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Mycoplasma pneumoniae incidence, phenotype, and severity in children and adolescents in Denmark before, during, and after the COVID-19 pandemic: a nationwide multicentre population-based cohort study

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Summary

Background *Mycoplasma pneumoniae* infections resurged globally in 2023–2024 after a three-year decline during the COVID-19 pandemic. We explored the incidence and severity of *M pneumoniae* infections in children and adolescents before, during, and after the pandemic.

Methods This nationwide, population-based cohort study included all Danish children and adolescents aged 0–17 years with a positive *M pneumoniae* PCR test from May 1, 2016, to April 30, 2024. We obtained clinical details for patients hospitalised for 24 h or more. Risk ratios for infections, hospitalisations, and disease manifestations in 2023–2024 versus pre-COVID-19 seasons were calculated using Fisher's exact and Pearson's χ^2 tests. A season was defined from May 1 to April 30.

Findings Among the Danish population of 1,152,000 children and adolescents, 14,241 with a positive PCR test for *M pneumoniae* were included. In 2023–2024, children and adolescents with a positive PCR rose 2.9-fold (95% CI 2.8–3.1; p < 0.0001) compared to the pre-COVID-19 seasons, and hospitalisations rose 2.6-fold (95% CI 2.0–3.3; p < 0.0001). *M pneumoniae*-induced rash and mucositis increased 5.3-fold (95% CI 1.8–15.3; p = 0.0007). In 2023–2024 compared to the pre-COVID-19 seasons, there was no difference in the proportion of hospitalisation (360 [4%] of 8165 versus 230 [4%] of 6009; p = 0.09), the median duration of hospital stay (3 days [IQR 2–5] versus 3 days [IQR 2–5]; p = 0.84), or paediatric intensive care unit admission (14 [4%] of 360 versus 9 [4%] of 230 p = 1.00).

Interpretation In Denmark, *M pneumoniae* infections and hospitalisations increased three-fold in 2023–2024 compared with the pre-COVID-19 seasons, indicating an immunity debt caused by the decline in *M pneumoniae* during the COVID-19 pandemic. While the severity of *M pneumoniae* infections did not change in 2023–2024, the five-fold increase in *M pneumoniae*-induced rash and mucositis in children and adolescents highlights *M pneumoniae* as an important pathogen causing mucocutaneous eruptions.

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Keywords: Mycoplasma; Mycoplasma pneumoniae; COVID-19; Resurgence; Mycoplasma induced rash and mucositis; MIRM; Reactive infectious mucocutaneous eruptions; RIME; Mycositis; Corticosteroids

Research in context

Evidence before this study

We searched MEDLINE for studies published between January 1, 2023, and July 1, 2024, investigating the incidence of *Mycoplasma pneumoniae* infections, the spectrum and severity of pulmonary and extrapulmonary manifestations in children and adolescents aged 0–17 years during the global resurgence in 2023–2024, compared to the period before the COVID-19 pandemic (i.e., before March 11, 2020). We used the search terms "*Mycoplasma pneumoniae*" OR "mycoplasma" AND "child" OR "paediatric" OR "pediatric" AND "2023" OR "2024" without language restrictions. We identified five surveillance-based studies from the Netherlands, France, China, the USA, and Denmark investigating the incidence of *M pneumoniae* infections in children and adolescents in 2023–2024 compared to pre-COVID-19 seasons. Four studies ended inclusions in 2023, and three did not provide detailed age-related incidences for children and adolescents. Two studies from China and Spain provided clinical details of children and adolescents with *M pneumoniae* infections in 2023–2024 but without comparison to the pre-COVID-19 years. We identified case reports of children and adolescents with *M pneumoniae*-induced rash and mucositis in 2023–2024, but no studies investigated the incidence or severity of *M pneumoniae*-induced rash and mucositis, or other extrapulmonary complications in 2023–2024 compared to the pre-COVID-19 years.

Added value of this study

To our knowledge, this nationwide, multicentre, population-based cohort study is the first to provide age-related incidences of *M pneumoniae* infections and hospitalisations before, during, and after the COVID-19 pandemic, as well as data on the spectrum and severity of pulmonary and extrapulmonary manifestations during the resurgence in 2023–2024, compared to seasons preceding the COVID-19 pandemic. Beyond confirming surveillance studies from the Netherlands, France and Denmark, reporting a three to four-fold increase in *M pneumoniae* infections in 2023–2024, we found the highest increase among adolescents. Only 1% of Danish children and adolescents hospitalised with pneumonia had necrotising pneumonia or required chest tube drainage across seasons, contrasting reports from China reporting parapneumonic effusion in 25% during the resurgence in 2023–2024. We found a five-fold increase in *M pneumoniae*-induced rash and mucositis in 2023–2024. Accordingly, we present the largest observational cohort of children and adolescents with *M pneumoniae*-induced rash and mucositis to date, suggesting a shorter disease course in those treated with corticosteroids. Overall, our data did not indicate increased severity of *M pneumoniae* infections in 2023–2024 based on the proportion of hospitalised patients, the duration of hospital admission, the need for paediatric intensive care unit admission, or mortality.

Implications of all the available evidence

In several European countries, *M pneumoniae* infections and hospitalisations in children and adolescents exceeded pre-pandemic levels two-to four-fold in 2023–2024, indicating a pronounced immunity debt caused by a decline in *M pneumoniae* during the COVID-19 pandemic. In Denmark, there was no change in the severity of *M pneumoniae* infections in 2023–2024 compared with the pre-COVID-19 era, but *M pneumoniae*-induced rash and mucositis rose five-fold in 2023–2024, highlighting *M pneumoniae* as an important pathogen causing mucocutaneous eruptions.

Introduction

A historic re-emergence in *Mycoplasma pneumoniae* infections was reported globally in 2023–2024, after an abrupt decline during the spring of 2020 following the implementation of non-pharmaceutical interventions to reduce the transmission of SARS-CoV-2, which included social distancing, mask-wearing, and heightened hand hygiene.[1–3] The almost complete disappearance of *M pneumoniae* during the COVID-19 pandemic, and long after the release of the non-pharmaceutical interventions, was striking compared to most other pathogens, such as respiratory syncytial virus (RSV), influenza virus, Group A *Streptococcus*, and *S pneumoniae*, which re-emerged in 2021 and 2022.[4–9] The incidence of *M pneumoniae* was reported to exceed pre-pandemic levels in the Netherlands,[10] France,[11] and Denmark[12] during the autumn of 2023, while incidences below pre-pandemic levels were observed in China and the USA.[13,14] Studies from the Netherlands and France indicated a rise in infected children and adolescents, compared to pre-COVID-19 levels,[10,11] and a minor shift in age distribution towards older children with *M pneumoniae* was observed in the Danish population.[12]

M pneumoniae typically causes respiratory tract infections, including pneumonia, often referred to as 'walking pneumonia' due to the relatively mild symptoms despite pronounced chest X-ray manifestations.[15,16] However, *M pneumoniae* may also cause severe

pneumonia requiring hospitalisation, including parapneumonic effusion, necrotising pneumonia and bronchiolitis obliterans, as well as extrapulmonary complications, such as meningoencephalitis and Guillain-Barré syndrome, dermatological disorders, gastrointestinal complications, haemolytic anaemia, glomerulonephritis, and rarely myocarditis and cardiac failure.[16,17] It is unknown if the clinical spectrum and severity of pulmonary and extrapulmonary complications changed during the large-scale outbreak in 2023–2024. A change of clinical manifestations was observed in invasive Group A *Streptococcus* infections during the resurgence in 2022–2023, where a significant rise occurred in parapneumonic effusions and severe soft tissue infections compared to usual Group A *Streptococcus* complications.[7–9] During the *M pneumoniae* re-emergence in 2023–2024, clusters of children with complicated *M pneumoniae* pneumonia with parapneumonic effusion were reported from China.[14] Additionally, case reports from several countries have described children and adolescents with mycoplasma-induced rash and mucositis (MIRM),[18] a common cause of reactive infectious mucocutaneous eruptions (RIME).[19–23]

We aimed to investigate the incidence of *M pneumoniae* infections among children and adolescents in Denmark before, during, and after the COVID-19 pandemic. We also aimed to assess whether the clinical spectrum and severity of pulmonary and extrapulmonary complications changed among hospitalised children and adolescents in 2023–2024 compared to four pre-COVID-19 seasons.

Methods

Study design and patients

In this nationwide, multicentre, population-based cohort study, we included all children and adolescents in Denmark aged 0–17 years tested for *M pneumoniae* with polymerase chain reaction (PCR) from May 1, 2016, to April 30, 2024. A *M pneumoniae* season was defined from May 1 to April 30 of the next year to capture the seasonal peaks during autumn and winter across seasons (Appendix p 1). Thus, the study included eight seasons encompassing four pre-COVID-19 seasons (2016–2017, 2017–2018, 2018–2019, and 2019–2020), three COVID-19 seasons (2019–2020, 2020–2021, and 2021–2022), and one post-COVID-19 season (2023–2024). Patients tested for *M pneumoniae*, a laboratory-notifiable disease in Denmark, were identified through the national surveillance system, the Danish Microbiology Database,[24] in which all Danish patients with a laboratory PCR test were registered in real-time. Throat swabs or lower respiratory tract specimens for *M pneumoniae* were taken by physicians at general practices and hospitals and analysed by real-time PCR at the local microbiology laboratories. PCR assays included qualitative monoplex in-house real-time PCR assays targeting P1 adhesin, as reported previously,[25–27] commercial qualitative multiplex assays using the BD MAX™ platform, allowing the detection of *M pneumoniae*, *C pneumoniae*, *C psittaci*, and *L pneumophila*,[28] and commercial qualitative multiplex assays, allowing the detection of several viral and bacterial respiratory tract infections simultaneously, including the BIOFIRE Respiratory Panel® (Biomérieux®) and the QIAstat-Dx Respiratory Panel Plus (Qiagen®).[29,30] *M pneumoniae*-serology was rarely used in Denmark as a diagnostic approach, and patients diagnosed with serology only were not included in this study. Individuals with more than one positive PCR test in a season were regarded as having one episode. *M pneumoniae*-associated hospital admission was defined as a hospital contact, retrieved from the Danish National Patient Registry,[31,32] and a positive *M pneumoniae* test within 14 days before or during hospital admission.[12] Death within 30 days after a positive *M pneumoniae* test was defined as an *M pneumoniae*-associated death.

Ethics Committee approval: The study was approved by the Danish Patient Safety Authority (R-23033438) and the Data Protection Agency (P-2019-05). A waiver of the requirement of informed consent was obtained from the Danish Patient Safety Authority.

Procedures

We retrieved electronic medical health records for patients with hospital admission for more than 24 h from all 18 paediatric hospital departments in Denmark using the unique social security number allocated to each person. Clinical details of the infectious episode, including clinical manifestations and sequelae; parent-reported date of disease onset; and sex (i.e., male or female, obtained from the social security number) were extracted from electronic medical records and captured in a REDCap database. Data on ethnicity were not available.

Patients were defined as being admitted due to an *M pneumoniae* infection if 1) having a positive PCR-test result, 2) clinical manifestations compatible with an *M pneumoniae* infection, and 3) the clinical manifestations were the cause of the hospital admission.[33] Patients with a positive PCR test who were hospitalised for other reasons, such as planned surgery, were excluded. Patients were categorised according to the primary complication of *M pneumoniae* infection leading to hospital admission. These were defined as pneumonia in case of dyspnoea and pathological findings on chest X-ray, respiratory infection in case of respiratory symptoms without pathological findings on chest X-ray (e.g., asthma), or extrapulmonary complications. Extrapulmonary complications were defined as 1) gastrointestinal manifestations in case of abdominal pain, diarrhoea, vomiting, hepatitis, pancreatitis, or hepatosplenomegaly; 2) neurological complications if diagnosed with Guillain-Barré syndrome, acute disseminated encephalomyelitis (ADEM),

meningoencephalitis, transverse myelitis, and neurological manifestations persisting for more than 24 h (i.e., depressed/altered level of consciousness, including lethargy or a significant personality change) leading to lumbar puncture and neuroimaging; 3) skin manifestations, such as MIRM, angioedema, urticaria, and purpuric rash); 4) glomerulonephritis; 5) rheumatological manifestations, such as arthritis; 6) haemolytic anaemia; and 7) cardiac complications, including cardiac failure, myopericarditis, and pericardial effusion.[33,34] In the case of hospitalisation due to both pulmonary and extrapulmonary manifestations, the extrapulmonary manifestation was defined as the primary reason for hospitalisation.

Statistical analyses

We calculated the incidence of *M pneumoniae* infections per 1,000,000 inhabitants aged 0–17 years in the pre-COVID-19 seasons, the COVID-19 seasons, and in 2023–2024 using the Danish population of 1,152,000 children and adolescents aged 0–17 years. Additionally, we calculated the risk ratios (RRs) for the incidences of *M pneumoniae* infections, hospitalisations, and pulmonary and extrapulmonary complications in 2023–2024 versus the four pre-COVID-19 seasons using Fisher's exact test and Pearson's χ^2 test. Furthermore, we calculated the RRs by sex and age.

For patients hospitalised for more than 24 h, we assessed the severity of *M pneumoniae* infections by comparing the following between the 2023-24 season and the four COVID-19 seasons: The proportion among test-positive individuals, the proportion receiving oxygen and intravenous therapy, the proportion admitted to a paediatric intensive care unit and hospital duration. We used non-parametric, two-tailed Mann–Whitney U test to compare continuous variables and Pearson's χ^2 or Fisher's exact test to compare categorical variables.

All statistical analyses were performed in R statistical software, version 4.3.3.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From May 1, 2016, to April 30, 2024, 14,241 children and adolescents aged 0–17 years with a positive *M pneumoniae* test were included. Of these, 51 (0.4%) had positive tests in two different seasons. A total of 8165 (yearly mean 2041 [SD 1254]) children and adolescents were identified in the four pre-COVID-19 seasons, 67 (yearly mean [22 (SD 16)] in the COVID-19 seasons, and 6009 in 2023–2024 (Table 1). This corresponded to a 2.9-fold (95% CI 2.8–3.1; p < 0.0001) increase in 2023–2024 compared to the four pre-COVID-19 seasons. The largest increase occurred among adolescents aged 13–17 years (RR 4.3 [95% CI 3.9–4.8]; p < 0.0001; Table 1). In 2023–2024, the epidemic emerged in autumn, like the pre-COVID-19 seasons (Appendix p 1).

The proportion of children and adolescents with a positive *M pneumoniae* PCR test among tested individuals was 8165 (15%) of 54,670 in the pre-COVID-19 seasons, 67 (0.3%) of 20,677 in the COVID-19 seasons, and 6009 (25%) of 24,484 in 2023–2024 (Fig. 1; Appendix p 2).

Hospitalisation of any duration, including emergency department visits, included 538 patients (yearly mean 135 [SD 66]) in the pre-COVID-19 seasons, 7 patients (yearly mean 2 [SD 2]) in the COVID-19 seasons, and 323 patients in 2023–2024 (Table 1). This corresponded to a 2.4-fold (95% CI 2.0–2.9; p < 0.0001) increase in 2023–2024 compared to the pre-COVID-19 seasons. Hospitalisation for more than 24 h included 360 patients (yearly mean 90 [SD 41]) in the pre-COVID-19 seasons, 4 patients (yearly mean 1 [SD 2]) in the COVID-19 seasons, and 230 patients in 2023–2024, corresponding to a 2.6-fold (95% CI 2.0–3.3; p < 0.0001) increased incidence in 2023–2024 compared to the four pre-COVID-19 seasons (Table 1). The proportion of children and adolescents with *M pneumoniae* requiring hospitalisation was unchanged in 2023–2024 (230 [4%] of 6009 versus 360 [4%] of 8165; p = 0.09; Table 1). The duration of hospitalisation, need for intravenous therapy, admission to paediatric intensive care unit, and the proportion of children with co-morbidities did not change in 2023–2024 (Table 2). The co-morbidities included asthma or other chronic lung diseases, immunosuppressive therapy, chronic heart and neurological disease, metabolic diseases, and haemolytic anaemia.

Pulmonary complications as the primary reason for hospitalisation for more than 24 h increased 2.3-fold in 2023–2024 (95% CI 1.8–3.1; p < 0.0001; Table 1), being the most frequent reason for hospitalisation across seasons (Table 2). In 2023–2024 and the pre-COVID-19 seasons, pulmonary complications required hospitalisation for more than 24 h in 176 (3%) of 6009 and 302 (4%) of 8165 individuals with a positive PCR test, respectively. Symptom duration prior to hospitalisation was a median of 7 days (IQR 5–11) in 2023–2024 and 8 days (IQR 6–12) in the pre-COVID-19 seasons, with most patients reporting fever and cough (Table 2). Parapneumonic effusions requiring chest tube drainage, necrotising pneumonia, and bronchiolitis obliterans occurred in 6 (1%) of 590 patients across seasons. The proportion of patients requiring oxygen therapy increased in 2023–2024 (Table 2). Viral co-infections among patients with pneumoniae were identified in 25 (16%) of 152 in 2023–2024 and 23 (8%) of 280 in the pre-COVID-19 seasons, most commonly RSV (n = 17), rhinovirus (n = 11), and influenza virus (n = 8) across seasons. Investigations of co-infections are detailed in the Appendix (p 3). The clinical manifestations of the cohort, excluding patients with coinfections, are provided in the Appendix (p 4).

	Children and adolescents with positive *M pneumoniae* PCR test			Yearly incidence per 1,000,000 population (95% CI)			Risk ratio (95% CI); p value
	Pre-COVID-19 seasons	COVID-19 seasons	Post-COVID-19 season	Pre-COVID-19 seasons	COVID-19 seasons	Post-COVID-19 season	Pre-COVID-19 versus post-COVID-19 seasons
	2016–2017, 2017–2018, 2018–2019, 2019-2020	2020–2021, 2021–2022, 2022–2023	2023–2024	2016–2017, 2017–2018, 2018–2019, 2019-2020	2020–2021, 2021–2022, 2022-2023	2023–2024	2016–2017, 2017–2018, 2018–2019, 2019–2020 versus 2023–2024
Total[a] (numbers)	8165	67	6009	1768 (1692–1846)[b]	19 (12–29)	5204 (5073–5357)	2.9 (2.8–3.1); p < 0.0001[c]
Sex							
Boys	4312 (53%)	36 (54%)	3126 (52%)	934 (879–991)	10 (5–18)	2707 (2613–2804)	2.9 (2.7–3.1); p < 0.0001
Girls	3853 (47%)	31 (46%)	2883 (48%)	834 (782–889)	9 (4–16)	2497 (2406–2589)	3.0 (2.8–3.2); p < 0.0001
Age (years)							
<1	64 (1%)	1 (1%)	22 (0%)	259 (148–421)	5 (0–70)	356 (223–539)	1.4 (0.7–2.6); p = 0.33
1–5	1661 (20%)	9 (13%)	754 (13%)	1326 (1202–1460)	10 (2–28)	2408 (2239–2586)	1.8 (1.6–2.1); p < 0.0001
6–12	4659 (57%)	26 (39%)	3327 (55%)	2674 (2523–2832)	20 (9–38)	7639 (7383–7902)	2.9 (2.7–3.1); p < 0.0001
13–17	1781 (22%)	31 (46%)	1906 (32%)	1293 (1176–1419)	30 (15–55)	5535 (5290–5789)	4.3 (3.9–4.8); p < 0.0001
Hospital admission[d]	538 (7%)	7 (10%)	323 (5%)	116 (98–138)	2 (0–7)	280 (250–312)	2.4 (2.0–2.9); p < 0.0001
Hospitalisation more than 24 h							
Total	360 (4%)[e]	4 (6%)	230 (4%)[e]	78 (63–96)	1 (0–5)	199 (174–227)	2.6 (2.0–3.3); p < 0.0001
Sex							
Boys	205 (57%)	2 (50%)	129 (56%)	87 (64–114)	1 (0–8)	218 (182–259)	2.5 (1.8–3.5); p < 0.0001
Girls	155 (43%)	2 (50%)	101 (44%)	69 (49–94)	1 (0–9)	180 (146–218)	2.6 (1.8–3.8); p < 0.0001
Age (years)							
<1	6 (2%)	0 (0%)	4 (2%)	24 (2–104)	–	65 (18–166)	2.7 (0.4–17.4); p = 0.69
1–5	101 (28%)	1 (25%)	50 (22%)	81 (52–119)	1 (0–14)	160 (119–210)	2.0 (1.2–3.2); p = 0.0043
6–12	176 (49%)	1 (25%)	119 (52%)	101 (73–136)	1 (0–10)	273 (226–327)	2.7 (1.9–3.8); p < 0.0001
13–17	77 (21%)	2 (50%)	56 (24%)	56 (34–87)	2 (0–14)	163 (123–211)	2.9 (1.7–4.9); p < 0.0001
Complications							
Pulmonary	302 (84%)	2 (50%)	176 (77%)	65 (51–82)	1 (0–4)	152 (131–177)	2.3 (1.8–3.1); p < 0.0001
Extrapulmonary	58 (16%)	2 (50%)	54 (23%)	13 (7–21)	1 (0–4)	47 (35–61)	3.7 (2.1–6.7); p < 0.0001

Data are n (%), risk ratio (95% CI), or p-value. p-values were derived from Pearson's chi-square or Fisher's exact test. [a]Fifty-one (0.4%) children and adolescents had positive PCR tests in two different seasons; the second episode was not included in the table. [b]The incidence was 3071 (95% CI 2971–3173) in 2016–2017, 1978 (95% CI 1898–2061) in 2017–2018, 440 (95% CI 403–480) in 2018–2019, and 1582 (95% CI 1511–1656) in 2019–2020. [c]The risk ratio was 1.7 (95% CI 1.6–1.8; p < 0.0001) in 2023–2024 versus 2016–2017, 2.6 (95% CI 2.5–2.8) in 2023–2024 versus 2017–2018, 11.8 [10.8–13.0]; p < 0.0001) in 2023–2024 versus 2018–2019, and 3.3 (95% CI 3.1–3.5) in 2023–2024 versus 2019–2020. [d]Hospitalisation of any duration, including emergency department visits. [e]The proportions of hospitalisation were not statistically different between seasons (p = 0.80 for pre-COVID-19 seasons versus COVID-19 seasons; p = 0.09 for pre-COVID-19 seasons versus 2023–2024).

Table 1: **Comparison of *Mycoplasma pneumoniae* infections, sex, age, hospitalisations, and complications among children and adolescents in Denmark before, during, and after the COVID-19 pandemic.**

Extrapulmonary complications as the primary reason for hospitalisation for more than 24 h increased 3.7-fold in 2023–2024 (95% CI 2.1–6.7; p < 0.0001) (Table 1). Among these, dermatological complications were most common, rising to 29 (13%) of 230 hospitalised patients in 2023–2024 from 24 (7%) of 360 in the pre-COVID-19 seasons (p = 0.0207) (Table 2). Dermatological complications were most frequently mucocutaneous eruptions, MIRM (Table 2), which increased to 21 patients in 2023–2024 from a yearly mean of 4 in the pre-COVID-19 seasons (RR 5.3 [95% CI 1.8–15.3], p = 0.0007). The clinical characteristics of patients with MIRM were similar in 2023–2024 and the pre-COVID-19 seasons (Table 3). Cutaneous lesions included targetoid lesions, vesiculobullous lesions, and maculopapular eruptions. The median duration of hospitalisation among patients with MIRM was 4 days (IQR 3–6) in 2023–2024 and 9 days (IQR 7–14) in the pre-COVID-19 seasons. Mucosal eruptions lasted for a median of 15 days (IQR 13–19) in 2023–2024 and 22 days (IQR 19–26) days in the pre-COVID-19 seasons (Table 3). Across seasons, 13 (33%) of 39 patients received systemic corticosteroids within 5 days of mucosal eruption onset. They had a disease duration of 14 days (IQR 13–19) versus 21 days (IQR 16–25) for the 26 (66%) of 39 patients who did not receive corticosteroids or started treatment after 5 days (p = 0.0251). Four (22%) of 18 children with more than one year of follow-up experienced one or more relapses of mucocutaneous eruptions (Table 3). Across seasons, 3 (8%) of 39 children had sequelae in the form of phimosis, with 2 requiring surgery.

Acute angiooedema of lips, tongue, and eyes, with or without urticaria, occurred in 7 (1%) of 590 patients

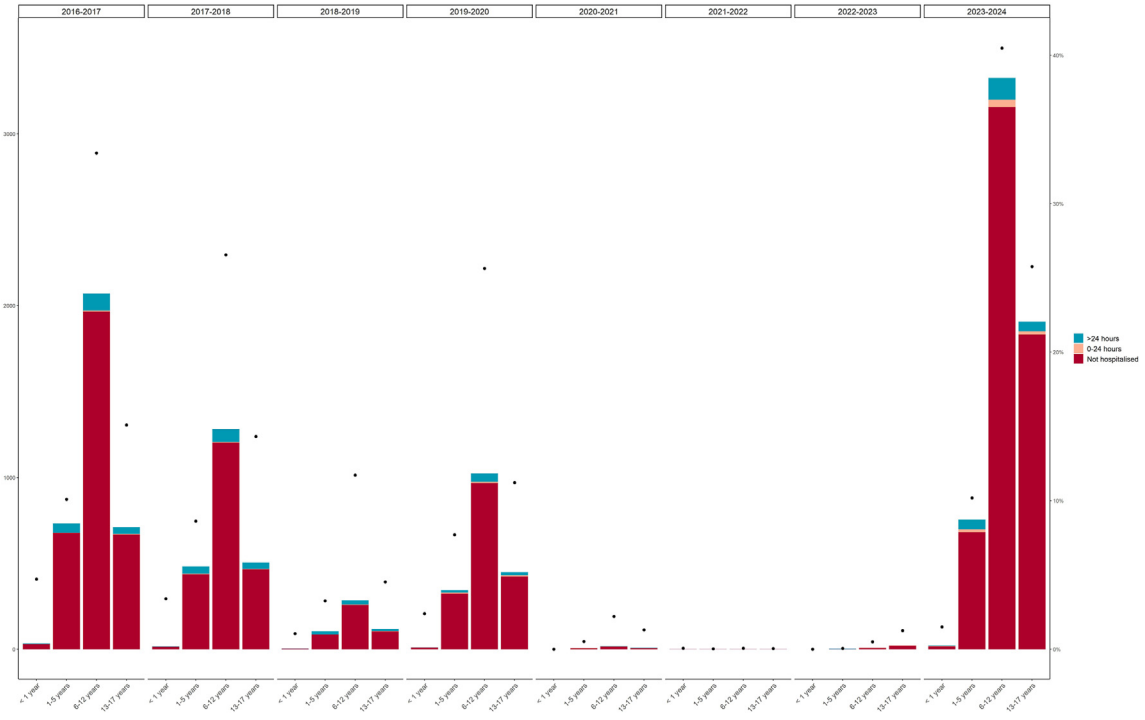

Fig. 1: Children and adolescents with a positive *Mycoplasma pneumoniae* test, and test positivity rate, in Denmark before, during, and after the COVID-19 pandemic. The bars show the distribution of hospitalisations (0–24 h and more than 24 h) and non-hospitalised children with *M pneumoniae* infections, corresponding to the left y-axis (number of cases). The black dots represent the percentage of *M pneumoniae*-positive individuals among tested children and adolescents per season, corresponding to the right y-axis with a percentage scale. During the COVID-19 pandemic (2020–2021, 2021–2022, and 2022–2023), 67 (0.3%) of 20,677 tested children and adolescents were positive. In the pre-COVID-19 seasons and 2023–2024, respectively, 8165 (15%) of 54,670 and 6009 (25%) of 24,484 were positive ($p < 0.0001$).

across seasons (Table 2). Four (57%) had dyspnoea and received epinephrine. None had stridor. Other triggers, including drugs, were excluded in all patients.

Severe gastrointestinal complications necessitating hospitalisation for more than 24 h were the second most common extrapulmonary complication, occurring in 14 (6%) of 230 and 19 (5%) of 360 in 2023–2024 and the pre-COVID-19 seasons, respectively (Table 2). Severe abdominal pain was the primary complaint, occurring in 21 (4%) of 590 hospitalised patients, including 4 (<1%) with appendicitis (2 perforated) and 8 (1%) with suspicion of appendicitis or ileus. Severe diarrhoea and vomiting necessitated hospitalisation in 12 (2%) of 590 patients. All patients hospitalised due to gastrointestinal complications also had clinical signs of pneumonia, and 23 (70%) of 33 were investigated with chest X-ray; all had pneumonic infiltrates.

Rare extrapulmonary complications involved severe CNS complications in 19 patients across seasons, including 5 with encephalitis, 4 with ADEM, 3 with Guillain-Barre syndrome, and one with transverse myelitis (Table 2). Furthermore, haemolytic anaemia occurred in 2 patients, glomerulonephritis in 3 patients, and acute cardiac failure and myocarditis, respectively, in 2 patients (Table 2).

Discussion

In this nationwide, multicentre, population-based cohort study, we found an overall three-fold increase in children and adolescents with *M pneumonia* infections and hospitalisations during the resurgence in 2023–2024 compared to the four seasons before the COVID-19 pandemic. The highest increase occurred among adolescents. During the three years of the COVID-19 pandemic, less than 0.3% of 20,000 children and adolescents tested positive for *M pneumoniae*, indicating no carriage in this period. Additionally, we found a five-fold increase in children and adolescents with mucocutaneous eruptions, namely MIRM. Overall, children and adolescents with *M pneumoniae* did not have a more severe disease course in 2023–2024, based on the proportion of hospitalisations, admission to paediatric intensive care unit, and admission duration.

The *M pneumoniae* resurgence in Denmark reflected the global resurgence reported in 2023,[1] with the first reports of clusters of children hospitalised with *M pneumoniae* from Northern China in November 2023.[2] A four-fold increase in incidence was reported in the Netherlands and France in December 2023 compared to the pre-pandemic seasons.[10,11] In contrast,

Clinical manifestations of *Mycoplasma pneumoniae*-associated hospital admission for 24 h or more

	Pre-COVID-19 seasons	COVID-19 seasons	Post-COVID-19 season	p-value
	2016–2017, 2017–2018, 2018–2019, 2019–2020	2020–2021, 2021–2022, 2022–2023	2023–2024	2016–2017, 2017–2018, 2018–2019, 2019–2020 versus 2023–2024
Total number of children and adolescents	360	4	230	-
Co-morbidity[a]	68 (19%)	-	43 (19%)	1.00
Symptoms				
Fever	317 (88%)	-	203 (88%)	1.00
Cough	332 (92%)	-	209 (91%)	0.67
Dyspnoea	186 (52%)	-	112 (49%)	0.54
Abdominal pain, vomiting, diarrhoea	92 (26%)	-	67 (29%)	0.39
Skin rash	38 (11%)	-	29 (13%)	0.53
Symptoms before hospitalisation (days)	8 (6–12)	-	7 (5–11)	0.15
C-reactive protein, max (mg/L)	37 (15–90)	-	46 (14–100)	0.24
Primary reason for hospitalisation				
Pulmonary complications	302 (84%)	2	176 (77%)	0.0342
Community-acquired pneumonia	280 (78%)	-	152 (66%)	0.0024
Parapneumonic effusion	3 (1%)	-	1 (<1%)	-
Necrotising pneumonia	0 (0%)	-	1 (<1%)	-
Bronchiolitis obliterans	0 (0%)	-	1 (<1%)	-
Treatment[b]				
Macrolides	310 (86%)	-	200 (87%)	0.87
IV antibiotics[c]	105 (29%)	-	66 (29%)	0.98
Oxygen therapy	183 (61%)	-	132 (75%)	0.0019
Beta-2 agonists	115 (38%)	-	74 (42%)	0.45
Chest tube drainage	2 (<1%)	-	1 (<1%)	-
Intensive care unit	12 (4%)	-	9 (5%)	0.72
Mechanical ventilation	6 (2%)	-	3 (2%)	-
Extrapulmonary complications	58 (16%)	2	54 (23%)	0.0342
Dermatological[d]	24 (7%)	2	29 (13%)	0.0207
M pneumoniae-induced rash and mucositis	16 (4%)	-	21 (9%)	0.0344
Angiooedema	2 (<1%)	-	5 (2%)	-
Gastrointestinal	19 (5%)	-	14 (6%)	0.82
Abdominal pain	13 (4%)	-	8 (4%)	-
Diarrhoea & vomiting	6 (2%)	-	6 (3%)	-
Central nervous system	11 (3%)	-	8 (3%)	0.96
Haematological	1 (<1%)	-	1 (<1%)	-
Renal	1 (<1%)	-	2 (<1%)	-
Cardiac	2 (<1%)	-	0 (0%)	-
IV therapy (fluid)	80 (22%)	-	50 (22%)	0.97
PICU	14 (4%)	-	9 (4%)	1.00
Hospitalisation (days)	3 (2–5)	-	3 (2–5)	0.84
Mortality	0 (0%)	-	0 (0%)	-

Data are n (%), median (IQR), or p-value. IV = intravenous, PICU = paediatric intensive care unit. '-' indicates non-applicability. Ten patients with cancer were excluded from the analyses. [a]Co-morbidity included asthma or other chronic lung diseases, immunosuppressive therapy, chronic heart and neurological disease, metabolic diseases, and haemolytic anaemia. [b]Proportion of the specified treatment (e.g., oxygen therapy) for pulmonary complications. [c]2023–2024: IV beta-lactam 55%, IV macrolide 21%, combined treatment 24%. Pre-COVID-19: IV beta-lactam 65%, IV macrolide 11%, combined treatment 24%. [d]Dermatological complications other than *M pneumoniae*-induced rash and mucositis and angiooedema was purpuric rash, urticaria, and diffuse erythematous rash (n = 6 in 2016–2017 to 2019–2020 and n = 3 in 2023–2024).

Table 2: **Clinical manifestations of *Mycoplasma pneumoniae*-associated hospital admissions for 24 h or more in children and adolescents in Denmark before, during and after the COVID-19 pandemic.**

the incidence was reported below pre-pandemic levels in China and the USA in the autumn of 2023,[13,14] which may reflect case numbers from the initial phase of the epidemic only. New *M pneumoniae* strains explaining the increased incidence have not been reported in 2023–2024.[35] Furthermore, increasing macrolide

Mycoplasma pneumoniae-induced rash and mucositis	Pre-COVID-19 seasons	COVID-19 seasons	Post-COVID-19 season	p-value
	2016–2017, 2017–2018, 2018–2019, 2019–2020	2020–2021, 2021–2022, 2022–2023	2023–2024	2016–2017, 2017–2018, 2018–2019, 2019–2020 versus 2023–2024
Number of patients	16	2	21	-
Yearly incidence per 1,000,000[a]	3 (1–9)	-	18 (11–27)	0.0007
Proportion of test-positive	0.2%	-	0.3%	0.11
Proportion of hospitalisations	4%	-	9%	0.0344
Sex				
Male	11 (69%)	-	19 (90%)	0.20
Female	5 (31%)	-	2 (10%)	0.20
Age (years)	11 (9–12)	-	11 (9–15)	0.78
Mycoplasma infection				
Prodrome (days)	5 (4–7)	-	5 (4–8)	0.76
X-ray with infiltrates	13 (81%)	-	13 (62%)	0.28
Oxygen therapy	4 (25%)	-	1 (5%)	0.14
Mucocutaneus lesions				
Oral	16 (100%)	-	21 (100%)	1.000
Ocular	11 (69%)	-	17 (81%)	0.46
Genital	10 (63%)	-	9 (43%)	0.39
Anal	1 (6%)	-	1 (5%)	-
Cutaneous lesions	11 (69%)	-	12 (57%)	0.70
Few < 10%	6 (38%)	-	6 (29%)	0.83
Many > 10%	5 (31%)	-	6 (29%)	0.73
Hospitalisation (days)	9 (7–14)	-	4 (3–6)	0.0014
PICU	0 (0%)	-	1 (5%)	-
Total duration (days)[a]	22 (19–26)	-	15 (13–19)	0.0090
Complications	2 (13%)		1 (5%)	-
Phimosis	2 (13%)	-	1 (5%)	-
Relapse	4 (25%)	-	NA	-
Mortality	0 (0%)	-	0 (0%)	-

Data are n (%), median (IQR), 95% CI, or p-value. PICU = paediatric intensive care unit. '-' indicates non-applicability. [a]Total duration of mucocutaneous lesions: When information on complete remission was unavailable, seven days were added to the time of discharge if the patient still had mucocutaneous eruptions at discharge.

Table 3: **Incidence, sex, age, and clinical characteristics of children and adolescents with *Mycoplasma pneumoniae*-induced rash and mucositis in Denmark before, during, and after the COVID-19 pandemic.**

resistance was not suggested to contribute to the increased incidence in 2023–2024 in Denmark, as macrolide resistance-associated mutations were found in only three (1.5%) of 197 samples in 2023–2024.[12] Thus, the global increase in 2023–2024 was most likely caused by a population immunity debt in children and adolescents, i.e., *M pneumoniae* naivety or waning immunity due to the absence of re-infections during the three years of low exposure during the COVID-19 pandemic. In other words, repetitive infections with shorter intervals than three years presumably occur during usual conditions, maintaining a certain level of immunity. Indications of such an immunity debt have also been reported for RSV, influenza virus, enterovirus, *Streptococcus pneumoniae*, and Group A *Streptococcus*, reaching at least two-fold higher levels during the re-surgences of the COVID-19 pandemic.[5–7] However, similar to what has been described for invasive Group A *Streptococcus* and RSV infections,[6,7] we did not observe a more severe course of *M pneumoniae* infections in 2023–2024, indicating that children's general immune function was unaltered following the COVID-19 pandemic, aside from a temporal increased susceptibility to various pathogens.[36] *M pneumoniae* infections rose among all age groups, but the highest increase occurred in school-aged children and adolescents, which may reflect their ability to mount a strong immune response, contributing to the inflammatory lesions in *M pneumoniae* pneumonia and extrapulmonary complications, including MIRM.[37–41]

The COVID-19 pandemic has shed light on several incompletely understood aspects of *M pneumoniae*. Our finding of an unprecedented, almost complete absence of children and adolescents with a positive *M pneumoniae* test during the COVID-19 pandemic, despite testing 20,000 individuals, is striking and consistent with global reports.[1] The absence of *M pneumoniae* carriage contrasts with that of *S pneumoniae*, which surprisingly remained unchanged during the COVID-19 pandemic.[42] Thus, a positive *M pneumoniae* test in an asymptomatic child may not indicate continuous carriage.[16] Instead, it may indicate an asymptomatic infection, or prolonged PCR-test positivity following a recent infection with mild symptoms not attributed to *M pneumoniae* as PCR positivity can persist for several months.[16] This is in accordance with previous studies finding that the proportion of asymptomatic children testing positive for *M pneumoniae* varies with the size of the epidemic.[43] The COVID-19 pandemic also suggested that viral co-infection does not play an important role in the pathogenesis of *M pneumoniae*, as it did not reappear during the viral resurgences in 2021–2022.[5] Furthermore, despite extensive investigation, we found viral co-infections in only approximately 10–15% of children and adolescents with serious *M pneumoniae* infections requiring hospitalisation in more than 24 h. This is in contrast to invasive *S pneumoniae* and Group A *Streptococcus* infections, where most patients were found to have a viral co-infection,[7] suggesting a pathogenesis facilitated by viral co-infections.[42]

The late reappearance of *M pneumoniae* in 2023 was notable by occurring long after the public health interventions to target COVID-19 were discontinued, in contrast to most other bacterial infections that reappeared in 2021–2022.[7] Explanations for the late resurgence could involve factors such as prolonged herd immunity from the last epidemic in 2019–2020, as well as the unique properties of *M pneumoniae*, including its slow growth, its long incubation period of approximately

three weeks, and the need for close contact for transmission.[1,16] Speculatively, the major resurgences of other respiratory viral and bacterial infections could have reduced mycoplasma infections either directly by viral-bacterial or bacterial–bacterial interference, or by changing the composition of the respiratory microbiota, which may influence the risk of *M pneumoniae* infection.[44–47]

M pneumoniae-associated pulmonary complications increased two-fold in 2023–2024 and accounted for two-thirds of hospitalised children and adolescents in 2023–2024. A higher proportion of patients required oxygen therapy in 2023–2024, which may reflect a trend to admit only patients with complicated pneumonia as the proportion of admission due to pulmonary complications decreased in 2023–2024. Very few (less than 1%) had necrotising pneumonia or need of chest tube drainage in 2023–2024, as also reported from Spain,[48] contrasting clusters of children with parapneumonic effusion reported from China during the resurgence in 2023–2024.[14] No patients were diagnosed with pulmonary embolism or plastic bronchitis, while only one patient was diagnosed with bronchiolitis obliterans. The term 'walking pneumonia' described our patients well across seasons, as the symptom duration prior to hospitalisation was long, often lasting 1–2 weeks. Hospital duration was relatively short, a median of three days, in contrast to the median hospital duration of eight days recently reported among children and adolescents with pneumonia caused by Group A *Streptococcus*.[7]

Extrapulmonary complications necessitating hospitalisation increased four-fold in 2023–2024, with dermatological complications being the most common. Beyond a non-specific skin rash in 10–15% of children and adolescents with *M pneumoniae* infection, as also described previously,[16,17,48] our cohort consisted of 50 patients hospitalised primarily due to complicated dermatological manifestations, previously only described in case reports, smaller case series, and case reviews.[22,23,49] These included *M pneumoniae*-associated angioedema, an important differential diagnosis to drug-induced anaphylactic reactions.[49] We found a five-fold increase in patients hospitalised with MIRM in 2023–2024. However, the phenotype and severity were unchanged across seasons. The rise in MIRM may be explained by the rise in adolescents with *M pneumoniae* infections in 2023–2024, as MIRM predominantly occurs in this age group.[23] Since the pathogenesis of MIRM is proposed to involve immune-mediated mechanisms,[22,23,38,39] the rise may also reflect that this specific age group has the capability of mounting a dysregulated immune response, as exemplified by other immune-mediated diseases in this age group, such as Henoch-Schönlein purpura and multisystem inflammatory disease in children (MIS-C).[50]

The treatment of MIRM among our children and adolescents consisted of supportive care. Approximately half of the patients also received systemic corticosteroids, although this has not been investigated in randomised controlled trials.[23] We found a shorter duration in patients receiving corticosteroids, although only a few patients were included, and the treatment could be biased towards severity. At least, there were no indications of a worse outcome following corticosteroid treatment. Patients with MIRM had a shorter duration of hospitalisation in 2023–2024, which most likely reflects that admission time among children with infectious diseases has generally decreased in recent years. It may also reflect an increased use of systemic corticosteroids in 2023–2024. Despite the painful and distressing disease, often with severe symptoms for several weeks and a risk of non-*M pneumoniae*-related relapse of 10–30%, the overall prognosis was favourable among our patients, as described previously.[21,23] No deaths have been reported since the 1940'es.[22,23,51] Indeed, given that drug-induced mucocutaneous eruptions are rare in children and adolescents, '*Think Mycoplasma (and other infections first)*' in children and adolescents with mucocutaneous eruptions, as recently proposed by Ramien and Bruckner, aligns with our results.[19]

Abdominal symptoms, including abdominal pain, vomiting, and diarrhoea, were reported in approximately 30% of children requiring hospital admission in 2023–2024, similar to the pre-pandemic era and consistent with findings from other studies.[17,48] However, severe gastrointestinal complications as the primary reason for hospitalisation, as observed in 6% of our included children, have been reported less frequently in other studies.[17,48] The clinical manifestations from less severe symptoms in one-third of infected children to rare severe manifestations requiring hospitalisation may represent a continuum of abdominal *M pneumoniae* complications with similar pathogenesis, with appendicitis as the most severe manifestation. The pathogenesis remains undetermined, but as suggested for other extrapulmonary complications, it may involve 1) direct invasion of *M pneumoniae* in the gastrointestinal tract, leading to local inflammation, in line with the finding of *M pneumoniae* in colon mucosa in case studies, 2) immune-mediated enteritis, and 3) vascular occlusion of the mesenteric arteries caused by vasculitis or thrombosis.[39]

Rare extrapulmonary complications, beyond dermatological and gastrointestinal complications, included CNS manifestations, haemolytic anaemia, glomerulonephritis, and cardiac manifestations, with no increase during the resurgence in 2023–2024. The clinical characteristics of our included patients were similar to those described in previous studies,[16,17,48,52] but our findings highlight that the well-recognised complication, *M pneumoniae*-induced haemolytic anaemia, is extremely rare, diagnosed in less

than one of 5000 children and adolescents infected with *M pneumoniae*.

The major limitation of this study was that children and adolescents with mild symptoms were possibly not tested for *M pneumoniae*. Therefore, the incidence of *M pneumoniae* in Denmark was underreported. Underreporting may also have stemmed from not including patients diagnosed with serology only. However, PCR-based methods are considered the gold standard for *M pneumonia* diagnostics in children.[33] Serology is decreasingly used in clinical settings due to low sensitivity and specificity and the need for repeated blood sampling.[1,33] In a recent Spanish study using both serology and PCR-based methods, children diagnosed with serology-only accounted for less than 5% of included children.[48] Thus, the absence of using serology in this study was unlikely to influence the data substantially. Furthermore, the inclusion criteria based on PCR diagnostics was equal across seasons, thereby less likely to influence the changes in incidences. A second limitation was that testing practice may have changed throughout the study period, including increased use of commercially available multiplex PCR test. This could have contributed to the rise in cases in 2023–2024. However, this was not likely to substantially impact the results concerning hospitalisation for more than 24 h. Third, a positive PCT test for *M pneumoniae* is not always indicative of an active infection, as a positive result can persist for months. Fourth, this study only identified pulmonary and extrapulmonary complications if patients were tested for *M pneumoniae*. Thus, the increase in MIRM may have been influenced by less frequent testing of patients with mucositis in the pre-pandemic years, as the disease entity, MIRM, was first clinically defined in 2015.[23] However, we included all patients admitted with mucositis and a positive *M pneumoniae* test, although other diagnostic terms were used, such as Steven Johnsons syndrome or Fuchs syndrome. Furthermore, since most children with MIRM had a prodrome of pneumonia, we do not think the testing practice could explain the entire increase we found in 2023–2024. A fifth limitation was the retrospective collection of clinical data, which, among others, prevented us from providing the exact duration of MIRM. Sixth, the causal relationship between *M pneumoniae* and rare manifestations, such as CNS complications, appendicitis, and heart failure, was not established. Seventh, the microbiological work-up for co-infections was not complete. Therefore, the true rate of co-infections was presumably underreported. Finally, the small population size of Denmark rendered the overall number of children and adolescents with rare complications low. It might have reduced our statistical power to explore changes over time.

The strengths of this study included the population-based design, the well-registered population of Denmark with universal public health care, and the nationwide continuous, centralised surveillance of *M pneumoniae* with logged data at the individual level. In conjunction with the Danish paediatric infectious diseases research collaboration, the logged data enabled the collection of detailed clinical data through electronic medical records for each hospitalised child and adolescent in Denmark in the study period. This facilitated a large patient cohort, including the largest clinical study of children and adolescents with MIRM to date.

In conclusion, the COVID-19 pandemic has highlighted several new aspects of *M pneumoniae*. The magnitude of infections and hospitalisations in 2023–2024 exceeded pre-pandemic levels three-fold, with the highest rise in adolescents. This likely reflected a pronounced immunity debt caused by the decline in *M pneumoniae* during the COVID-19 pandemic. The five-fold increase in children and adolescents with MIRM emphasised *M pneumoniae* as an important pathogen causing mucocutaneous eruptions. The fact that we did not find an increased severity of *M pneumoniae* infections in 2023–2024, compared to the pre-pandemic era, indicated that children's general immune function was unaltered following the COVID-19 pandemic, apart from the increased susceptibility to *M pneumoniae*.

Contributors

KHSD, MH, MJHR, and UN. UN obtained funding. All authors except ACN and SU identified and/or registered clinical details for the included children. KHSD and UN directly assessed and verified all registered data. KHSD, MH, UH, MJHR, and UN analysed the data. KHSD, MH, MJHR, and UN drafted the first version of the manuscript. All authors contributed to data interpretation. All authors revised the manuscript critically for important intellectual content. All authors approved the final work. KHSD and UN had the final responsibility for the decision to submit for publication.

Data sharing statement

According to Danish data-protection legislation, the data used in this study will not be made available.

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2024.101103.

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