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ORIGINAL ARTICLE

# Invasive *Streptococcus pyogenes* infections in a highly complex pediatric hospital: clinical presentation and molecular characterization

## Infecciones invasoras por *Streptococcus pyogenes* en un hospital pediátrico de alta complejidad: presentación clínica y caracterización molecular

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**What do we know about the subject matter of this study?**

Worldwide, starting in the second half of 2022, an increase in cases of invasive S. pyogenes disease has been reported. In the United Kingdom, the emergence of a clone called M1UK was identified, corresponding to a new lineage of the pandemic strain M1T1 (M1global). Later, cases of this virulent clone were reported in the USA, Canada, the Netherlands, Denmark, and Australia, displacing the epidemic M1global clone.

**What does this study contribute to what is already known?**

This article explores the clinical forms and molecular epidemiology of invasive S. pyogenes infections in a high-complexity pediatric hospital in Argentina between 2018 and 2023. In addition, it describes the circulating clones and warns about the circulation in Argentina of the M1UK clone.

## Abstract

Invasive *Streptococcus pyogenes* (*S. pyogenes*) infections are associated with high morbidity and mortality. It is characterized by the appearance of new clones, which may be associated with certain virulence factors. An increase in cases of invasive *S.pyogenes* disease was reported in 2022. **Objective:** To describe clinical, microbiological, and molecular characteristics of invasive *S. pyogenes* infections in hospitalized children in a high-complexity pediatric hospital. **Patients and Method:** Retrospec-

**Keywords:**
*Streptococcus pyogenes*;
Invasive Bacterial Diseases;
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tive cohort. Patients with *S. pyogenes* isolation in a sterile site hospitalized at the Garrahan Hospital between 01/01/2018 and 31/12/2023 were included. Electronic medical records were reviewed and demographic, clinical, and microbiological data were recorded. Bacteriological subtyping was performed using routine methods and genotyping was performed using whole genome sequencing. **Results:** 105 patients were included. 63 were male (60%). The median age was 76 months (IQR 37-117). 36 patients (34.3%) had underlying disease; the most frequent was oncohematological pathology with 7 (6.7%) patients. The most frequent clinical presentations were skin and soft tissue infection with 45 (42.9%) patients, osteoarticular infections with 31 (29.5%) patients, and pneumonia with 9 (8.6%) patients. 17 patients (16.2%) required intensive care. One patient died related to the infection. 76 serotypes were available for subtyping. M1 predominated during the study period. In 2023, M12 incidence increased. **Conclusions:** Active epidemiological surveillance showed changes in the circulating *S. pyogenes* serotypes and the clinical characteristics of the patients.

## Introduction

*Streptococcus pyogenes* has been recognized as an important pathogen for human health. It is a frequent cause of mild infections such as pharyngitis, impetigo, or cellulitis, but sometimes it can cause invasive disease (ID) and be associated with severe manifestations with high morbidity and mortality[1].

Invasive *S. pyogenes* infections manifest as bacteremia, sepsis, pneumonia, meningitis, osteoarticular infection, or necrotizing fasciitis. In addition, bacterial toxin expression can cause a systemic inflammatory response and cause streptococcal toxic shock syndrome (STSS)[2].

Traditional typing of *S. pyogenes* isolates is performed by using a serotype-specific antiserum produced against the M protein, an immunodominant surface antigen and key virulence determinant[3]. Currently, *S. pyogenes* strains are typed by sequencing the 5' variable region of the *emm* gene encoding the M protein, of which there are more than 200 types. Large-scale epidemiological studies have shown differences in the distribution of *emm* types in geographically and socioeconomically distinct regions of the world[4]. Some studies report an association between different serotypes and specific clinical manifestations[5].

In 2022, the World Health Organization reported an increase in the number of cases of ID due to *S. pyogenes*, some of them associated with the expansion of a specific clone[6,7,8]. The Pan American Health Organization (PAHO) also issued a statement in the same year reporting the increase in the number of cases reported in Uruguay[9]. In Argentina, *S. pyogenes* IDs have been mandatory notifiable diseases since 2018[10]. From that year to the present, the National Ministry of Health warns of an increase in the number of cases from epidemiological week 42 of 2022, with a peak in epidemiological week 25 of 2023. However, underreporting makes it difficult to know the true incidence of the disease in our country[11].

The objective of this work is to describe the clinical, microbiological, and molecular characteristics of *S. pyogenes* IDs in children admitted to a high-complexity hospital and to compare them according to the year of presentation during 2018-2023.

## Patients and Method

Retrospective cohort study, in which patients with ID due to *S. pyogenes* hospitalized at the *Hospital de Pediatría Profesor Doctor Juan Pedro Garrahan*, from January 01, 2018, to December 31, 2023, were included as well as all patients with documentation of *S. pyogenes* on at least one sterile site and clinical picture compatible with infection. Patients in whom microbiological documentation was performed at another institution were excluded. Patients were identified from the records of the hospital's Microbiology Department. Electronic medical records were reviewed and demographic, clinical, and microbiological data were recorded.

The study was conducted in a high-complexity, nationally referred pediatric hospital with more than 600 inpatient beds, 5 intensive care units (ICU), and one neonatal intensive care unit.

Samples of abscesses, bone biopsies, pleural fluid, joint fluid, and cerebrospinal fluid were collected, processed, and incubated according to established protocols. Blood samples were inoculated in PF Plus culture bottles (bioMérieux, Marcy-l'Étoile, France), for isolation of aerobic bacteria in pediatric patients, and FN plus bottles (bioMérieux, Marcy-l'Etoile, France), for isolation of anaerobic bacteria. Then, they were incubated for 5 days in the automated BacT/ALERT 3D system (bioMérieux, Marcy-l'Etoile, France) until September 2021 and subsequently the BacT/ALERT Virtuo system (bioMérieux, Marcy-l'Etoile, France) was used.

Samples from sterile sites were seeded on solid media (chocolate agar and blood agar) and thioglycollate

broth. Solid media were incubated for 48-72 hours and broth for 7 days, while positive blood culture bottles were subcultured on solid media. Bacterial growth was obtained in conventional culture media between 24-48 hours of incubation. The βhemolytic colonies were identified by matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry [Vitek® MS, Knowledge base (KB) version 3.2] following the manufacturer's recommendations. To determine antimicrobial sensitivity, the procedures recommended by the Clinical and Laboratory Standards Institute[12] (CLSI) were carried out using the diffusion method on Mueller-Hinton agar with 5% sheep blood. The working protocols of the National Antimicrobial Resistance Surveillance Network (WHONET-ARGENTINA) were followed and discs of penicillin 10 IU (PEN), levofloxacin 5 µg (LEV), erythromycin 15 µg (ERY), and clindamycin 2 µg (CLI) were tested. These discs were placed 12 mm apart to infer the resistance mechanism (D-test)[13]. The plates were incubated in a 5% CO2 atmosphere at 35ºC. All data were recorded in the microbiology management system (Kern-Mic® v.9.0.194).

Since October 2018, *S. pyogenes* isolates recovered from sterile sites were referred to the National Reference Laboratory of ANLIS, Dr. Carlos G. Malbrán for molecular characterization, as part of epidemiological surveillance. Subtyping by routine method and genotyping by whole genome sequencing (WGS) were performed.

*Emm*-type analysis was performed according to CDC protocol (www.cdc.gov/ncidod/biotech/strep/protocol_emmtype). MLST analysis of *de novo* assemblies was performed against the PubMLST database (https://pubmlst.org/organisms/streptococcus-pyogenes) of all sequenced isolates and *emm* types were confirmed by BLAST analysis against the CDC *emm* type database.

Continuous variables were summarized as median and interquartile range (IQR). Categorical variables were summarized as number and proportion. Patient characteristics were compared according to the year of presentation. The $Chi^2$ test was performed for categorical variables and the Mann-Whitney test for continuous variables. The STATA16 statistical software was used.

The study was conducted in full compliance with current national and international regulations on Health Research. The study data were evaluated confidentially and anonymously, with restricted access only for the participating researchers. This study was approved by the Ethics Committee of the *Hospital Garrahan*.

## Results

During the study period, 105 patients presenting ID due to *S. pyogenes* were identified. Figure 1 shows the temporal distribution.

63 patients were male (60%). The median age was 76 months (IQR 37-117). 36 patients (34.3%) had some underlying diseases. The most frequent were oncohematological diseases with 7 cases (6.7%), lymphatic malformation with 6 cases (5.7%), atopic der-

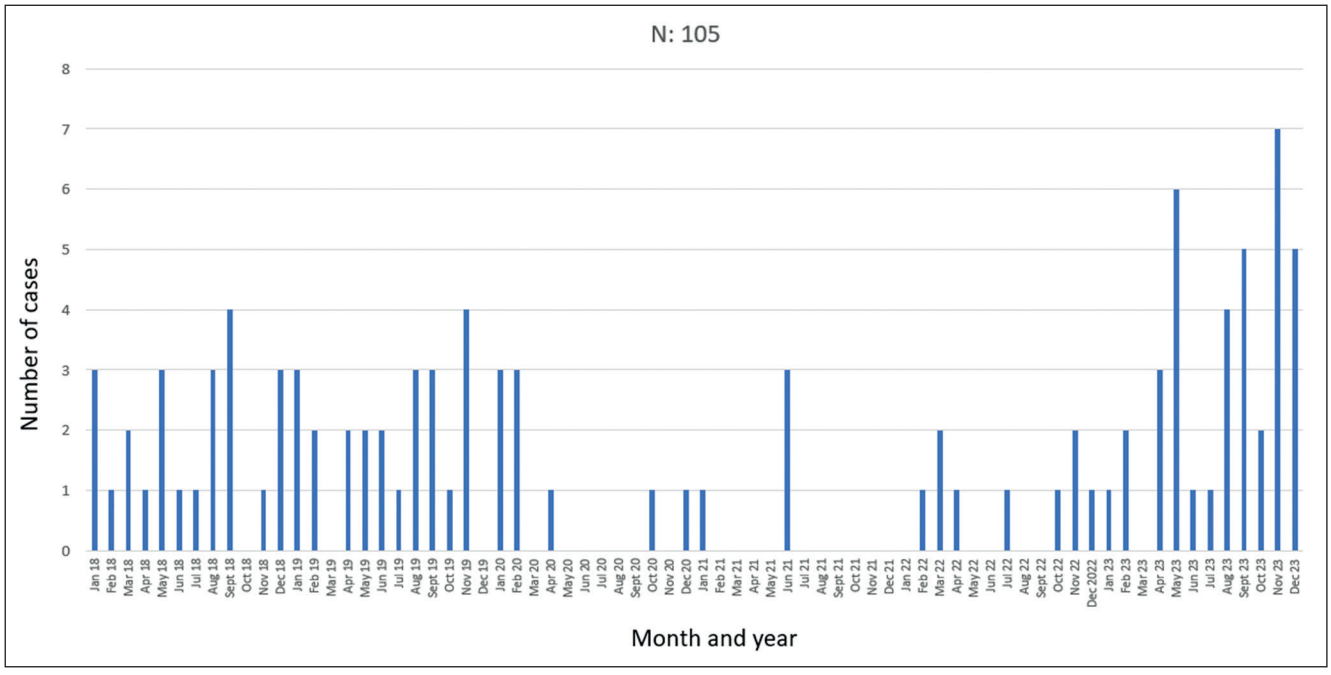


**Figure 1.** Monthly number of invasive *Streptococcus pyogenes* infections (Jaunary 2018 - December 2023).

matitis with 5 cases (4.8%), genetic syndrome with 4 cases (3.8%), neurological disease with 4 cases (3.8%), and chronic liver disease with 3 cases (2.9%). 5 patients had a history of *S. pyogenes* pharyngitis and 4 patients of chickenpox in the 30 days before the onset of ID.

A clinical focus of infection was found in 98 patients (93.3%). The most frequent were skin and soft tissue infections with 45 cases (42.9%), followed by osteoarticular infection with 31 cases (29.5%), pneumonia with 9 cases (8.6%), central nervous system infection with 5 cases (4.8%), and otomastoiditis with 5 cases (4.8%). 8 patients (7.6%) presented primary bacteremia. Septic shock was diagnosed in 17 patients (16.2%) and STSS in 7 (6.7%).

*S. pyogenes* was identified in blood cultures in 60 patients (57.1%). Other identification samples were bone with 20 cases (19%), deep tissue sample with 7 cases (6.7%), pleural fluid with 5 cases (4.8%), joint fluid with 5 cases (4.8%), and cerebrospinal fluid with 4 cases (3.8%). Table 1 shows the main demographic and clinical characteristics of the cohort.

54 patients (51.4%) required surgical drainage, 10 of them (9.5%) at least twice.

Empirical antibiotic treatment was adequate in all cases. 63 patients (60%) received a beta-lactam agent in combination with CLI. The median duration of intravenous antibiotic treatment was 7 days (IQR 7-10), and the total duration of treatment was 14 days (IQR 10-42).

17 patients (16.2%) were admitted to the ICU, one of whom (1%) died due to the infection.

Table 2 shows the frequencies and distribution of microbiological and clinical characteristics in each year evaluated. The statistically significant difference in the frequency of bacteremia stands out.

Coinfection with another microorganism was identified in 19 patients (18.1%). *Staphylococcus aureus* was predominant (n:10). Other agents found were adenovirus (n:4), rhinovirus (n:3), respiratory syncytial virus (n:1), herpes simplex virus (n:1), varicella zoster virus (n:1), *Escherichia coli* (n:1), and *Pseudomonas aeruginosa* (n:1).

All isolates were sensitive to PEN, CLI, and other macrolides. LEV was tested in 60 sensitive isolates.

Subtyping of 76 serotypes was available. Of these,

**Table 1. Clinical and demographic characteristics of patients hospitalized for iGAS infections (n: 105)**

| Variable | | n (%) |
|---|---|---|
| Sex | | |
| Male | | 63 (60) |
| Female | | 42 (40) |
| Median age in months (IQR) | | 76 (37-117) |
| Underlying conditions | | 36 (34,3) |
| Type of infection | Skin and soft tissue | 45 (42,9) |
| | Osteoarticular | 31 (29,5) |
| | Pneumonia | 9 (8,6) |
| | Central nervous system | 5 (4,8) |
| | Otomastoiditis | 5 (4,8) |
| | Endocarditis | 1 (1) |
| | Necrotizing fasciitis | 2 (1,9) |
| Septic shock | | 17 (16,2) |
| Bacteremia | | 60 (57,1) |
| PICU admission | | 17 (16,2) |
| Empirical treatment | Ceftriaxone+Clindamycin | 57 (54,3) |
| | Clindamycin | 17 (16,2) |
| | Ceftriaxone | 9 (8,6) |
| | Ceftriaxone+Vancomycin+Clindamycin | 6 (5,7) |
| | Other* | 16 (15,2) |
| Mediana de días de internación (RIC) | | 10 (7-14) |

*Other: ampicillin (n: 5), piperacillin tazobactam-vancomycin (n:5), penicillin (n: 4) meropenem (n: 2). iGAS: invasive Group A Streptococcus. IQR: interquartile range. PICU: Pediatric Intensive Care Unit

**Table 2. Clinical features of patients hospitalized for iGAS by year**

| Variable n (%) | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 | p* |
|---|---|---|---|---|---|---|---|
| Total | 23 | 23 | 9 | 4 | 9 | 37 | - |
| Median age in months (IQR) | 56 (32-105) | 59 (35-137) | 71 (45-95) | 18 (21-80) | 76 (53-132) | 95 (40-117) | 0.3 |
| Skin and soft tissue | 11 (48) | 12 (52) | 3 (30) | 2 (50) | 5 (56) | 10 (27) | 0.24 |
| Septic shock | - | 3 (13) | 2 (20) | 1 (25) | 1 (11) | 10 (27) | 0.59 |
| PICU admission | 1 (4) | 2 (9) | 2 (20) | 1 (25) | 1 (11) | 10 (27) | 0.07 |
| Coinfection | 3 (13) | 7 (30) | 2 (20) | - | 3 (33) | 4 (11) | 0.9 |
| Bacteremia | 12 (52) | 7 (30) | 5 (50) | 3 (75) | 5 (56) | 28 (76) | 0.04 |

*Chi2 was performed for categorical variables and Mann-Whitney test for continuous variables. PICU: Pediatric Intensive Care Unit. IQR: interquartile range

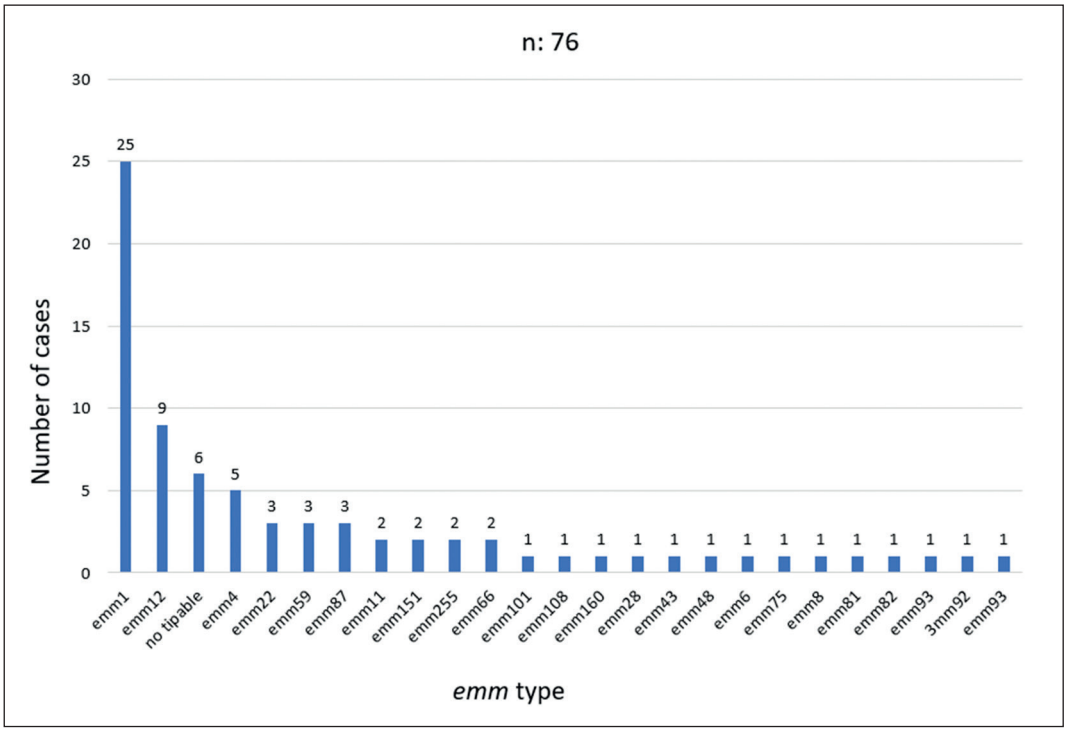


**Figure 2.** Invasive group A *Streptococcus* emm types (n:76)

6 were non-typable. The most frequent subtypes were *emm*1 25 (33%) and *emm*12 9 (12%) (Figure 2). Of the isolates that were subtyped in 2018 – 2021, the dominant clone in invasive disease was *emm*1.

In two patients presenting in March and September 2023, the National Reference Laboratory identified the M1UK clone. These were a previously healthy 9-year-old male who presented with *S. pyogenes* osteoarticular infection complicated by deep vein thrombosis, and an 8-year-old male with STSS and septic arthritis. Both received initial treatment with beta-lactam, CLI, and intravenous gamma globulin and presented favorable outcomes.

## Discussion

Worldwide, as of the second half of 2022, an increase in cases of invasive *S. pyogenes* disease has been reported, even when compared to events reported before the COVID-19 pandemic[8].

In Argentina during 2023, 890 cases of invasive infection by *S. pyogenes* were reported, of which 118 died. Of the reported cases, 47.3% were under 16 years of age. In 2019, 60 cases of ID were reported nationwide[14].

As reported in other countries, the increase in Argentina has been sustained since the last months of 2022, coinciding with the increase in the circulation of respiratory viruses for that same year[11]. However, the increase in cases was sustained worldwide, with no clear causality identified. xv

Extreme age, chronic skin diseases, immunosuppression, varicella-zoster virus infection, diabetes, and a history of respiratory disease[16] are some of the predisposing factors described for *S. pyogenes* ID[17]. In the series presented, the median age coincides with that described in other studies; however, a higher proportion of patients with comorbidities was observed[18]. On the other hand, the history of clinical varicella was infrequent, probably in relation to the universal vaccination of all children since 2015[19].

In line with other pediatric series[17,20], the most frequent clinical form was skin and soft tissue infection, followed by osteoarticular involvement.

The frequency of positive blood cultures was 57% in this cohort, similar to those reported in the multicenter study conducted in Argentina by Cancellara et al. in 2016[18].

The severity of the disease is determined, among other variables, by the type of clinical focus and host characteristics. Patients with ID due to *S. pyogenes* frequently require intensive care and surgical treatment. xxi In our series, 16% required ICU admission, and 38% required surgery.

The reported case fatality rate in children ranges from 2-8% in children[21,22]. Mortality is higher when *S. pyogenes* presents as necrotizing fasciitis or STSS[23].

In our study, mortality was lower than reported in the literature. The low frequency of STSS and necrotizing fasciitis in the series should be noted. Lopardo et al, in a multicenter study published in 2014, also report lower mortality in patients with *S. pyogenes* ID in the period 2011-2012 compared to previous years. Improved care processes, the incorporation of CLI, and better patient registration are suggested as probable causes[24].

In the cohort presented, all patients received adequate empirical treatment and a high proportion combined with CLI. Early use of CLI has been shown to improve the prognosis of patients with *S. pyogenes* ID[25]. The use of beta-lactam antibiotics for the treatment of *S. pyogenes* is the treatment of choice.

In this study, no strains of *S. pyogenes* resistant or with decreased sensitivity to PEN were observed. This coincides with the national report of the National Surveillance of Antimicrobial Resistance[13]. However, epidemiologic surveillance should be maintained, since, in recent years, the emergence of *S. pyogenes* with reduced susceptibility to beta-lactam antibiotics has been reported[26].

In recent years, subtyping of strains by sequencing the *emm* gene has become more relevant. Its usefulness lies in the possibility of identifying variations in the disease pattern and is especially relevant for vaccine development[27]. A systematic review that included 38 studies carried out in Europe and North America reported that *emm*1 is the main subtype found in these regions. 70% of isolates were identified within *emm*1, *emm*28, *emm*89, *emm*3, *emm*12, *emm*4, and *emm*6. xxviii The emergence of the M1UK clone, corresponding to a new lineage of the pandemic strain M1T1 (M1global), was identified in the cases reported in the United Kingdom in 2023. This M1UK strain differs from M1global by 27 chromosomal single nucleotide polymorphisms (SNPs). Cases of this virulent clone were later reported in the USA, Canada, the Netherlands, Denmark, and Australia, displacing the epidemic M1global clone.

In Argentina, strains of ID are sent to the National Reference Laboratory (LNR), Special Bacteriology Service, Bacteriology Department, INEI ANLIS Malbrán for molecular characterization.

Surveillance of circulating clones and analysis of virulence genes, such as speA, speG, speJ, and smeZ superantigens, is performed. In addition, possible mutations in the gene machinery that regulates virulence factors and/or other exotoxin genes are evaluated by bioinformatics analysis of the genome of the prevalent M-type isolates. As of 2018, it is observed that *emm*1/sequence type 28 is the most prevalent and frequently associated with ID, followed by *emm*12.[11]

As reported by the National Ministry of Health, of the total number of *S. pyogenes* samples received during the first semester of 2023, the analysis of the genomes of prevalent M1 isolates (*emm*1/sequence type 28) detected 3 isolates that present the 27 SNPs and correspond to the M1UK clone. These three isolates represent 8% (3/36) of the *S. pyogenes* type M1 isolates received during this period.

In addition, during the same period, a cluster of 7 genetically closely related *S. pyogenes* M1 isolates was identified. This M1 sublineage has acquired a mobile genetic element encoding for the superantigen toxin SpeC. These isolates do not show the SNPs of the emerging strains M1UK (UK) and M1DK (Denmark).

In coincidence with the above, the patients reported in this study, the *emm*1 type had the highest incidence, including two patients with identification of the M1UK clone. Also noteworthy in 2023 is the higher frequency of the *emm*12 type compared to previous years.

The main limitations of this study are related to its retrospective nature. In addition, it is a study carried out in a single highly complex center and referral from other institutions, so there may be a greater representation of severe cases.

The main strength of this study is the systematic recording of clinical and microbiological information that allows us to know the characteristics of the population studied, and the clinical-microbiological correlation.

Clinical and laboratory epidemiological surveillance is key to determining the expansion and prevalence of the different circulating clones and their clinical impact, identifying variations in the characteristics of the disease, and associating it with microbiological and molecular findings.

## Conclusions

In this cohort study of children with *S. pyogenes* ID, skin and soft tissue and osteoarticular infections predominated. There were no cases of PEN or ERY resistance in this series. The *emm*1 type predominated throughout the study period. The increase in cases of *emm*12 type in the isolates of 2023 stands out. Two patients with the M1UK clone are reported. Mortality in this cohort was low.

Continued active epidemiological surveillance is required to know the changes in case characteristics of invasive *S. pyogenes* infections.

## Ethical Responsibilities

**Human Beings and animals protection:** Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World

Medical Association regarding human experimentation developed for the medical community.

**Data confidentiality:** The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

**Rights to privacy and informed consent:** The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

## Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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