respiratory Panel, bioMérieux–BioFire Diagnostics, Salt Lake City, UT, USA)	Children	Inpatients and outpatients	Targeted	No	Yes
Portugal						
Coimbra						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, microarray; FilmArray Respiratory Panel, bioMérieux–BioFire Diagnostics, Salt Lake City, UT, USA)	Children	Inpatients and outpatients	Variable	No	Yes
Viseu						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, microarray; FilmArray Respiratory Panel, bioMérieux–BioFire Diagnostics, Salt Lake City, UT, USA)	Children	Inpatients and outpatients	Untargeted	No	Yes
Hospital–clinical laboratory (tertiary)	CLIA (single-sample IgM and IgG)†	Children	Inpatients and outpatients	Targeted	..	..
Spain						
Santiago de Compostela (Galicia)						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, real-time; Allplex Respiratory Panel 4, Seegene, Seoul, Republic of Korea)	Children and adults	Inpatients and outpatients	Targeted	No	Yes
Slovenia						
Ljubljana						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, real-time; Chlamydia–Myco pneumo R-GENE; bioMérieux–ARGENE, Marcy-l'Étoile, France)	Children and adults	Inpatients and outpatients	Targeted	Yes	Yes
Croatia						
Zagreb						
Hospital–clinical laboratory (tertiary)	PCR (real-time; in-house)	Children and adults	Inpatients and outpatients	Targeted	Yes	Yes
Greece						
Athens (A)						
Hospital–clinical laboratory (tertiary)	ELISA (single-sample IgM and IgG)	Children	Inpatients and outpatients	Targeted	No	No
Athens (B)						
Hospital–clinical laboratory (tertiary)	ELISA (single-sample IgM and IgG)	Children	Inpatients and outpatients	Targeted	No	No

(Table 1 continues on next page)

	Test method* (technique; in-house or product)	Patient cohort	Setting	Testing strategy	MRM*p* determination*	Clinical information
(Continued from previous page)						
Asia (western)						
Israel						
Jerusalem						
Hospital–clinical laboratory (tertiary)	PCR (single, real-time; in-house)	Children and adults	Inpatients and outpatients	Targeted	No	Yes
Asia (eastern)						
China						
Beijing						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, real-time; Mole Biotechnology, Jiangsu, China)	Children	Inpatients and outpatients	Targeted	Yes	No
Zhengzhou (Henan)						
Hospital–clinical laboratory (tertiary)	Isothermal amplification (single, real-time; Haier Biopharmaceutical, Qingdao, China)	Children	Inpatients and outpatients	Targeted	No	No
Baoding (Hebei)						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, real-time; Mole Biotechnology, Jiangsu, China)	Children	Inpatients	Targeted	Yes	No
Jingmen (Hubei)						
Hospital–clinical laboratory (tertiary)	PCR (single, real-time; Sansure Biotech, Changsha, China)	Children and adults	Inpatients and outpatients	Targeted	No	Yes
Shenzhen (Guangdong)						
Hospital–clinical laboratory (tertiary)	PCR (single, real-time; Sansure Biotech, Changsha, China; and multiplex, real-time; Health Gene Technologies, Ningbo, China)	Children	Inpatients	Targeted	No	Yes
Suzhou (Jiangsu)						
Hospital–clinical laboratory (tertiary)	PCR (single, real-time; Daan Gene, Guangzhou, China)	Children	Inpatients	Targeted	Yes	Yes
Hospital–clinical laboratory (tertiary)	Colloidal gold-based immunochromatographic assay (single-sample IgM)†	Children	Outpatients	Targeted	..	..
South Korea						
Seoul						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, real-time; AmpliSens *Mycoplasma pneumoniae–Chlamydophila pneumoniae*, Ecoli Dx, Prague, Czech Republic)	Children and adults	Inpatients and outpatients	Targeted	Yes	Yes
Seongnam						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, real-time; NxTAG Respiratory Pathogen Panel, Luminex, Toronto, Canada)	Children and adults	Inpatients and outpatients	Targeted	No	Yes
Seoul (Boramae)						
Hospital–clinical laboratory (secondary)	PCR (multiplex, real-time; AmpliSens *Mycoplasma pneumoniae–Chlamydophila pneumoniae*, Ecoli Dx, Moscow, Russia; Allplex PneumoBacter Assay, Seegene, Seoul, Republic of Korea)	Children and adults	Inpatients and outpatients	Targeted	Yes	Yes
Japan						
Kurashiki City (Okayama)						
Hospital–clinical laboratory (tertiary)	PCR (single, real-time; in-house)	Children	Inpatients and outpatients	Targeted	Yes	Yes
Mitaka City (Tokyo)						
Hospital–clinical laboratory (tertiary)	Rapid antigen test (SAI; Fuji Dri-Chem Immuno, Fujifilm, Kanagawa, Japan)	Children and adults	Inpatients and outpatients	Targeted	No	No
Tsurugashima City (Saitama)						
Hospital–clinical laboratory (tertiary)	Culture	Children and adults	Inpatients and outpatients	Targeted	Yes	No
Taiwan						
Taoyuan						
Hospital–clinical laboratory (tertiary)	PCR (single, real-time; in-house)	Children	Inpatients and outpatients	Targeted	Yes	Yes
Changhua City						
Hospital–clinical laboratory (tertiary)	PCR (single, real-time; in-house)	Children	Inpatients and outpatients	Targeted	Yes	No

(Table 1 continues on next page)

	Test method* (technique; in-house or product)	Patient cohort	Setting	Testing strategy	MRMp determination*	Clinical information
(Continued from previous page)						
Asia (southeastern)						
Singapore						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, microarray; FilmArray Respiratory Panel, bioMérieux–BioFire Diagnostics, Salt Lake City, UT, USA)	Children	Inpatients and outpatients	Targeted	No	No
Asia (south)						
India						
New Dehli						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, real-time; in-house)	Children and adults	Inpatients and outpatients	Targeted	No	No
Hospital–clinical laboratory (tertiary)	ELISA (single-sample IgM)†	Children and adults	Inpatients and outpatients	Targeted	..	..
Americas (northern)						
Canada						
Vancouver, BC						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, microarray; FilmArray Respiratory Panel, bioMérieux–BioFire Diagnostics, Salt Lake City, UT, USA; and single, real-time; in-house)	Children	Inpatients and outpatients	Variable	No	No
USA						
Chicago, IL						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, microarray; FilmArray Respiratory Panel, bioMérieux–BioFire Diagnostics, Salt Lake City, UT, USA)	Children and adults	Inpatients and outpatients	Targeted	No	No
Rochester, MN						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, microarray; FilmArray Respiratory Panel, bioMérieux–BioFire Diagnostics, Salt Lake City, UT, USA; and single, real-time; in-house)	Children and adults	Inpatients and outpatients	Targeted	No	No
Aurora, CO						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, microarray; FilmArray Respiratory Panel, bioMérieux–BioFire Diagnostics, Salt Lake City, UT, USA)	Children	Inpatients and outpatients	Targeted	No	No
Americas (Caribbean)						
Cuba						
National surveillance						
National reference laboratory (national; 11·3 million population)	PCR (single, real-time; in-house)	Children and adults	Inpatients and outpatients	NA	Yes	Yes
Oceania						
Australia						
Darlinghurst, NSW (Sydney)						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, real-time; EasyScreen Respiratory Pathogen Detection Kit, Genetic Signatures, Sydney, Australia)	Children and adults	Inpatients and outpatients	Targeted	No	No
Hospital–clinical laboratory (tertiary)	CLIA (single-sample IgM and IgG)†	Children and adults	Inpatients and outpatients	Targeted	..	..
New Zealand						
Auckland						
Hospital–clinical laboratory (tertiary)	PCR (multiplex, microarray; FilmArray Respiratory Panel, bioMérieux–BioFire Diagnostics, Salt Lake City, UT, USA; and multiplex, real-time; in-house)	Children and adults	Inpatients and outpatients	Untargeted	No	No

Data are stratified by UN subregion. CLIA=chemiluminescent immunoassay. ELISA=enzyme-linked immunosorbent assay. MRMp=macrolide-resistant *M pneumoniae*. NA=not available. *Further information and reporting characteristics, such as references to in-house test methods, products, and MRMp determination, as well as information about de-duplication and exclusion are given separately for each site in the appendix (pp 6–87). Clinical information was only requested from sites reporting *M pneumoniae* detections by PCR. †In addition to PCR also serological data separately reported for the same site. ‡Exclusively positive test numbers (and no total test numbers) available or reported. §Denmark is the only country where *M pneumoniae* infections are laboratory notifiable. Information about nationwide detections is recorded in the national microbiology database that is available for continuous surveillance at the national public health and research institute (Statens Serum Institut, Copenhagen).

Table 1: **Laboratory information and reporting characteristics of participating sites for *Mycoplasma pneumoniae***

data on *M pneumoniae* detections by PCR were considered for the modelling analysis. The tsiR package was used for the analysis.[19]

The TSIR model was developed on the basis of comprehensive epidemiological data from the national microbiology database of Denmark. *M pneumoniae* infections are laboratory notifiable in Denmark and information is recorded in the National Microbiology Database, which is available for continuous surveillance at the national public health and research institute (Statens Serum Institut,

Copenhagen, Denmark).[4] The following epidemiological data from Denmark were used for the development of the TSIR model: national weekly total and positive *M pneumoniae* test numbers (2011–23; data not shown), data on NPIs with definition and implementation (appendix p 95), and yearly population and annual birth cohort. The TSIR model was first fitted to the pre-NPI detection rate in Denmark (January, 2011–March, 2020). The forward simulations from April, 2020 to December, 2023 were generated by means of the estimated seasonal transmission rates, the actual population and birth rate for Denmark during the period, and assuming that NPIs started from week 14 of 2020 and ended at week 5 of 2022 (96 weeks). The percentage reduction in transmission rate during the NPI period was estimated by comparing the model simulations with detections of *M pneumoniae* during the NPI lifting period. The TSIR model was also applied to the four different UN regions under assumptions listed in the appendix (pp 129–31). The four UN regions were treated as independent, as the TSIR model does not explicitly model the spatial effects.

Analyses were done with R software, version 4.4.0. In all tests, significance was defined as a p value of less than 0·05.

Role of the funding source

There was no funding source for this study.

Results

The global dataset included 65 sites in 29 countries from four UN regions: Europe (17 countries, 41 sites), Asia (7 countries, 17 sites), the Americas (3 countries, 5 sites), and Oceania (2 countries, 2 sites). Laboratory information and reporting characteristics of participating sites are detailed in table 1. The detection methods included direct test methods at 61 sites (PCR at 58 sites; isothermal amplification at one site; rapid antigen test at one site; and culture at one site), exclusively serological testing at two sites, and combined PCR and serology at two sites (with no distinction possible between detection methods, but predominantly serology). The patient cohorts included children at 63 (96·92%) sites, adults at 41 (63·08%) sites, and both children and adults at 39 sites (60·00%; appendix pp 6–87).

The global evolution of *M pneumoniae* detections by PCR after the implementation and lifting of NPIs is shown in figure 1. During the 3 years following the initial implementation of NPIs (April, 2020–March, 2023), the mean detection rate was 0·50% (SD 0·86) in Europe, 0·18% (0·22) in the Americas, and 0·03% (0·01) in Oceania (table 2). The mean detection rate in Asia, excluding China, during this period was 1·78% (4·68). The large dataset from China, which included six sites that have only joined our global prospective surveillance network since November, 2023,[8] was the only country to show retrospectively significant increases in cases and detection rates around the annual transition 2020–21 and 2021–22 (8·99%, SD 7·25; table 2).

A discrepancy was again found between detection rates by PCR and serology;[3,6] detections by serology continued despite the implementation of NPIs (figure 2).

A global re-emergence of *M pneumoniae* cases by PCR detection was noted from the second half of 2023 (figure 1). At this point, NPIs had long been discontinued in all countries (appendix pp 88–118). The mean detection rates in this fourth year after the initial implementation of NPIs (April, 2023–March, 2024) were 10·30% (SD 12·34) in Europe, 19·66% (23·10) in Asia, 1·34% (1·63) in the Americas, and 0·56% (0·08) in Oceania. Detection rates varied widely across the different sites and countries (table 2). The highest detection rate was reported with 4344 (67·45%) of 6440 from eastern China (Suzhou, Jiangsu) among hospitalised children (table 2). Absolute test numbers by PCR were increased in the same period compared with the pre-pandemic period in Europe with 403·55% (SD 528·80), Asia 393·48% (660·45), the Americas 217·00% (188·27), and Oceania 230·10% (131·91). In 16 (57·14%) countries in the UN regions, the re-emergence peaked by PCR before the end of the study period in March, 2024 (figure 1).

The MEM identified the re-emergence in all four UN regions as epidemics (figure 3). The re-emergence started in ten countries at calendar week 40 in 2023 (appendix pp 119–20). When examining the re-emergence, an association between the country latitude and beginning of the epidemic period was not observed globally (northern hemisphere; p=0·28, R^2=0·05), but for Europe and Israel (p=0·03, R^2=0·30)[5]: northern countries within Europe had the start of the re-emergence earlier than those in the south and Israel (figure 3).

Data about macrolide-resistant *M pneumoniae* were received from 18 sites, four of which were national surveillance (table 3). There were no significant increases in macrolide-resistant *M pneumoniae* rates found during the re-emergence (April, 2023–March, 2024) compared with before the implementation of NPIs (April, 2017–March, 2020). The mean macrolide-resistant *M pneumoniae* rate during the re-emergence for reporting sites was 2·02% (SD 1·35) in Europe (France, Belgium, England, Denmark, and Slovenia) and 71·22% (37·05) in Asia (China, South Korea, and Taiwan; table 3).

Clinical data from PCR-positive cases were available from 34 sites in 18 countries and shown separately for children and adults in table 4. Increased rates of hospitalisations during the re-emergence were found in adults in two countries (two of ten; ie, Switzerland from 158 [37·18%] of 425 pre-NPI to 197 [54·72%] of 360, and the Netherlands from 40 [48·78%] of 82 pre-NPI to 88 [67·69%] of 130), and for children in two countries (two of 14; ie, Switzerland from 201 [32·11%] of 626 pre-NPI to 299 [44·36%] of 674, and Portugal from 24 [21·24%] of 113 pre-NPI to 102 [31·19%] of 327; table 4). More frequent ICU admission rates were reported for adults in one country (one of nine; ie, Norway from zero of 457 pre-NPI to two [2·14%] of 83), and for

For **data on yearly population and annual birth cohort** see https://www.statbank.dk

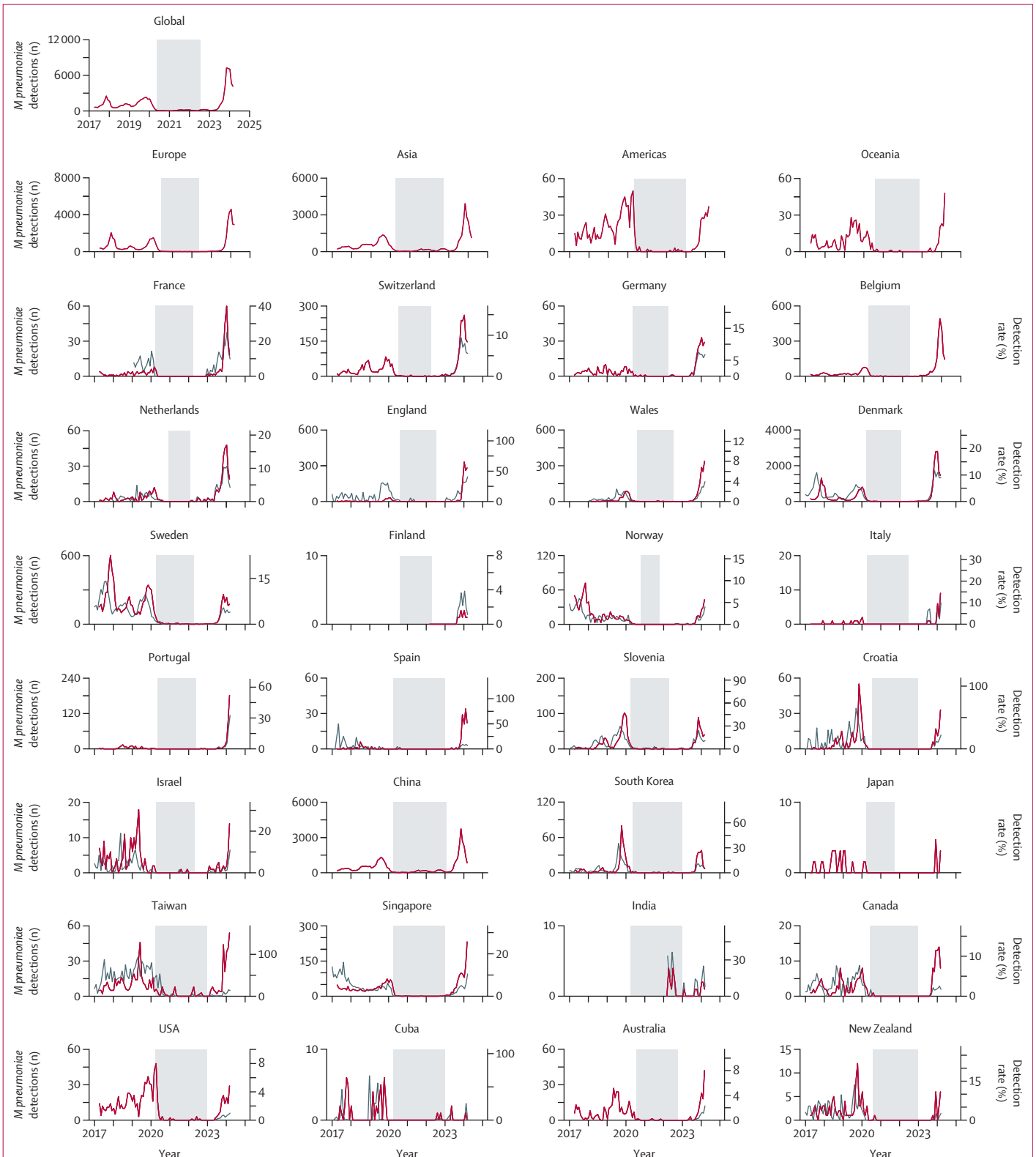

Figure 1: **Global detections of *Mycoplasma pneumoniae* by PCR before, during, and after COVID-19 pandemic restrictions, 2017–24**

The red line represents *M pneumoniae* detection numbers (primary y-axis) and the grey line the detection rates (secondary y-axis). The secondary y-axis includes only data from national surveillances where the total number of tests is available or reported, or from periods where the total number of tests is available for all sites if more than one site per country is included. Note the different scaling of y-axes for detection numbers and detection rates between panels. The grey background indicates the presence of NPIs against COVID-19. Globally, the period of NPIs spanned May, 2020–July, 2022; Europe, May, 2020–May, 2022; Asia, April, 2020–October, 2022; the Americas, April, 2020–December, 2022; and Oceania, May, 2020–November, 2022. Detailed detection numbers separately for each site and corresponding NPI periods are shown in the appendix (pp 6–87 and 88–118, respectively). The NPI period for the global and UN regions is defined as the average of NPIs of all countries involved. NPI=non-pharmaceutical intervention.

	Test method	2017–20 (pre-NPI)		2020–21 (first year)		2021–22 (second year)		2022–23 (third year)		2023–24 (fourth year)		2017–20 *vs* 2023–24	
		Positive tests (n/N)	Detection rate (%)	Positive tests (n/N)	Detection rate (%)	Positive tests (n/N)	Detection rate (%)	Positive tests (n/N)	Detection rate (%)	Positive tests (n/N)	Detection rate (%)	Detection rate change (%)*	p value†
Europe (western)													
France													
Bordeaux	PCR	82/1825	4·49%	5/526	0·95%	0/564	0	4/478	0·84%	192/1263	15·20%	238·33%	<0·0001
Switzerland													
Geneva	PCR	169/4847	3·49%	5/1194	0·42%	2/1478	0·14%	6/1870	0·32%	292/3246	9·00%	158·00%	<0·0001
Lausanne (A)	PCR	30/1435	2·09%	0/277	0	0/542	0	0/1087	0	198/2314	8·56%	309·29%	<0·0001
Lausanne (B)	PCR	134/2271	5·90%	1/712	0·14%	0/884	0	7/1027	0·68%	218/1918	11·37%	92·63%	<0·0001
Fribourg	PCR	15/84	17·86%	1/18	5·56%	0/25	0	0/21	0	48/179	26·82%	50·17%	0·23
Bern	PCR	90/421	21·38%	1/86	1·16%	0/95	0	1/160	0·63%	79/427	18·50%	–13·46%	0·40
Lucerne	PCR	36/NA	NA	1/206	0·49%	0/352	0	1/504	0·20%	59/634	9·31%	..	..
Bellinzona	PCR	129/3345	3·86%	0/803	0	0/1665	0	6/2266	0·26%	56/2855	1·96%	–49·14%	<0·0001
Zurich (A)	PCR	108/4132	2·61%	11/1823	0·60%	2/1829	0·11%	1/1851	0·05%	55/1695	3·24%	24·15%	0·22
Zurich (B)	PCR	97/428	22·66%	3/1659	0·18%	0/1593	0	0/987	0	78/1301	6·00%	–73·55%	<0·0001
Zurich (C)	PCR	NA	..	1/143	0·70%	0/147	0	0/233	0	26/320	8·13%	..	..
Zurich (D)	PCR	NA	..	NA	..	NA	..	3/4857	0·06%	26/4983	0·52%	..	..
St Gallen	PCR	18/57	31·58%	1/8	12·50%	0/12	0	0/10	0	41/93	44·09%	39·61%	0·34
Aarau	PCR	168/4970	3·38%	10/1601	0·62%	0/746	0	6/1087	0·55%	50/823	6·08%	79·73%	0·0008
Aarau	ELISA IgM	56/640	8·75%	13/183	7·10%	2/12	16·67%	4/77	5·19%	16/51	31·37%	258·54%	0·0002
Aarau	ELISA IgG	141/640	22·03%	46/183	25·14%	1/12	8·33%	27/77	35·06%	22/51	43·14%	95·80%	0·019
Basel (A)	PCR	77/9501	0·81%	2/2669	0·07%	0/2880	0	1/3338	0·03%	44/3528	1·25%	53·89%	0·030
Basel (A)	ELISA IgM	NA	..	4/27	14·81%	2/42	4·76%	1/34	2·94%	3/49	6·12%	..	..
Basel (A)	ELISA IgG	NA	..	8/27	29·63%	11/43	25·58%	13/33	39·39%	14/49	28·57%	..	..
Basel (B)	PCR	25/2555	0·98%	6/563	1·07%	0/1493	0	0/1507	0	36/1227	2·93%	199·85%	<0·0001
Basel (B)	ELISA IgM	NA	..	11/50	22·00%	7/48	14·58%	0/38	0	1/33	3·03%	..	..
Basel (B)	ELISA IgG	NA	..	6/48	12·50%	6/48	12·50%	2/38	5·26%	6/33	18·18%	..	..
Germany													
Homburg	PCR	46/7489	0·61%	1/2570	0·04%	0/2341	0	1/2195	0·05%	22/1912	1·15%	87·33%	0·022
Homburg	CLIA IgM	208/1522	13·67%	70/588	11·90%	64/587	10·90%	34/498	6·83%	41/441	9·30%	–31·97%	0·034
Homburg	CLIA IgG	909/1522	59·72%	331/588	56·29%	347/587	59·11%	42/498	8·43%	50/441	11·34%	–81·02%	<0·0001
Würzburg	PCR	42/2490	1·69%	4/948	0·42%	0/1067	0	0/1054	0	31/1036	2·99%	77·40%	0·019
Würzburg	ELISA IgM	63/710	8·87%	14/234	5·98%	10/154	6·49%	9/140	6·43%	12/163	7·36%	–17·03%	0·64
Würzburg	ELISA IgG	318/710	44·79%	113/234	48·29%	86/154	55·84%	72/140	51·43%	87/163	53·37%	19·17%	0·26
Düsseldorf	PCR	47/3023	1·55%	5/627	0·80%	0/684	0	1/739	0·14%	73/1102	6·62%	326·07%	<0·0001
Düsseldorf	ELISA IgM	121/1314	9·21%	56/349	16·05%	60/371	16·17%	57/358	15·92%	50/375	13·33%	44·79%	0·044
Düsseldorf	ELISA IgG	NA	..	224/349	64·18%	202/371	54·45%	204/358	56·98%	224/375	59·73%	..	..
Datteln—Witten—Herdecke	PCR	1/59	1·69%	1/37	2·70%	0/36	0	0/87	0	45/272	16·54%	876·10%	0·0042
Saxony	Combination	3911/NA	..	293/NA	..	219/NA	..	297/NA	..	2377/NA	..	..	..
Belgium													
National surveillance	PCR	760/NA	..	44/NA	..	10/NA	..	27/NA	..	1892/NA	..	..	..
Antwerp	PCR	60/4276	1·40%	3/1080	0·28%	2/1029	0·19%	2/970	0·21%	73/1269	5·75%	309·97%	<0·0001
Netherlands													
Rotterdam	PCR	13/276	4·71%	1/230	0·43%	0/195	0	2/232	0·86%	30/321	9·35%	98·42%	0·056
Rotterdam	CLIA IgM	NA	..	14/128	10·94%	14/131	10·69%	15/127	11·81%	30/139	21·58%	..	..
Rotterdam	CLIA IgG	NA	..	17/128	13·28%	32/131	24·43%	19/127	14·96%	30/139	21·58%	..	..
Haarlem	PCR	98/8893	1·10%	12/2788	0·43%	1/2353	0·04%	11/2934	0·37%	206/3536	5·83%	428·66%	<0·0001

(Table 2 continues on next page)

	Test method	2017–20 (pre-NPI)		2020–21 (first year)		2021–22 (second year)		2022–23 (third year)		2023–24 (fourth year)		2017–20 vs 2023–24	
		Positive tests (n/N)	Detection rate (%)	Positive tests (n/N)	Detection rate (%)	Positive tests (n/N)	Detection rate (%)	Positive tests (n/N)	Detection rate (%)	Positive tests (n/N)	Detection rate (%)	Detection rate change (%)*	p value†
(Continued from previous page)													
Europe (northern)													
England													
National surveillance	PCR	177/600	29·50%	13/180	7·22%	3/149	2·01%	2/133	1·50%	1055/1668	63·25%	114·40%	<0·0001
Wales													
National surveillance	PCR	NA	..	25/148 673	0·02%	15/793 709	0	5/231 839	0	1227/85 649	1·43%	..	..
Denmark‡													
National surveillance	PCR	11 006/289 131	3·81%	181/67 584	0·27%	15/99 461	0·02%	89/97 378	0·09%	12 163/159 016	7·65%	100·94%	<0·0001
Sweden													
National surveillance	PCR	7582/114 135	6·64%	133/23 394	0·57%	27/28 714	0·09%	19/33 117	0·06%	1382/44 884	3·08%	–53·65%	<0·0001
Finland													
National surveillance	Combination	5460/NA	..	455/NA	..	282/NA	..	347/NA	..	553/NA	..	..	..
Turku	PCR	NA	..	NA	..	NA	..	0/700	0	9/674	1·34%	..	..
Turku	ELISA IgM	NA	..	NA	..	NA	..	36/1859	1·94%	75/1845	4·07%	..	..
Turku	ELISA IgG	NA	..	NA	..	NA	..	1/1845	0·05%	0/1843	0	..	..
Norway													
Trondheim	PCR	740/33 497	2·21%	5/3699	0·14%	0/6462	0	2/7873	0·03%	143/9807	1·46%	–34·00%	<0·0001
Europe (southern)													
Italy													
Rome	PCR	NA	..	NA	..	NA	..	0/374	0	11/75	14·67%	..	..
Padua	PCR	10/219	4·57%	0/100	0	0/251	0	0/352	0	8/362	2·21%	–51·60%	0·14
Portugal													
Coimbra	PCR	111/2811	3·95%	0/161	0	0/2136	0	0/3096	0	268/3016	8·89%	125·03%	<0·0001
Viseu	PCR	2/71	2·82%	0/19	0	0/84	0	2/248	0·81%	59/639	9·23%	227·78%	0·11
Viseu	CLIA IgM	53/190	27·89%	9/11	81·82%	3/18	16·67%	6/28	21·43%	0/11	0	–100·00%	0·13
Viseu	CLIA IgG	33/190	17·37%	1/13	7·69%	1/18	5·56%	6/28	21·43%	1/11	9·09%	–47·66%	1·00
Spain													
Santiago de Compostela (Galicia)	PCR	23/478	4·81%	1/191	0·52%	0/228	0	0/343	0	118/1002	11·78%	144·75%	<0·0001
Slovenia													
Ljubljana	PCR	670/6153	10·89%	20/1241	1·61%	7/1669	0·42%	5/1680	0·30%	358/3055	11·72%	7·62%	0·30
Croatia													
Zagreb	PCR	243/1125	21·60%	2/94	2·13%	0/134	0	0/179	0	87/680	12·79%	–40·77%	<0·0001
Greece													
Athens (A)	ELISA IgM	137/705	19·43%	34/167	20·36%	44/230	19·13%	76/274	27·74%	73/254	28·74%	47·90%	0·018
Athens (A)	ELISA IgG	111/702	15·81%	41/167	24·55%	47/230	20·43%	46/274	16·79%	66/254	25·98%	64·33%	0·0047
Athens (B)	ELISA IgM	51/597	8·54%	14/172	8·14%	10/193	5·18%	17/259	6·56%	21/325	6·46%	–24·36%	0·37
Athens (B)	ELISA IgG	239/597	40·03%	44/172	25·58%	140/193	72·54%	133/259	51·35%	122/325	37·54%	–6·23%	0·65
Asia (western)													
Israel													
Jerusalem	PCR	153/4271	3·58%	0/666	0	2/1039	0·19%	3/1294	0·23%	33/1241	2·66%	–25·77%	0·13
Asia (eastern)													
China													
Beijing	PCR	2704/8953	30·20%	23/720	3·19%	348/1623	21·44%	152/822	18·49%	1555/3179	48·91%	61·96%	<0·0001
Zhengzhou (Henan)	AMP	NA	..	NA	..	NA	..	NA	..	25 300/55 240	45·80%	..	..
Baoding (Hebei)	PCR	NA	..	NA	..	281/615	45·69%	684/979	69·87%	4249/6706	63·36%	..	..

(Table 2 continues on next page)

	Test method	2017–20 (pre-NPI)		2020–21 (first year)		2021–22 (second year)		2022–23 (third year)		2023–24 (fourth year)		2017–20 *vs* 2023–24	
		Positive tests (n/N)	Detection rate (%)	Positive tests (n/N)	Detection rate (%)	Positive tests (n/N)	Detection rate (%)	Positive tests (n/N)	Detection rate (%)	Positive tests (n/N)	Detection rate (%)	Detection rate change (%)*	p value†
(Continued from previous page)													
Jingmen (Hubei)	PCR	NA	..	NA	..	NA	..	NA	..	1677/6948	24·14%	..	..
Shenzhen (Guangdong)	PCR	6693/55 685	12·02%	83/10 775	0·77%	240/13 808	1·74%	484/14 390	3·36%	5127/25 385	20·20%	68·04%	<0·0001
Suzhou (Jiangsu)	PCR	8046/37 226	21·61%	223/7606	2·93%	777/5515	14·09%	142/508	27·95%	4344/6440	67·45%	212·08%	<0·0001
Suzhou (Jiangsu)	ELISA IgM	50 707/228 265	22·21%	4107/49 433	8·31%	9598/76 149	12·60%	5672/52 525	10·80%	64 352/188 175	34·20%	53·95%	<0·0001
South Korea													
Seoul	PCR	190/2831	6·71%	3/696	0·43%	2/941	0·21%	2/1370	0·15%	64/2033	3·15%	−53·09%	<0·0001
Seongnam	PCR	111/1219	9·11%	1/233	0·43%	0/296	0	0/440	0	85/957	8·88%	−2·46%	0·88
Seoul (Boramae)	PCR	14/384	3·65%	0/76	0	0/95	0	0/155	0	12/339	3·54%	−2·91%	1·00
Japan													
Kurashiki City (Okayama)	PCR	21/128	16·41%	0/5	0	0/NA	..	0/170	0	5/184	2·72%	−83·44%	0·0001
Mitaka City (Tokyo)	RAT	128/1086	11·79%	4/120	3·33%	0/373	0	0/167	0	0/182	0	−100·00%	<0·0001
Tsurugashima City (Saitama)	Culture	84/489	17·18%	0/38	0	0/74	0	0/73	0	5/127	3·94%	−77·08%	0·0002
Taiwan													
Taoyuan	PCR	274/518	52·90%	8/193	4·15%	0/948	0	1/2039	0·05%	209/4073	5·13%	−90·30%	<0·0001
Changhua City	PCR	136/287	47·39%	20/143	13·99%	12/67	17·91%	18/164	10·98%	21/160	13·13%	−72·30%	<0·0001
Asia (south eastern)													
Singapore													
Singapore	PCR	1307/28 507	4·58%	33/8835	0·37%	1/12627	0·01%	16/26 174	0·06%	897/25 913	3·46%	−24·50%	<0·0001
Asia (south)													
India													
New Dehli	PCR	NA	..	NA	..	NA	..	14/122	11·48%	7/82	8·54%	..	..
New Dehli	ELISA IgM	56/770	7·27%	16/153	10·46%	14/96	14·58%	12/122	9·84%	12/90	13·33%	83·33%	0·10
Americas (northern)													
Canada													
Vancouver, BC	PCR	99/2946	3·36%	3/1201	0·25%	0/2706	0	0/4154	0	64/5169	1·24%	−63·16%	<0·0001
USA													
Chicago, IL	PCR	77/13 410	0·57%	2/1695	0·12%	0/5646	0	0/8450	0	18/8174	0·22%	−61·65%	0·0001
Rochester, MN	PCR	203/19 338	1·05%	18/6707	0·27%	1/8758	0·01%	3/10 224	0·03%	42/12 638	0·33%	−68·34%	<0·0001
Aurora, CO	PCR	320/17 735	1·80%	55/8106	0·68%	0/10 998	0	1/9768	0·01%	72/9917	0·73%	−59·76%	<0·0001
Americas (Caribbean)													
Cuba													
National surveillance	PCR	42/1808	2·32%	0/4	0	0/4	0	2/353	0·57%	3/72	4·17%	79·37%	0·25
Oceania													
Australia													
Darlinghurst, NSW (Sydney)	PCR	283/49 024	0·58%	19/70 807	0·03%	3/17 986	0·02%	0/14 777	0	113/22 360	0·51%	−12·46%	0·25
Darlinghurst, NSW (Sydney)	CLIA IgM	NA	..	NA	..	NA	..	47/641	7·33%	41/660	6·21%	..	..
Darlinghurst, NSW (Sydney)	CLIA IgG	NA	..	NA	..	NA	..	93/641	14·51%	94/660	14·24%	..	..
New Zealand													
Auckland	PCR	88/2387	3·69%	4/2721	0·15%	0/5011	0	0/6163	0	16/2573	0·62%	−83·13%	<0·0001

The annual figures always refer to the 12-month period April 1 to March 31 (eg, April 1, 2017–March 31, 2020). AMP=isothermal amplification. CLIA=chemiluminescent immunoassay. Combination=combination of PCR and serology with no distinction possible between detection methods, but predominantly serology. MRMp=macrolide-resistant *M pneumoniae*. NA=not available. NPI=non-pharmaceutical intervention. RAT=rapid antigen test. *Detection rate change (%) between April 1, 2017–March 31, 2020 (pre-NPI period) and April 1, 2023–March 31, 2024 (re-emergence), calculated as follows: ([detection rate re-emergence (%)–detection rate pre-NPI period (%)]/detection rate pre-NPI period [%]) × 100. †Proportions of total numbers of positive–total tests from April 1, 2017 to March 31, 2020 (pre-NPI period) were compared with positive–total tests from April 1, 2023 to March 31, 2024 (re-emergence) by Fisher's exact test. ‡Denmark is the only country where *M pneumoniae* infections are laboratory notifiable. Information about nationwide detections is recorded in the national microbiology database that is available for continuous surveillance at the national public health and research institute (Statens Serum Institut, Copenhagen).

***Table 2:* *Mycoplasma pneumoniae* testing and detection rates before, during, and after COVID-19 pandemic restrictions, 2017–24 by UN country, city, or region**

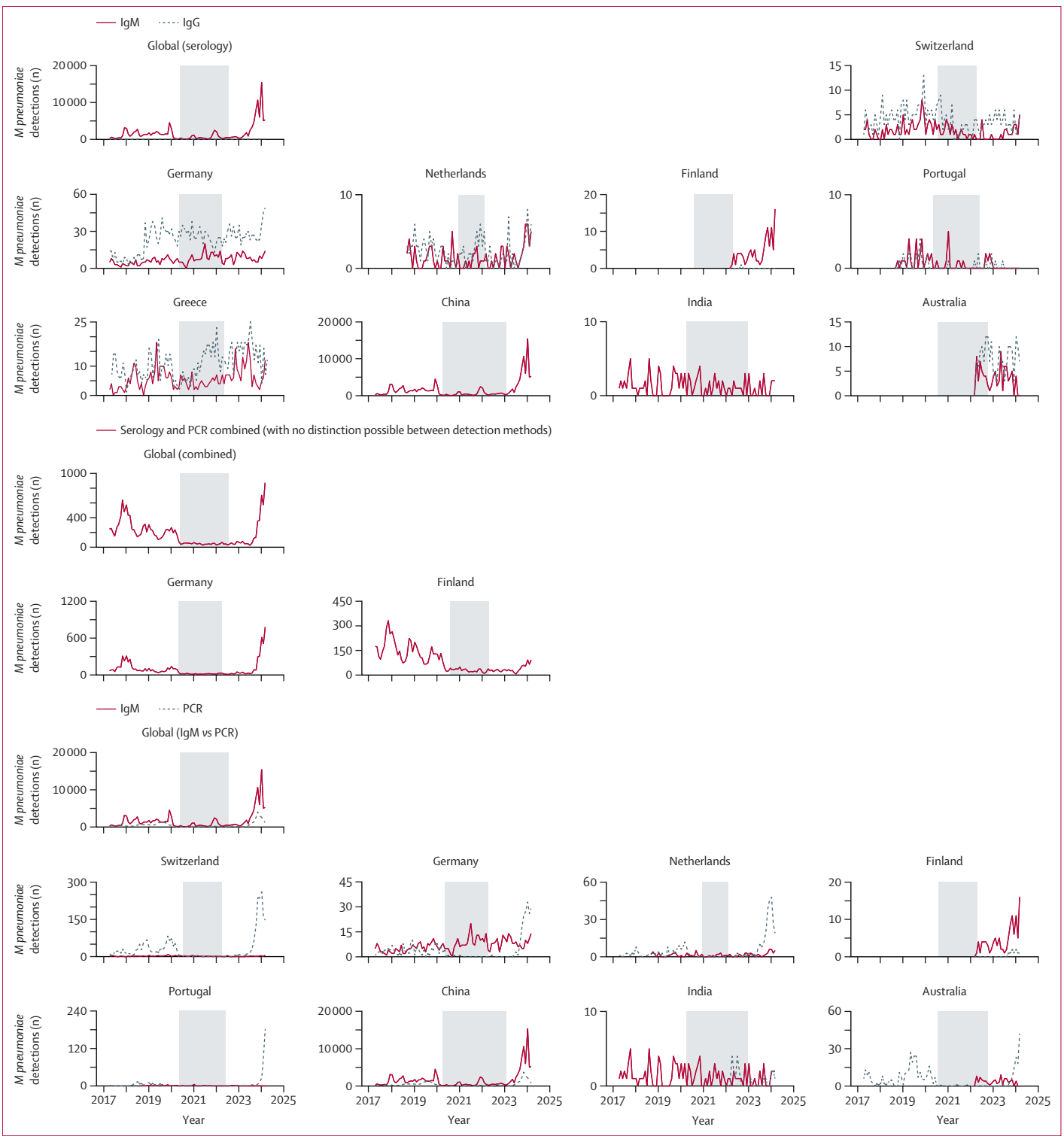

Figure 2: **Global detections of *Mycoplasma pneumoniae* by serology before, during, and after COVID-19 pandemic restrictions, 2017–24**

Detections are shown for serology (IgM and IgG), combined (serology and PCR combined with no distinction possible between detection methods, but predominantly serology), and IgM versus PCR (direct comparison of detections with PCR and single-sample IgM serology from the 12 sites from eight different countries that reported data separately for each method). The grey background indicates the presence of NPIs against COVID-19 as defined in the Methods section. Detailed detection numbers separately for each site and corresponding NPI periods are shown in the appendix (pp 6–87 and 88–118, respectively). The global NPI period is defined as the average of NPIs of all countries involved. It is important to note the different scaling of y-axes between panels. NPI=non-pharmaceutical intervention.

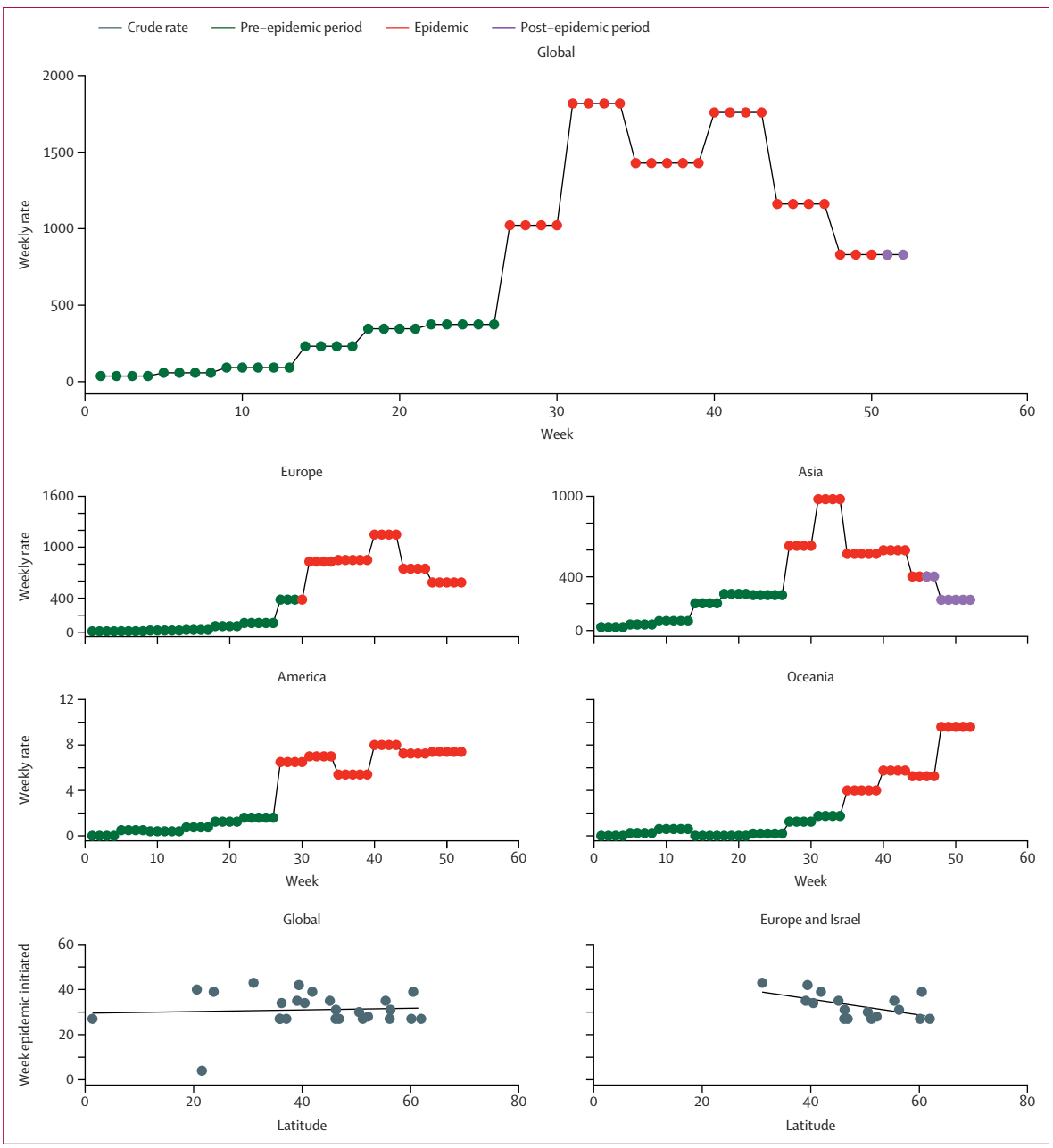

Figure 3: **Global analysis of the *Mycoplasma pneumoniae* re-emergence by use of the MEM, 2023–24**
Week numbers represent epidemic week period (week 1 represents calendar week 14; April, 2023). Green dots represent the pre-epidemic period, red dots represent the epidemic period and violet dots represent the post-epidemic period, as calculated by the MEM.[17] Correlation between country latitude and epidemic week is shown globally and for Europe and Israel (according to previous observations from epidemic periods, 2011–16).[5] A significant association between the week in which the country epidemic began and the country latitude was observed for Europe and Israel (p=0·03; R^2=0·30). MEM=moving epidemic method.

children in two countries (two of 14; ie, Croatia from one [0·53%] of 190 pre-NPI to 5 [8·33%] of 60, and Cuba from zero of 28 pre-NPI to one [33·33%] of three).

In total, 65 deaths (0·11%) of 56 711 cases were reported, six in children (0·01%) of 41 234 and 59 in adults (0·38%) of 15 499 (p<0·0001; table 4). 55 deaths (84·62%, of which 7 were reported in 2020–2021 and are therefore not included in table 4; see footnote there) of 65 within 30 days after *M pneumoniae* detection were reported from Denmark (death rate, 55 [0·23%] of 23 454), where *M pneumoniae* detections are laboratory notifiable and information about nationwide detections is recorded in the national microbiology database (appendix p 41). All deaths in Denmark occurred in adults and the vast majority were older than 75 years (data not shown). The remaining ten deaths were spread across Europe (the Netherlands, two children) and

	2017–20 (pre-NPI)		2020–21 (first year)		2021–22 (second year)		2022–23 (third year)		2023–24 (fourth year)		2017–20 *vs* 2023–24	
	Positive tests (n/N)	Detection rate (%)	Positive tests (n/N)	Detection rate (%)	Positive tests (n/N)	Detection rate (%)	Positive tests (n/N)	Detection rate (%)	Positive tests (n/N)	Detection rate (%)	MRM*p* detection rate change (%)*	p value†
Europe												
France												
Bordeaux	6/58	10·34%	0/4	0	NA/0	..	1/3	33·33%	3/176	1·70%	−83·52%	0·012
Switzerland												
Zurich (A)‡	10/14	71·43%	NA/0	..	NA/0	..	1/1	100·00%	3/6	50·00%	−30·00%‡	1·00
Zurich (B)‡	0/1	0	NA/0	..	NA	..	NA	..	1/1	100·00%	100·00%‡	1·00
Belgium¶	2/82	2·44%	0/2	0	0/5	0	0/5	0	3/149	2·01%	−17·45%	1·00
England¶	6/177	3·39%	0/13	0	0/3	0	1/2	50·00%	38/1055	3·60%	6·26%	1·00
Denmark§,¶	14/47	29·79%	<5/<20	50·00%	<5/<20	50·00%	NA/0	..	11/395	2·78%	−90·65%	<0·0001
Slovenia												
Ljubljana	7/587	1·19%	0/16	0	0/7	0	0/5	0	0/90	0	−100·00%	0·60
Croatia												
Zagreb	0/53	0	NA	..	NA	..	NA	..	NA	..	..	..
Asia												
China												
Beijing	1304/1417	92·03%	36/36	100·00%	269/281	95·73%	281/282	99·65%	1507/1555	96·91%	5·31%	0·33
Baoding (Hebei)	NA	..	NA	..	269/281	95·73%	667/684	97·51%	4095/4249	96·38%	..	..
Suzhou (Jiangsu)	NA	..	NA	..	NA	..	NA	..	1314/1531	85·83%	..	..
South Korea												
Seoul	80/103	77·67%	NA	..	NA	..	15/16	93·75%	NA	..	..	..
Seoul (Boramae)	NA	..	NA	..	NA	..	NA	..	5/8	62·50%	..	..
Japan												
Kurashiki City (Okayama)	23/229	10·04%	20/103	19·42%	NA	..	NA	..	NA	..	..	..
Tsurugashima City (Saitama)‖	19/84	22·62%	0	..	NA/0	..	NA/0	..	5/5	100·00%	NA‖	NA‖
Taiwan												
Taoyuan	210/274	76·64%	6/7	85·71%	NA/0	..	NA/0	..	18/21	85·71%	11·84%	0·74
Changhua City	55/136	40·44%	17/20	85·00%	0/18	0	0/18	0	0/21	0	−100·00%	0·0026
Americas												
Cuba¶	4/23	17·39%	NA	..	NA	..	0/2	0	0/3	0	−100·00%	1·00

The annual figures always refer to the 12-month period April 1–March 31 (eg, April 1, 2017–March 31, 2020). MRM*p*=macrolide-resistant *M pneumoniae*. NA=not available. NPI=non-pharmaceutical intervention. *Detection rate change (%) between April 1, 2017–March 31, 2020 (pre-NPI period) and April 1, 2023–March 31, 2024 (re-emergence), calculated as follows: ([detection rate re-emergence (%)–detection rate pre-NPI period (%)]/detection rate pre-NPI period [%]) × 100. †Proportions of total numbers of positive–total tests from April 1, 2017 to March 31, 2020 (pre-NPI period) were compared with positive–total tests from April 1, 2023 to March 31, 2024 (re-emergence) by Fisher's exact test. ‡Done only on request from a physician in case of clinically suspected MRM*p* infection. §In the years 2017–22, MRM*p* testing was done only in the case of clinically suspected MRM*p* infection. During this period, MRM*p* was detected in 16 out of 51 isolates. According to the local ethical regulations, the denominator and numerator for MRM*p* determination had to be at least 20 and 5 cases, respectively (but exact numbers were available for statistical analyses). ¶Data from national surveillance or national reference laboratory. ‖MRM*p* determination on culture-positive cases and therefore not included in the analysis (as all other sites determined MRM*p* on PCR-positive cases).

Table 3: **Macrolide-resistant *Mycoplasma pneumoniae* detection before, during, and after COVID-19 pandemic restrictions, 2017–24 by UN country, city, or region**

Asia (China, four children; Israel, three adults; and South Korea, one adult). Overall, there was no statistical difference between deaths during the re-emergence (21 [0·09%] of 24 672) and before the implementation of NPIs (April, 2017–March, 2020; 35 [0·12%] of 29 653; p=0·28). Clinical information on deaths was provided if a corresponding ethics approval was available (n=10; appendix pp 135–36). The cause of death was only in half of the patients related to *M pneumoniae* according to the assessment of the treating physicians at the participating site. All of them had underlying diseases.

The TSIR model was fitted on the basis of comprehensive epidemiological data from Denmark to the *M pneumoniae* detection rate before the implementation of NPIs (appendix p 123). The modelling analysis indicated that when considering a generation time (ie, time interval between infection of a primary case and its secondary case[21]) for *M pneumoniae* of 3 weeks[1] and a reduction in transmission rate after the implementation of NPIs of 90%, the TSIR model can accurately predict the observed delayed re-emergence of *M pneumoniae* in the autumn of 2023 in Denmark (figure 4).

To test how the length of generation time affects the above results, we also fitted the TSIR model assuming generation times other than 3 weeks (ie, 1 week, 2 weeks, and 4 weeks). To this end, data were re-arranged by means of a time step of the corresponding generation time (appendix pp 124–25). Under the same reduction in transmission rate (ie, 90%) during the presence of NPIs, the TSIR model was not able to reproduce the delayed re-emergence of *M pneumoniae*

	Hospitalisations				ICU admissions				Deaths*			
	2017–20	2023–24	OR (95% CI)	p value	2017–20	2023–24	OR (95% CI)	p value	2017–20	2023–24	OR (95% CI)	p value
Europe												
France (1 site)												
Children	NA/53	125/129 (†NA)	..	..	NA/53	8/129 (6·20%)	..	..	NA/53	0/129	..	..
Adults	NA/29	60/63 (†NA)	..	..	NA/29	9/63 (14·29%)	..	..	NA/29	0/63	..	..
Switzerland (12 sites)												
Children	201/ 626 (32·11%)	299/674 (44·36%)	1·7 (1·3–2·1)	<0·0001	8/ 626 (1·28%)	18/674 (2·67%)	2·2 (0·9–5·0)	0·071	0/626	0/674	..	1·00
Adults	158/425 (37·18%)	197/360 (54·72%)	2·0 (1·5–2·7)	<0·0001	14/425 (3·29%)	11/360 (3·06%)	0·9 (0·4–2·1)	0·85	0/425	0/360	..	1·00
Germany (1 site)												
Children	1/1 (†NA)	45/45 (†NA)	..	..	0/1	0/45	..	1·00	0/1	0/45	..	1·00
Belgium (national)												
Children	13/27 (48·15%)	7/22 (31·82%)	0·5 (0·2–1·6)	0·25	2/27 (7·41%)	1/22 (4·55%)	0·6 (0·1–7·0)	0·68	0/27	0/22	..	1·00
Adults	19/33 (57·58%)	10/51 (19·61%)	0·2 (0·1–0·5)	0·0006	1/33 (3·03%)	2/51 (3·92%)	1·3 (0·1–15·0)	0·83	0/33	0/51	..	1·00
Netherlands (2 sites)												
Children	14/29 (48·28%)	52/106 (49·06%)	1·0 (0·5–2·3)	0·94	1/29 (3·45%)	7/106 (6·60%)	2·0 (0·2–16·8)	0·53	1/29 (3·45%)	1/106 (0·94%)	0·3 (0·0–4·4)	0·36
Adults	40/82 (48·78%)	88/130 (67·69%)	2·2 (1·2–3·9)	0·0065	6/82 (7·32%)	14/130 (10·77%)	1·5 (0·6–4·2)	0·41	0/82	0/130	..	1·00
Denmark (national)‡												
Children	333/4654 (7·16%)	300/5412 (5·54%)	0·8 (0·6–0·9)	0·0009	NA/4654	0/5412	..	1·00	0/4654	0/5412	..	1·00
Adults	1475/6351 (23·22%)	1072/6751 (15·88%)	0·6 (0·6–0·7)	<0·0001	NA/6351	0/6751	..	1·00	28/6352 (0·44%)	20/6751 (0·30%)	0·7 (0·4–1·2)	0·17
Norway (1 site)												
Children	23/283 (8·13%)	4/60 (6·67%)	0·8 (0·3–2·4)	0·70	1/283 (0·35%)	0/60	1·6 (0·1–38·7)	0·79	0/283	0/60	..	1·00
Adults	74/457 (16·19%)	18/83 (21·69%)	1·4 (0·8–2·6)	0·22	0/457	2/83 (2·41%)	28·1 (1·3–590·0)	0·032	0/457	0/83	..	1·00
Italy (1 site)												
Children	7/9 (77·78%)	3/8 (37·50%)	0·2 (0·0–1·4)	0·10	0/9	0/8	..	1·00	0/9	0/8	..	1·00
Portugal (2 sites)												
Children	24/113 (21·24%)	102/327 (31·19%)	1·7 (1·0–2·8)	0·045	4/113 (3·54%)	24/327 (7·34%)	2·2 (0·7–6.4)	0·16	0/113	0/327	..	1·00
Spain (1 site)												
Children	12/21 (57·14%)	9/110 (8·18%)	0·1 (0·0–0·2)	<0·0001	1/21 (4·76%)	1/110 (0·91%)	0·2 (0·0–3·1)	0·24	0/21	0/110	..	1·00
Adults	0/2	6/6 (†NA)	..	..	2/2 (100·00%)	0/6	0·0 (0·0–1·0)	0·050	0/2	0/6	..	1·00
Slovenia (1 site)												
Children	187/540 (34·63%)	38/288 (13·19%)	0·3 (0·2–0·4)	<0·0001	NA/540	NA/288	..	1·00	NA/540	NA/288	..	1·00
Croatia (1 site)												
Children	24/190 (12·63%)	5/60 (8·33%)	0·6 (0·2–1·7)	0·37	1/190 (0·53%)	5/60 (8·33%)	17·2 (2·0–150·2)	0·010	0/190	0/60	..	1·00
Adults	15/53 (28·30%)	3/27 (11·11%)	0·3 (0·1–1·2)	0·093	0/53	0/27	..	1·00	0/53	0/27	..	1·00
Asia												
Israel (1 site)												
Children	72/83 (86·75%)	20/26 (76·92%)	0·5 (0·2–1·5)	0·23	8/83 (9·64%)	2/26 (7·69%)	0·8 (0·2–3·9)	0·76	0/83	0/26	..	1·00
Adults	58/70 (82·86%)	6/7 (85·71%)	1·2 (0·1–11·3)	0·85	22/70 (31·43%)	0/7	0·1 (0·0–2·6)	0·19	3/70 (4·29%)	0/7	1·3 (0·1–27·4)	0·87
China (2 sites)												
Children	13 793/14 739 (†NA)	8527/9471 (†NA)	..	..	120/14 739 (0·81%)	51/9471 (0·54%)	0·7 (0·5–0·9)	0·013	2/14 739 (0·01%)	0/9471	0·3 (0·0–6·5)	0·45
South Korea (3 sites)												
Children	57/292 (19·52%)	25/149 (16·78%)	0·8 (0·5–1·4)	0·48	2/292 (0·68%)	2/149 (1·34%)	2·0 (0·3–14·1)	0·50	0/292	0/149	..	1·00
Adults	13/23 (56·52%)	1/12 (8·33%)	0·1 (0·0–0·6)	0·018	3/23 (13·04%)	1/12 (8·33%)	0·6 (0·1–6·5)	0·68	1/23 (4·35%)	0/12	0·6 (0·0–15·9)	0·76

(Table 4 continues on next page)

	Hospitalisations				ICU admissions				Deaths*			
	2017–20	2023–24	OR (95% CI)	p value	2017–20	2023–24	OR (95% CI)	p value	2017–20	2023–24	OR (95% CI)	p value
(Continued from previous page)												
Japan (1 site)												
Children	NA/21	4/5 (80·00%)	..	..	NA/21	0/5	..	..	NA/21	0/5	..	..
Taiwan (1 site)												
Children	266/274 (97·08%)	118/209 (56·46%)	0·0 (0·0–0·1)	<0·0001	3/274 (1·09%)	0/209	0·2 (0·0–3·6)	0·27	0/274	0/209	..	1·00
Americas												
Cuba (national)												
Children	8/28 (28·57%)	2/3 (66·67%)	5·0 (0·4–63·2)	0·21	0/28	1/3 (33·33%)	34·2 (1·1–1079·4)	0·045	0/28	0/3	..	1·00
Adults	1/14 (7·14%)	0	9 (0·1–642·1)	0·31	0/14	0/14	..	1·00	0/14	0/0	..	1·00

Data are n/N (%) unless stated otherwise. Differences between groups were determined by Fisher's exact test (proportions). ICU=intensive care unit. NA=not available. NPI=non-pharmaceutical intervention. OR=odds ratio. *Nine deaths (seven adults from Denmark and two children from China) were reported during the first year after the implementation of NPIs and are not shown in this table. One site each from France, China, and Japan were only able to provide clinical data from April, 2023 to March, 2024 and were therefore not considered for statistical analyses and are not included in this table. †Only patients who were expected to be admitted were tested. ‡Denmark is the only country where *M pneumoniae* infections are laboratory notifiable. Information about nationwide detections is recorded in the national microbiology database that is available for continuous surveillance at the national public health and research institute (Statens Serum Institut, Copenhagen).

Table 4: **Comparison of clinical severity (hospitalisations and ICU) and outcome (deaths) of cases with *Mycoplasma pneumoniae* detection between pre-COVID-19 pandemic and re-emergence by UN country, city, or region**

with a shorter generation time (ie, 1 week or 2 weeks; appendix p 126). By varying reduction in transmission rates during the presence of NPIs, the delayed re-emergence of *M pneumoniae* could be reproduced with 84% reduction and 4-week generation time or with 99% reduction and 2-week generation time (appendix p 127).

The parameters of the TSIR model that were obtained from fit to observational data were used to predict the re-emergence of *M pneumoniae* also for the four UN regions (appendix pp 132–34). Under these assumptions, the model was also able to predict the delayed re-emergence for the four UN regions (figure 4).

Discussion

This is, to our knowledge, the largest and most comprehensive global description for *M pneumoniae* detection that contextualised the spatial and temporal dynamics of the delayed re-emergence of *M pneumoniae* after COVID-19 pandemic restrictions between 2023 and 2024 in four UN regions. The results showed that case numbers escalated to historic rates during the re-emergence in most countries. Despite the exceptionally large wave of infections, there was overall no indication of a statistically increased proportion in severity or worse outcome compared with pre-pandemic epidemics from sites reporting clinical data.

Our results illustrate that the re-emergence of *M pneumoniae* substantially affected the world population, which had low exposure to *M pneumoniae* for 3 years. The re-emergence started in ten countries at exactly the same week in early October, which was in line with the characteristic pre-pandemic seasonal pattern of *M pneumoniae* epidemics during autumn and early winter in the northern hemisphere.[3–5] This was also the case in China, although circulation of *M pneumoniae* was already observed again previously around the annual transition 2020–21 and 2021–22. The circulation at that time was also substantially reduced compared with pre-NPI periods, but it was surprising that China was the only country with relevant detections from 2021 to 2022.[22] NPIs in 2020 in China were the most sustained and stringent. The reason for these detections in 2021 and 2022 is unknown. One speculation is that the dynamic zero-COVID policy since 2021, under which regional lockdown and relaxation were alternating, allowed for low-level circulation in a highly endemic country for *M pneumoniae* before the NPI lifting in early 2023.

We could not identify an association between the start of the re-emergence and the geographical location of the country globally, but our data corroborated previous findings that more northern countries within Europe had the start of the re-emergence earlier than those in the southern regions and in Israel.[5] These findings support that the re-emergence might consist of pre-existing bacterial strain lineages shared between geographically diverse regions[8] that then followed a usual spread.

The nearly unchanged global macrolide-resistant *M pneumoniae* rates with more than 80% in China also

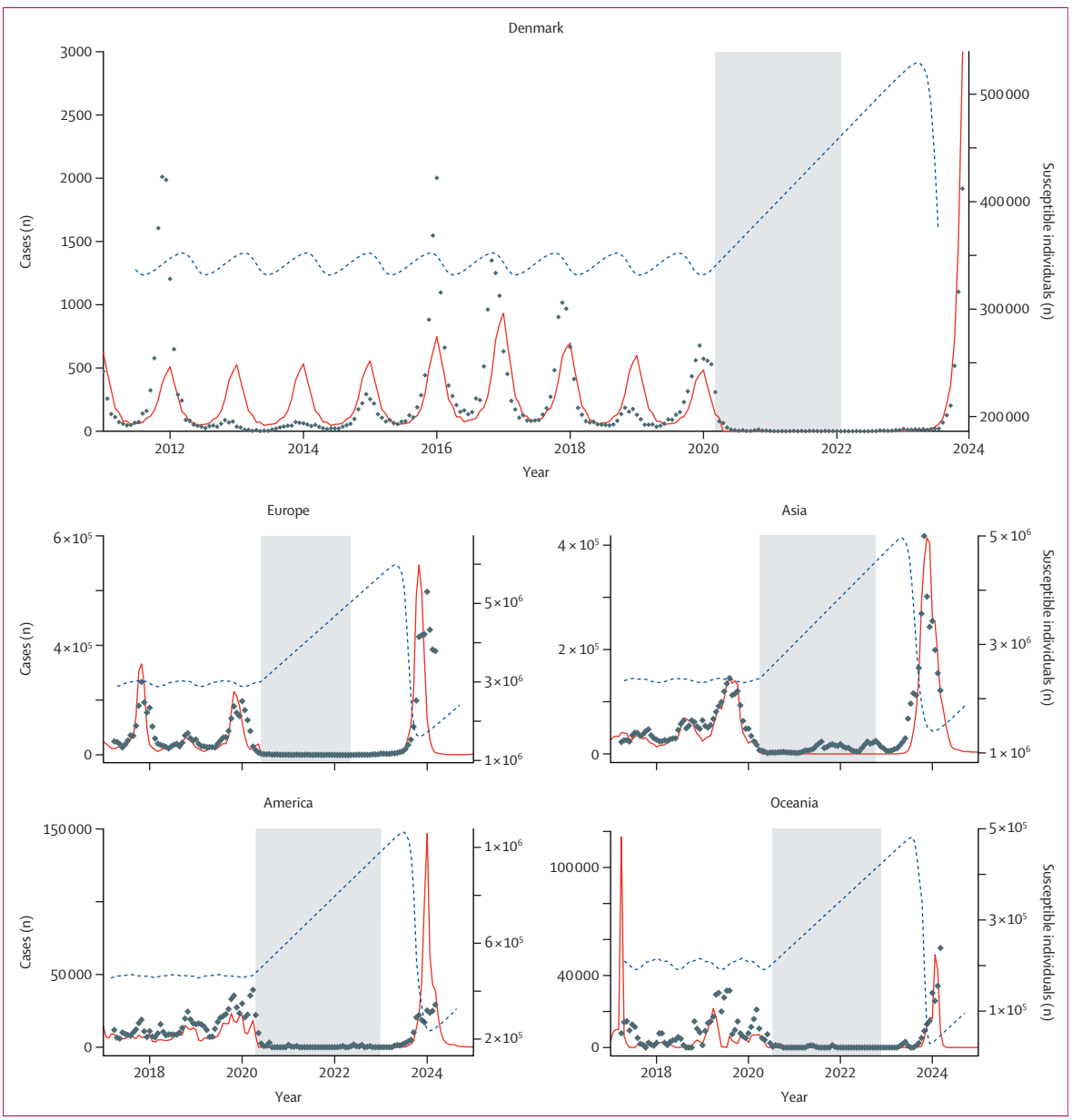

Figure 4: **Model predictions of the delayed re-emergence of *Mycoplasma pneumoniae***
Time-series susceptible-infected-recovered model predictions of the re-emergence of *M pneumoniae* for Denmark and for the four UN regions. The grey dots represent *M pneumoniae* detections (primary y-axis), the red line the model predictions (primary y-axis), and the blue dashed line the number of susceptible individuals in the population (secondary y-axis). The reduction in transmission rate during the presence of non-pharmaceutical interventions against COVID-19 (grey background, as defined in the Methods section) was 90% for Denmark and 84–94% for the four UN regions (appendix p 134).

assumes the re-emergence of local strains within a region and not the spread of strains between different regions or countries. Data published from the participating site Suzhou in China showed the presence of two primary epidemic macrolide-resistant *M pneumoniae* clones during the re-emergence, one of which has been isolated throughout east Asia since 2010 and another which has emerged from non-resistant strains first identified in 2019 in Taiwan and in 2020 in Beijing.[22] These findings suggest that the local macrolide-resistant *M pneumoniae* clones could have caused epidemics across China already in 2020 without COVID-19 pandemic restrictions, and also support the re-emergence of local strains.[23,24]

On the basis of sites that reported clinical data, our findings indicate that the *M pneumoniae* re-emergence did not result in an increase in severe disease. There was some indication of more frequent hospitalisations in adults and hospitalisation and ICU admission in children in a few countries, as previously reported by participating sites.[25–27] Although the overall proportion per region or country

might not have been statistically different to pre-pandemic epidemics, there were many sites across the world that observed a high number of hospital admissions with *M pneumoniae* infection and also frequent severe disease courses with extrapulmonary manifestations.[25–27] As with hospitalisations, more deaths were observed in adults than in children, although there was no significant difference compared with pre-pandemic periods. Our data show that *M pneumoniae* infections affect children more frequently, but that they have a significantly better outcome than adults.

The exceptionally delayed re-emergence of *M pneumoniae* infections was striking as it occurred long after NPIs were discontinued. As postulated for the occurrence of *M pneumoniae* epidemics, transient herd immunity from the last epidemic period in several countries in Europe and Asia between April, 2019, and March, 2020 could have led to the delayed re-emergence considering an interval of up to 3 years between epidemics in these UN regions.[1,3,5] A decline in detections of *M pneumoniae*-specific IgM and IgG antibodies from 2020 to 2023, observed at sites in these European regions that reported data separately for PCR and serology, was indicative of waning immunity.[7,9] However, re-emerging infections were neither observed in these regions within this 3-year period nor in countries where the last epidemic occurred even longer ago (eg, Germany, Finland, and Norway; all in 2017–18).[3,9] Thus, the atypical characteristics that distinguish *M pneumoniae* from other respiratory pathogens were considered as hypothesised reasons for the delayed re-emergence, such as the long incubation period (3 weeks)[1] and the low transmissibility (R_0 [basic reproduction number; ie, the expected number of cases directly generated by one case in a population where all individuals are susceptible to infection]=1·7; 95% CI 1·6–1·9),[28] respectively.[9]

A TSIR model developed to examine the effect of NPI implementation and lifting on *M pneumoniae* detections over time by use of comprehensive epidemiological data from Denmark showed that a long generation time (ie, time interval between infection of a primary case and its secondary case) of 3 weeks and the low transmission rate might have accounted for the delayed re-emergence in the autumn of 2023 in Denmark after NPIs were lifted. By use of a generation time of only 1 week, the TSIR model predicted the re-emergence by summer 2022, more than 1 year earlier than observed. The model was also able to predict the delayed re-emergence for the four UN regions. These data suggest that a longer generation time due to the long incubation period might be the reason for the delayed re-emergence of *M pneumoniae*.

There are several limitations to our study. First, as previously reported,[3] the reporting methods and testing criteria were variable for each site; therefore, the conclusions based on the analysis across countries need to be interpreted with caution.

Second, the serological detections were reported by most sites from single-sample serology and not confirmed by the detection of a significant antibody concentration change in convalescent sera as the serological gold standard for *M pneumoniae* infection. In this way, it is not possible to exclude the possibility of false-positive results caused by poor assay performance (eg, cross-reactivity with other pathogens), past infection, or asymptomatic carriage.[10,29] In fact, a reduction in *M pneumoniae* detections after the introduction of NPIs was observed with PCR but not with IgM and IgG enzyme immunoassays.[3] This discrepancy between PCR and serological data might be explained by the long-lasting nature of specific antibodies rather than by poor assay performance, as *M pneumoniae*-specific IgM and IgG antibodies persist for months to years after infection, and significantly longer than *M pneumoniae* DNA in the upper respiratory tract.[29]

Third, the study lacks representation from Africa and South America. Various efforts were made in different ways since the initiation of our international collaborative network in 2021 to also include these regions. Potential participants and sites from these regions were identified and contacted through email (possible contacts included departments of microbiology and infectious diseases of large university centres or authors of articles on *M pneumoniae* or pneumonia in PubMed), through our societies (the European Society of Clinical Microbiology and Infectious Diseases [ESCMID], ESGMAC, International Organisation for Mycoplasmology [IOM], European Society for Paediatric Infectious Diseases [ESPID]), and social media (ESCMID, ESGMAC, IOM, ESPID, and personal accounts of potential participants or authors). Although this enabled us to identify potential collaborators from these regions, it has not yet been possible to obtain data, mainly owing to a lack of testing in Africa or for additional administrative reasons in South America (personal communications). We hope that our surveillance study will be able to obtain data from these regions in the future because of even greater visibility (as was the case for sites from China).

Fourth, the clinical data are heterogeneous and influenced by local testing strategies. For example, *M pneumoniae* infections are laboratory notifiable in Denmark and information about nationwide detections is recorded in the national microbiology database. All age groups are tested resulting in high numbers of detections in adults in Denmark compared with the other participating sites and countries. As a result, more deaths (defined as any death within 30 days after detection) were probably associated with *M pneumoniae*, with the majority of deaths reported at the age of 75 years and above. The data on clinical severity and outcome from Denmark are therefore highly relevant, but they make comparison with clinical data reported at other participating sites difficult. Information is also missing as to whether patients were admitted or died with *M pneumoniae* detection or because of *M pneumoniae* infection. The difficulty in differentiating infection from carriage is a fundamental problem and is not limited to this study.[30] *M pneumoniae* detection by PCR in the upper respiratory tract was reported in less than 3% to 56% of healthy children

and 0% to less than 2% in healthy adults, respectively.[10,29] The reasons for the different carriage rates in the published studies are not readily apparent (particularly because studies with very low carriage rates in children were also done during strong epidemics) and no data are yet available on carriage rates during the re-emergence. Nevertheless, the detection of *M pneumoniae* by PCR in upper respiratory tract samples might be a better indicator of infection in adults than in children. The assignment of one or more causative pathogens from several potential pathogens detected in the upper respiratory tract during a pneumonia episode is also a major challenge for other pathogens, more so in children than in adults.[30] We were not able to provide information on the co-detection of *M pneumoniae* with other pathogens. It is unclear whether such co-detections with other pathogens are related to the severity of *M pneumoniae* infection.[10]

Finally, in several countries, the number of tests was low in the pre-pandemic period and detection rates varied widely, making it difficult to compare the re-emergence with pre-pandemic periods. The increase in cases owing to the increased testing might be due to the growing awareness caused by the re-emergence. However, the increased detection rate provides some arguments against the notion that increased detection is simply due to increased testing, as one would expect that the percentage of positive cases among those tested would be decreasing or remain unchanged if increased testing was the primary cause of the increase in cases. We also assume that the number of positive cases was underestimated, as our global surveillance study mainly included data from tertiary centres and thus missed the majority of mild and self-limiting infections managed by general practitioners or at primary and secondary care centres.

In conclusion, this study represents a large global dataset for *M pneumoniae* detections over time. Although there was an unprecedented high number of detections across many countries in late 2023, the severity and number of deaths remained low. Our data indicate that the delayed re-emergence of *M pneumoniae* globally after the lifting of NPIs might be related to the long incubation period of *M pneumoniae* infection. With the high rates of antimicrobial resistance against macrolides in some regions and the global mobility, there is a need to continue this surveillance to monitor international trends in *M pneumoniae* infections.

ESGMAC MAPS study group members

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Contributors

Patrick M Meyer Sauteur and Michael L Beeton conceptualised the study. All authors and the ESGMAC MAPS study group members contributed to the acquisition of data. Patrick M Meyer Sauteur, Semjon Sidorov, Ester Osuna, and Beat M Greiter managed the database. Xu-Sheng Zhang conceived and designed the modelling study, developed the model, and did all model analyses. Patrick M Meyer Sauteur, Michael L Beeton, and Xu-Sheng Zhang did additional data analyses. Patrick M Meyer Sauteur and Michael L Beeton contributed to data interpretation. Patrick M Meyer Sauteur wrote a first draft of the manuscript, which was first commented on by Michael L Beeton, and then by all other authors. All authors read and approved the final manuscript. All authors had full access to and verified all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests. ESGMAC MAPS study group members are listed as coauthors and ESGMAC MAPS study group collaborators are listed in the appendix (pp 4–5).

Data sharing

All aggregated and anonymised epidemiological datasets presented in this study are included in the appendices. The aggregated and anonymised clinical datasets can be provided on request to the corresponding author.

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