IJID Regions 11 (2024) 100349

Contents lists available at ScienceDirect

IJID Regions

journal homepage: www.elsevier.com/locate/ijregi

Assessing the influence of the COVID-19 pandemic on the incidence, clinical presentation, and clindamycin resistance rates of *Streptococcus pyogenes* infections

Daniel N. Marco[1], José Canela[1], Maria Brey[1], Alex Soriano[1,2], Cristina Pitart[3], Sabina Herrera[1,*]

[1] *Hospital Clínic, Department of Infectious Diseases, Barcelona, Spain*
[2] *Centro de Investigación Biomedical en Red en Enfermedades Infecciosas CIBERINFEC, Madrid, Spain*
[3] *Hospital Clínic, Department of Microbiology, Barcelona, Spain*

ARTICLE INFO

Keywords:
S. pyogenes
Invasive group A streptococcal infections
Clindamycin resistance
COVID-19 pandemic

ABSTRACT

Objectives: *Streptococcus pyogenes* (group A *Streptococcus* [GAS]) is a prevalent cause of community-acquired bacterial infections, with invasive GAS (iGAS) infections presenting severe morbimortality. Clindamycin is generally used based on its antitoxin effect. This study investigates changes in iGAS incidence, clinical presentation, outcomes, and clindamycin resistance in an adult cohort.

Methods: This is a retrospective analysis of *S. pyogenes* episodes from a tertiary adult hospital in Barcelona (Spain) between 2015 and 2023. The pre-pandemic period includes data from 2015-2019. The pandemic period, from 2020-2021, and post-pandemic period comprised 2022 to the first semester of 2023.

Results: The global incidence of GAS infections in the pre-pandemic and post-pandemic periods were 2.62 and 2.92 cases per 10.000 hospital admissions, whereas for iGAS cases, they were 1.85 and 2.34. However, a transient decrease was observed during the pandemic period: 1.07 and 0.78 per 10.000 hospital admissions. There was a significant decrease in GAS and iGAS infections during the pandemic period compared with the pre-pandemic incidence (P <0.001 for GAS infections and $P = 0.001$ for iGAS cases) and the post-pandemic incidence ($P = 0.032$ for GAS infections and $P = 0.037$ for iGAS cases). The most common source of infection was skin and soft tissue infections with 264 (54%) cases. Skin and soft tissue infections and cases of necrotizing fasciitis increased during the pandemic. Clindamycin resistance occurred in 13.5% of isolations during the pre-pandemic and 17.5% in post-pandemic period ($P = 0.05$).

Conclusions: Our study revealed a temporary reduction in iGAS infections, followed by resurgence in the post-pandemic period. The observed rise in clindamycin resistance emphasizes the importance of monitoring local resistance patterns for tailored treatment.

Introduction

Streptococcus pyogenes (group A *Streptococcus* [GAS]) is a major cause of community-acquired acute bacterial infections and is the most common cause of bacterial pharyngitis and frequently isolated in deep infections grouped under the term invasive GAS (iGAS) infections. The most important iGAS include cellulitis, necrotizing fasciitis, and pneumonia, which still account for high morbidity and mortality rates [1,2]. Over the last years, an increase in the incidence of iGAS has been notified in adults and children [3–6].

S. pyogenes has somatic constituents (capsule, M protein) that are responsible of its resistance to phagocytosis, favoring tissue or bloodstream invasion. In addition, *S. pyogenes* produce many extracellular products implicated in tissue invasiveness (e.g. DNAses, streptokinases, and hyaluronidases) and immune evasion (e.g. SpeB protease, C5a peptidase) and produces pyrogenic exotoxins (e.g. scarlatina toxins, erythrotoxins) that are potent immune stimulators (superantigens) responsible for streptococcal toxic shock syndrome, still associated with a high mortality rate [7]. *S. pyogenes* remains susceptible to penicillin, and it is the cornerstone of antibiotic treatment for iGAS. However, the mortality rate in streptococcal toxic shock syndrome, even treated with penicillin, is high and three interventions, in order of importance, are considered necessary to improve the outcome: (i) early aggressive surgical debridement, (ii) clindamycin in combination with penicillin, and (iii) immunoglobulins. Clindamycin binds to 23S ribosomal RNA and, *in vitro,* immediately reduces the toxin production by *S. pyogenes* (antitoxin effect) [8,9]. To date, the benefit of the antitoxin effect has been thoroughly demonstrated in animal models [10] and this practice is

* Corresponding author.
E-mail address: sherrera@clinic.cat (S. Herrera).

https://doi.org/10.1016/j.ijregi.2024.03.004
Received 31 January 2024; Received in revised form 5 March 2024; Accepted 7 March 2024

accepted worldwide, with a strong recommendation in guidelines [11–13]. However, the clinical data supporting this recommendation are scarce and it explains that the recommendation is based on low-quality evidence [10,14]. More recently, Babiker et al. [15] have shown in a retrospective multi-center study that clindamycin also reduces the mortality rate in other iGAS infections, including pneumonia, skin and soft tissue infections (SSTIs), and bacteremia. The recently reported increase in clindamycin-resistant strains is, therefore, concerning [16–18].

This study aimed to describe the changes in the incidence, clinical presentation, and outcomes of iGAS, as well as the evolution of resistance to clindamycin in an adult cohort before, during, and after the COVID-19 pandemic.

Methods

We conducted a retrospective study at a 900-bed tertiary university hospital attending adult patients in Barcelona (Spain), with an area of influence of 400,000 inhabitants. Using a routine purpose-designed surveillance database, all documented microbiological isolations of *S. pyogenes* from the first semester of 2015 to the first semester of 2023 (both included) were recorded. For each isolate, the following variables were recorded: date of infection, source and type of infection, clinical sample, antibiotic treatment, intensive care unit (ICU) admission, 30-day mortality, and antibiotic resistance profile. The COVID-19 epidemic was declared in Spain on March of 2020. Thus, the pre-pandemic period comprised the first semester of 2015 until the second semester of 2019. Thus, the post-pandemic period comprised 2022 to the first semester of 2023. Although COVID-19 was recognized by the World Health Organization as a global emergency until the May 5, 2023, the clinical burden in our center was higher during 2020 and 2021, affecting the normal epidemiology trends, with a normalization afterward. Thus, the pandemic period has been regarded the period from the first semester of 2020 to the second semester of 2021.

Definition of group A streptococcal infections

Non-invasive GAS infections were considered when the strain was isolated from a mucosal surface (pharyngeal swab) and the patient had local symptoms of infection (e.g. pharyngitis). iGAS was defined as the isolation of *S. pyogenes* from a normally sterile site (soft tissue, blood, cerebrospinal fluid, pleural fluid, ascites, and/or synovial fluid) and the patient had local (e.g. erythema) and systemic (e.g. fever) signs of infection. SSTIs were classified according to the Working Group on Severe Streptococcal Infections [19], including cellulitis, pressure ulcer site infection, subcutaneous abscess, myositis, and necrotizing fasciitis. Necrotizing fasciitis was diagnosed if there were necrotic findings in the surgical samples. Severe episodes of GAS, defined by admission to the ICU, were also recorded.

Microbiological procedures

Samples from blood cultures were inoculated into aerobic and anaerobic vials and processed by Bactec 9240 System (Becton-Dickinson, Block Scientific Inc Bellport, NY, USA). Other samples were cultured in blood agar plates for 5 days before being discarded as negative. The phenotypic identification of *S. pyogenes* from positive cultures was performed based on the presence of beta-hemolysis and colony morphology, followed by the detection of A Lancefield antigen.

Antimicrobial susceptibility testing was performed using a microdilution system or E-test. Susceptibility to antimicrobials was established according to the Clinical and Laboratory Standards Institute break points until mid-2011 and to the current European Committee on Antimicrobial Susceptibility Testing criteria.

Statistical analysis

All calculations were performed with the SPSS statistical package (version 18.0; SPSS, Chicago, IL, USA). Categorical variables were compared using the χ^2 or Fischer's exact test, as appropriate. All statistical tests were two-tailed, and the threshold of statistical significance was set at $P < 0.05$.

The incidence of GAS and iGAS infections was calculated as a ratio between the total number of cases with an isolation of *S. pyogenes* and the number of hospital admissions for each semester. The incidence is given per 10,000 hospital admissions. Incidences between periods were compared using two-sided Student's *t*-test and the threshold of statistical significance was set at $P < 0.05$. Aside from severe cases requiring ICU admission, patients affected by necrotizing fasciitis or pneumonia or those with positive blood cultures were analyzed separately.

Results

Group A streptococcal and invasive group A streptococcal incidence across the pandemic

During the study period, a total of 487 episodes of *S. pyogenes* infections were recorded from 480 different patients. Of these, 356 were considered as iGAS episodes according to the definition. The global incidence of GAS infections in the pre-pandemic and post-pandemic periods were 2.62 and 2.92 cases per 10.000 hospital admissions, respectively (Figure 1). Similarly, the incidence for iGAS cases were 1.85 and 2.34 cases per 10.000 hospital admissions for the same periods. The incidence of GAS between pre-pandemic and post-pandemic periods were similar (2.62 vs 2.92 cases per 10.000 admissions, $P = 0.71$); however, an increasing trend was seen in the incidence of iGAS cases comparing the pre- and post-pandemic periods (1.85 vs 2.34 cases per 10,000 admissions, $P = 0.27$).

The GAS incidence during pandemic period was 1.07 cases per 10.000 hospital admissions, whereas 0.78 cases per 10,000 hospital admissions of iGAS were reported during pandemic period. Thus, there was a significant decrease in GAS and iGAS infections during the pandemic period compared with the previous pre-pandemic incidence ($P < 0.001$ for GAS infections and $P = 0.001$ for iGAS cases) and the subsequent post-pandemic incidence ($P = 0.032$ for GAS infections and $P = 0.037$ for iGAS cases).

Descriptive analysis of group A streptococcal and invasive group A streptococcal episodes

The most common source of infection was SSTIs with 264 (54%) cases, followed by otitis and pharyngitis with 126 (26%) cases. Accordingly, the majority of *S. pyogenes* were isolated from skin or soft tissue samples in 237 (46%) cases and pharyngeal swabs in 89 cases (18%). Other samples included blood cultures (62, 13%), osteoarticular tissue (41, 8%), and deep fascia (17, 3.5%). Table 1 summarizes the main epidemiologic variables of GAS infection episodes during the three periods of the study. We noticed an increasing trend in the percentage of SSTIs before and after pandemic (49% vs 66.7%), coupled with a decrease in non-invasive GAS infections: 28.2% vs 19.2%. Altogether, SSTIs between the pre-pandemic period and post-pandemic period were 52.2% versus 57.7% ($P = 0.07$). Specifically, confirmed cases of necrotizing fasciitis were also increased after the COVID-19 pandemic (1.8% vs 6.3%, $P = 0.03$).

The most common treatment for *S. pyogenes* infections was monotherapy with a β-lactam agent (37%), followed by clindamycin (2.7%) and quinolones (2.7%). However, nearly half (42%) of the episodes were treated with a combination of two active agents. The preferred combinations were a β-lactam plus clindamycin (24%) and a β-lactam plus linezolid (16%). The prescribed antibiotic treatment did not differ across the three periods of the study. Regarding the clindamycin

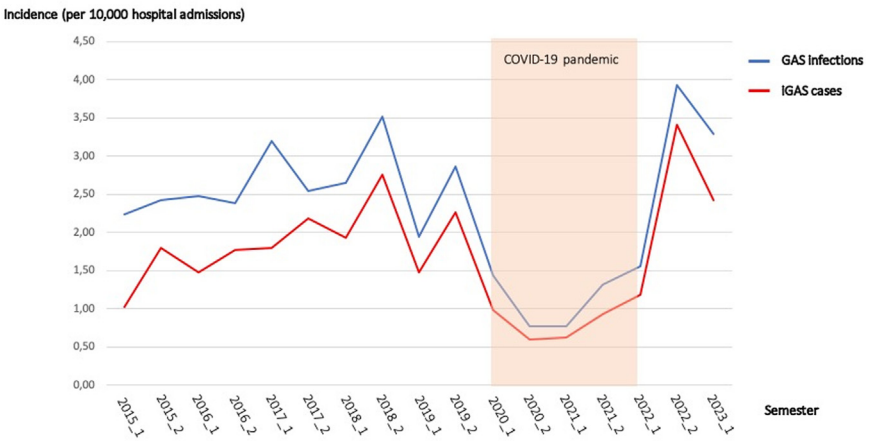

Figure 1. Line graph showing the evolution of the incidence of GAS and iGAS cases across the three periods of study: pre-pandemic period from the first semester of 2015 to the second semester of 2019, pandemic period from the first semester of 2020 to the second semester of 2021 (shadowed), and post-pandemic period from the first semester of 2022 to the first semester of 2023.
GAS, group A *Streptococcus*.
iGAS, invasive group A *Streptococcus*.

Table 1
Clinical, microbiological characteristics, and outcomes of patients with *S. pyogenes* infections.

Characteristics	Total episodes N = 487	Pre-pandemic period N = 312	Post-pandemic period N = 175	vs *P*-value
Infection source				
Skin and soft tissues	264 (54.2)	163 (52.2)	101 (57.7)	0.07
Necrotizing fasciitis	17 (3.5)	6 (1.9)	11 (6.3)	0.03
Otitis or Pharyngitis	126 (26)	88 (28.2)	38 (21.7)	0.39
Pulmonary	22 (4.5)	17 (5.4)	5 (2.9)	0.54
Osteoarticular	20 (4.1)	16 (5.1)	4 (2.3)	0.59
Other	55 (11.3)	42 (13.5)	27 (15.4)	1
Clinical sample				
Skin and soft tissues	237 (48.7)	137 (43.9)	100 (57.1)	0.09
Pharyngeal swab	89 (18.3)	63 (20.2)	26 (14.9)	0.34
Blood culture	62 (12.7)	42 (13.5)	20 (9.1)	0.62
Respiratory	15 (3.1)	10 (3.2)	5 (2.9)	1
Osteoarticular	13 (2.7)	10 (3.2)	3 (1.8)	0.77
Other[a]	71 (14.6)	50 (16)	21 (12)	0.41
Antibiotic treatment				
Beta-lactam monotherapy	180 (37)	119 (38.1)	61 (34.9)	0.47
Beta-lactam + clindamycin	118 (24.2)	78 (25)	40 (22.9)	0.7
Beta-lactam + linezolid	77 (15.8)	46 (14.7)	31 (17.7)	0.82
Quinolone monotherapy	13 (2.7)	9 (2.9)	4 (2.3)	1
Other	99 (20.3)	60 (19.2)	39 (22.3)	0.61
Clindamycin resistance	76 (15.6)	42 (13.5)	34 (19.4)	0.05
Severity				
Intensive care unit admission	33 (7)	28 (9)	5 (2.9)	0.01
Mortality	8 (1.6)	7 (2.2)	1 (0.6)	0.27

All values are expressed as absolute count and percentages.
[a] Includes all clinical samples obtained with unspecified methods.

resistance, we detected a rise in clindamycin-resistant strains: 13.5% in the pre-pandemic period versus 19.5% in the post-pandemic period ($P = 0.05$).

Descriptive analysis of severe invasive group A streptococcal episodes

A total of 33 (7%) patients were admitted to the ICU in the whole study period. The most common source of these infections was pneumonia in 13 (39%) and SSTIs in 10 patients (30%); in 27% of them, bacteremia was documented. The 30-day mortality rate in patients in the ICU was 24% and we did not find an increase in the number of deaths across the COVID-19 pandemic (2.4% vs 0.6%, $P = 0.27$).

Four of 13 (31%) patients admitted to the ICU due to *S. pyogenes* pneumonia and four of 10 (40%) admitted due to a SSTI died. Combined, the patients affected by necrotizing fasciitis or pneumonia or those with positive blood cultures were more prone to be admitted in the ICU (24.4% vs 3%, $P < 0.001$) and had a higher mortality (7.9% vs 0.3%, $P < 0.001$). All patients admitted to the ICU received treatment with a β-lactam and 32 (97%) of them in combination with another active antibiotic: clindamycin in 19 (58%) cases, linezolid in nine (27%), and other antibiotics in three (9%) cases.

A total of 47 (62%) patients with bacteremia and necrotizing fasciitis received treatment with clindamycin, whereas 25 (33%) of them received linezolid treatment, with no significant differences in terms of ICU admission (17% vs 24%, $P = 0.4$) or mortality (2.4% vs 0%, $P = 0.31$). Patients with isolation of clindamycin-resistant strains did not present a significant increase in ICU admissions (13.9% for sensitive vs 7.7% for resistant strains, $P = 1$) or mortality (3.2% for sensitive vs 0% for resistant strains, $P = 0.67$).

With respect to pneumonia cases, during the study period, we identified 22 cases of pneumonia. From those, 13 were admitted to the ICU and four died. All of them, except one, received a β-lactam as the mainstay treatment. Most of them associated a second antibiotic, which was not deliberately chosen to treat *S. pyogenes* but used empirically as a coverage of other common respiratory pathogens (four azithromycin, five quinolones, two vancomycin and, finally, five linezolid).

Discussion

In our cohort, we found a notable decline in the incidence of GAS and iGAS infections during the COVID-19 pandemic period, with a subsequent return to the previous incidence in the post-pandemic period. Moreover, during the pandemic period, there was an increase in the

proportion of clindamycin-resistant isolations, partially rectified in the post-pandemic period.

A few studies have reported an increase in the number of iGAS pediatric cases in 2022 compared with the lower incidences reported during the COVID-19 pandemic and previous years [4–6]. Our results are in line with a recent Spanish study that showed a transient decrease of iGAS during 2020-2021, with a rebound to the previous incidence measured in 2018-2019 [3]. Some experts hypothesize that during the early stages of the COVID-19 pandemic, nonpharmaceutical interventions such as mask-wearing and social distancing played a role in the decline of various infectious diseases. However, when COVID-19 control measures were scaled back or removed, unintended consequences emerged. This relaxation led to significant outbreaks of non–COVID-19 infections because more susceptible individuals were exposed [20].

Adjunctive therapy with clindamycin was associated with improved survival in a recent multi-center French cohort [15], and this effect was also seen in patients with invasive iGAS infection who did not present with septic shock or necrotizing fasciitis. Unfortunately, the rate of clindamycin resistance in *S. pyogenes* in our center is increasing, in line with recent studies [16,18]. Between 2011 and 2018, the US Centers of Disease Control and Prevention Active Bacterial Core surveillance program reported an increase from 8.9% to 24.2% of *S. pyogenes* isolates that were non-susceptible to clindamycin [6]. These data raise the question of its convenience as an empiric therapy or if it should be substituted by other agents with antitoxin activity, such as oxazolidinones (e.g. linezolid) and good penetration to tissues (lung or cerebrospinal fluid) [8,21]. A recent study found no differences in patients with invasive soft tissue infection or necrotizing fasciitis who underwent surgical debridement and received either linezolid or clindamycin [22]. Our results also support that linezolid could be an alternative for iGAS. Knowing the local resistance epidemiology can help tailor empirical treatment of GAS infections.

Our study has several limitations, including the retrospective design, single-center setting, and the absence of pediatrics population in our cohort. In addition, the comorbidity variables were not assessed and, with respect to clindamycin resistance patterns, it would be convenient to distinguish constitutive versus inducible patterns of resistance in future investigations. Furthermore, because the majority of cases of GAS infections are mild, the potential benefits of combination therapy will have to be evaluated separately in this subset of patients.

In summary, in our cohort of GAS infections, we found a significant decrease in the incidence during the pandemic period. Moreover, after the outbreak of COVID-19, we observed a rapid return to the previous incidence of these infections and an increase in the resistance to clindamycin, with one in every five isolates being resistant in the last period.

Declarations of competing interest

On behalf of all authors, the corresponding author states that there is no conflict of interest. No funding or financial support was received for the production of the present work.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

The ethical approval of this study was waived according to our center's policy.

Author contributions

Marco DN: writing, data analysis, literature search, and figures; **Canela J**: data collection; **Brey M:** data collection, data analysis, and figures; **Soriano A:** study design and data interpretation; **Pitart C:** data collection and data.

References

[1] Babiker A, Kadri SS. ICU management of invasive β-hemolytic streptococcal infections. *Infect Dis Clin North Am* 2022;**36**:861–87. doi:10.1016/J.IDC.2022.07.007.
[2] González-Abad MJ, Alonso Sanz MA. Invasive Streptococcus pyogenes infections (2011–2018): EMM-type and clinical presentation. *An Pediatr (Engl Ed)* 2020;**92**:351–8. doi:10.1016/J.ANPEDI.2019.10.014.
[3] de Ceano-Vivas M, et al. Streptococcus pyogenes infections in Spanish children before and after the COVID pandemic. Coming back to the previous incidence. *Enferm Infecc Microbiol Clin (Engl)* 2024;**42**:88–92. doi:10.1016/J.EIMCE.2023.04.021.
[4] De Gier B, Marchal N, de Beer-Schuurman I, Te Wierik M, Hooiveld M, de Melker HE, et al. Increase in invasive group A streptococcal (Streptococcus pyogenes) infections (iGAS) in young children in the Netherlands, 2022. *Euro Surveill* 2023;**28**:2200941. doi:10.2807/1560-7917.ES.2023.28.1.2200941.
[5] Ladhani SN, Guy R, Bhopal SS, Brown CS, Lamagni T, Sharp A. Paediatric group A streptococcal disease in England from October to December, 2022. *Lancet Child Adolesc Health* 2023;**7**:e2–4. doi:10.1016/S2352-4642(22)00374-1.
[6] Centers for Disease Control and Prevention. Surveillance for Group A strep disease, https://www.cdc.gov/groupastrep/surveillance.html; 2022 [accessed 16 December 2023].
[7] Bartoszko JJ, Elias Z, Rudziak P, Lo CK, Thabane L, Mertz D, et al. Prognostic factors for streptococcal toxic shock syndrome: systematic review and meta-analysis. *BMJ Open* 2022;**12**:e063023. doi:10.1136/BMJOPEN-2022-063023.
[8] Coyle EA, Cha R, Rybak MJ. Influences of linezolid, penicillin, and clindamycin, alone and in combination, on streptococcal pyrogenic exotoxin a release. *Antimicrob Agents Chemother* 2003;**47**:1752–5. doi:10.1128/AAC.47.5.1752-1755.2003.
[9] Tanaka M, Hasegawa T, Okamoto A, Torii K, Ohta M. Effect of antibiotics on group A streptococcus exoprotein production analyzed by two-dimensional gel electrophoresis. *Antimicrob Agents Chemother* 2005;**49**:88–96. doi:10.1128/AAC.49.1.88-96.2005.
[10] Andreoni F, Zürcher C, Tarnutzer A, Schilcher K, Neff A, Keller N, et al. Clindamycin affects Group A streptococcus virulence factors and improves clinical outcome. *J Infect Dis* 2017;**215**:269–77. doi:10.1093/INFDIS/JIW229.
[11] Sartelli M, Guirao X, Hardcastle TC, Kluger Y, Boermeester MA, Raşa K, et al. 2018 WSES/SIS-E consensus conference: recommendations for the management of skin and soft-tissue infections. *World J Emerg Surg* 2018;**13**:58. doi:10.1186/S13017-018-0219-9.
[12] Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, et al. Executive summary: practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the infectious diseases society of America. *Clin Infect Dis* 2014;**59**:147–59. doi:10.1093/cid/ciu444.
[13] Esposito S, Bassetti M, Concia E, De Simone G, De Rosa FG, Grossi P, et al. Diagnosis and management of skin and soft-tissue infections (SSTI). A literature review and consensus statement: an update. *J Chemother* 2017;**29**:197–214. doi:10.1080/1120009X.2017.1311398.
[14] Fernández-Galilea A, Estella Á, García-Garmendia JL, Loza A, Palacios-García I, Sierra-Camerino R, et al. Clindamycin but not intravenous Immunoglobulins reduces mortality in a retrospective cohort of critically ill patients with bacteremic Group A Streptococcal infections. *Rev Esp Quimioter* 2022;**35**:475–81. doi:10.37201/REQ/030.2022.
[15] Babiker A, Li X, Lai YL, Strich JR, Warner S, Sarzynski S, et al. Effectiveness of adjunctive clindamycin in β-lactam antibiotic-treated patients with invasive β-haemolytic streptococcal infections in US hospitals: a retrospective multicentre cohort study. *Lancet Infect Dis* 2021;**21**:697–710. doi:10.1016/S1473-3099(20)30523-5.
[16] DeMuri GP, Sterkel AK, Kubica PA, Duster MN, Reed KD, Wald ER. Macrolide and clindamycin resistance in group a streptococci isolated from children with pharyngitis. *Pediatr Infect Dis J* 2017;**36**:342–4. doi:10.1097/INF.0000000000001442.
[17] Chuang PK, Wang SM, Lin HC, Cho YH, Ma YJ, Ho TS, et al. The trend of macrolide resistance and emm types of group A streptococci from children at a medical center in southern Taiwan. *J Microbiol Immunol Infect* 2015;**48**:160–7. doi:10.1016/j.jmii.2013.08.015.
[18] Fay K, Onukwube J, Chochua S, Schaffner W, Cieslak P, Lynfield R, et al. Patterns of antibiotic nonsusceptibility among invasive Group A streptococcus infections-United States, 2006–2017. *Clin Infect Dis* 2021;**73**:1957–64. doi:10.1093/CID/CIAB575.
[19] Breiman RF, Davis JP, Facklam RR, Gray BM, Hoge CW, Kaplan EL, et al. Defining the Group A streptococcal toxic shock syndrome. Rationale and consensus definition. The Working Group on Severe Streptococcal Infections. *JAMA* 1993;**269**:390–1. doi:10.1001/JAMA.1993.03500030088038.
[20] Hollingsworth B, Okamoto KW, Lloyd AL. After the honeymoon, the divorce: unexpected outcomes of disease control measures against endemic infections. *PLOS Comput Biol* 2020;**16**:e1008292. doi:10.1371/journal.pcbi.1008292.
[21] Cortés-Penfield N, Ryder JH. Should linezolid replace clindamycin as the adjunctive antimicrobial of choice in Group A streptococcal necrotizing soft tissue infection and toxic shock syndrome? A focused debate. *Clin Infect Dis* 2023;**76**:346–50. doi:10.1093/CID/CIAC720.
[22] Heil EL, Kaur H, Atalla A, Basappa S, Mathew M, Seung H, et al. Comparison of Adjuvant clindamycin vs linezolid for severe invasive Group A Streptococcal skin and soft tissue infections. *Open Forum Infect Dis* 2023;**10**:ofad588. doi:10.1093/ofid/ofad588.