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Genomic analysis and clinical characteristics of a seasonal upsurge of *Streptococcus pyogenes* emm12

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Abstract

Purpose *Streptococcus pyogenes* cause invasive infections with variable incidence over time. In 2023, an increase in invasive *S. pyogenes* infections caused by *emm*-types 1 and 12 was reported globally. In Southern Sweden an increase in *S. pyogenes* emm12 severe infections was also noted and we set out to determine if this increase was caused by a single genetic sublineage.

Methods Data on severe *S. pyogenes* infections notified between July 1st 2016 and June 30th 2023, including *emm*-types, was obtained from the Regional Centre for Communicable Disease Control. All *emm*12 isolates recovered during November–April each season were sequenced, analysed by core genome multilocus sequence typing (cgMLST), and compared with international *emm*12 isolates. Clinical information was obtained from the medical records.

Results During the 2022/23 season, 157 cases of severe *S. pyogenes* infection were reported, of which 32 (20%) were caused by *emm*12 isolates. Forty-four *emm*12 isolates from 2016 to 2023 were analyzed. The patients had a median age of 45 years; soft tissue infection was the most common focus and two patients died. The isolates were genetically diverse and those recovered in the 2022/23 season did not form a closely related cluster. Instead, they were found among isolates from previous seasons and with international isolates, mostly from Denmark. There was no correlation between isolate clustering and type or severity of infection.

Conclusion The surge of *emm*12 infections recorded in Southern Sweden during the 2022/23 season was multiclonal, suggesting that host-related factors may have played a predominant role in the increased incidence of these infections.

Keywords *Streptococcus pyogenes* · Bacteremia · *emm*-type · Group A *Streptococcus* · Whole genome sequencing

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Introduction

Streptococcus pyogenes (Group A *Streptococcus*, GAS) is a human pathogen known for causing a wide range of infections, from pharyngitis and impetigo to more severe conditions, such as post-partum endometritis, necrotizing fasciitis, and toxic shock-like syndrome [1, 2]. The incidence of severe *S. pyogenes* infections is variable [3]. There is typically a pattern of relatively few cases for several years, followed by an upsurge. Often there is also a seasonal pattern, where most cases are reported during winter and spring [3, 4]. The dominant *S. pyogenes* *emm*-types also present temporal fluctuations. The *emm*-typing is based on sequence analysis of a 180-base pair hypervariable gene segment of the *emm* gene [5]. Lately whole-genome sequencing (WGS) has demonstrated advantages over *emm*-typing as a tool for epidemiological surveillance and phylogenetic analysis of *S. pyogenes* outbreaks [6–8]. WGS provides a much higher resolution for the discrimination of clonal lineages and has enabled the identification of multiple intra-*emm*-type sublineages [9–12].

Between the end of 2022 and the spring of 2023, there was an increase of reported cases of invasive GAS (iGAS) infections in several different countries across the globe [13–21]. A majority of cases in these reports were caused by *emm1* and *emm12* isolates. Some studies reported an increase especially among children < 5 years of age, while others reported a more even age distribution [22–24].

In the Skåne healthcare region in Southern Sweden, with ten hospitals and a population of approximately 1.4 million, all isolates from potentially severe GAS infections are routinely *emm*-typed. Historically, *emm1* has been the most common type in severe infections. However, during the 2022/23 season, an increase in the proportion of *emm12* isolates was noticed. We therefore aimed to investigate if this increase was caused by a single clone and to describe the clinical characteristics of the cases.

Methods

Microbiology and identification of cases

According to the Communicable Diseases Act and the Communicable Diseases Ordinance in Sweden, *S. pyogenes* is notifiable if detected in blood cultures, cerebrospinal fluid, synovial fluid or any other sterile location, or with clinical presentation as necrotizing fasciitis, streptococcal toxic shock syndrome or post-partum infection. Therefore, in the clinical microbiology laboratory in Lund, which serves the healthcare system in the Skåne region, isolates from such infections were routinely subjected to *emm*-typing using PCR and Sanger sequencing [25]. Furthermore, isolates

were stored at −70 °C allowing for additional analyses. Data on *emm*-types of *S. pyogenes* from all notifiable infections 2016–2023 was extracted from the Regional Centre for Communicable Disease Control. A season was defined as starting on July 1 st and ending on June 30th the next year. All *emm12* isolates from November 1 st to April 30th from each season were selected for WGS. The medical charts from patients infected with those isolates were reviewed.

Whole genome sequencing and bioinformatic analysis

Bacteria stored at −80 °C were cultivated on blood agar and DNA extraction was performed using the DNeasy Blood and tissue kit (Qiagen). The Illumina DNA Prep kit was used for preparing genomic libraries. Libraries were amplified and purified to ensure the appropriate fragment sizes, and the quality of the libraries was assessed using a Qubit fluorometer and an Agilent TapeStation. The Illumina NextSeq 2000, with a P1 300-cycle flow cell platform, was used for sequencing, which generated 150 bp paired-end reads.

Draft genomes were *de novo* assembled with the INNUca v4.2.3 pipeline [26] and annotated with Prokka 1.14.6 [27], as previously described [18]. The *emm* subtype was determined with *emmtyp* v0.2.0 [28] using the CDC database (available at <https://www2.cdc.gov/vaccines/biotech/strepblast.asp>). The multilocus sequence type (ST) was predicted with MLST v2.23.0 [29] and the PubMLST database (available at <https://pubmlst.org/organisms/streptococcus-pyogenes/>). Whole genome multilocus sequence typing profiles were determined with chewBBACA v3.2.0 [30] using a *S. pyogenes* schema [12], and the allelic profiles of core loci (shared by 100% of the isolates under analysis) were used to create minimum spanning trees (MSTs) in PHYLOViZ online [31]. The presence of antimicrobial resistance genes was determined with ABRicate and the NCBI database [32].

Raw sequencing data obtained in this study and sample metadata were deposited in the European Nucleotide Archive (ENA) under project accession number PRJEB113721.

Review of medical records

The patients' medical records were systematically reviewed. Information about medical history, focus of infection, vital signs, blood analysis, radiologic findings, need for intensive care and outcomes such as death, length of hospital stay, and need for surgery was documented. The Sepsis-3 criteria were used for the definition of sepsis in adult patients, and the Phoenix Sepsis Score was used for children (0–18 years old) [33, 34].

Septic shock was defined as SOFA-score of 2 points or more and the requirement for vasoactive agents or Phoenix Sepsis Score of 2 points and cardiovascular dysfunction. Nosocomial infection was defined as a positive blood culture obtained from a patient 48 h or more after arrival at the hospital.

Ethical approval

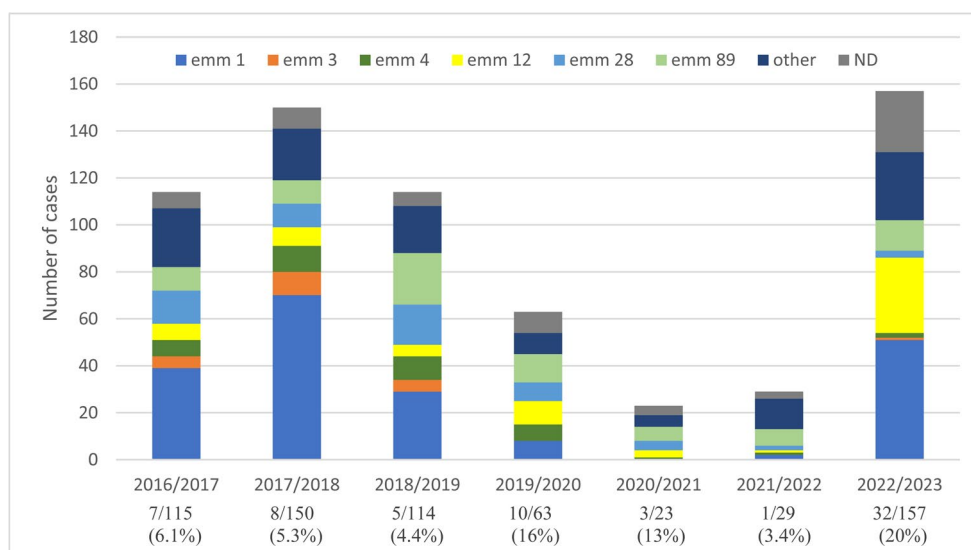
The study was approved by the Swedish Ethical Review Authority (2022–01226 and 2025–03827). Due to the retrospective observational design, the need for individual patient consent was waived by the ethical review authority.

Results

Notifiable GAS infections in Skåne 2016–2023

The total number of reported cases of GAS and the distribution of *emm*-types for the seasons 2016/17–2022/23 is shown in Fig. 1. A total of 66 patients with *emm12* were reported, of which 32 (48%) were identified in the 2022/23 season. The median number of *emm12* cases per season for the previous six seasons was 6 (range 1–10) or 3–16% of all *S. pyogenes* cases per season. Of the 66 clinical *emm12* isolates, 44 isolates (67%) from 44 patients with notifiable infection, reported from November 1st to April 30th each season, were subjected to WGS, phylogenetic analysis and corresponding chart review. Of these 44 isolates, 29 (66%) were cultured from blood, 5 (11%) from the female genital tract, 4 (9%) from synovial fluid, 3 (7%) from wound, and 1 (2%) each from abdominal fluid and nasopharyngeal exudate.

Fig. 1 Number of reported cases and distribution of *emm*-types per season. The proportion of *emm12* isolates relative to the total number of isolates is indicated below each season. The “Other” category groups isolates not belonging to the six most common *emm*-types, whereas “ND” (not determined) is used for isolates that were not *emm*-typed



Patients and clinical presentation

Table 1 shows the background characteristics for the 44 patients, with age, gender distribution and underlying diseases. The clinical presentation of the cases is presented in Table 2, including focus of infection, sites of GAS isolation, severity of infection and empirical antibiotic treatment.

Genomic analysis of *emm12* isolates

Among the 44 sequenced isolates, 41 (93%) were characterized as *emm12.0*-ST36, 1 (2%) as *emm12.128*-ST36, 1 as *emm12.37*-ST242, and 1 as *emm12.101*-ST242, in which ST36 and ST242 are single-locus variants. Based on core-genome multilocus sequence typing (cgMLST) analysis, the isolates presented a considerable level of genetic diversity, with a mean distance of 97.9 allelic differences (range 0–159) from a total of 1,385 compared loci. Isolates from 2022/23 were also genetically diverse (mean distance of 101.4 allelic differences, range 0–155). Accordingly, these isolates were scattered throughout the MST based on the cgMLST profiles of the isolates (Fig. 2A). There was also no clear association between clinical presentation and specific clusters or seasons (Fig. 2B).

To put the Swedish isolates into a geographically broader context, an additional cgMLST analysis was performed on a larger dataset including *emm12* isolates recovered in Denmark, the Czech republic and Portugal in periods encompassing the 2022/23 upsurge [18, 20, 21], and genetically diverse *emm12* isolates recovered worldwide during 2001–2015 [35] (Fig. 3). While most isolates from Sweden clustered together with isolates from the upsurge in Denmark, the Czech republic and Portugal, there were a few, including

Table 1 Background characteristics of 44 patients with *emm12* isolates selected for WGS

	No. patients (%) ¹
Sex	
Male	22 (50)
Female	22 (50)
Age	
Median (IQR) ²	45 (29–67)
Municipality	
Malmö	10 (23)
Lund	3 (7)
Klippan	3 (7)
Ängelholm	3 (7)
Svedala	2 (5)
Ystad	2 (5)
Bromölla	2 (5)
Other ³	19 (43)
Underlying conditions	
Diabetes mellitus	6 (14)
Immunosuppressive drugs	4 (9)
Malignancy	3 (7)
Rheumatological disease	3 (7)
Congestive heart failure	2 (5)
Any underlying disease	15 (34)

¹Except where indicated otherwise

²IQR- interquartile range, children < 6 years: *n* = 5; two of these children had their infection during the 2022/23 season

³Municipalities with only one reported case

some from 2022/23, that were more closely related to older isolates from Brazil, New Zealand, Lebanon, Canada and the UK (Fig. 3).

Antimicrobial resistance genes, namely the *mef(A)*-*msr(D)* pair associated with macrolide resistance [36], were found in only two *emm12*.0-ST36 isolates, one from 2016/17 and the other from 2022/23. These two isolates were not clustered together, nor were they grouped with international *emm12* isolates carrying *mef(A)*-*msr(D)*. Instead, the isolate from 2016/17 was linked (48 allelic differences) to an *emm12*.21-ST991 isolate recovered in Lebanon in 2007–2010 with no resistance genes, while the isolate from 2022/23 was linked (63 allelic differences) to an *emm12*.0-ST36 isolate recovered in Canada during 2010–2013, also with no resistance genes.

Discussion

The number of reported notifiable GAS cases per season in our region varied over time, with distinct peaks in 2017/18 and 2022/23. The very low incidence of GAS observed during the COVID-19 pandemic years (2020–2022) was likely due to societal measures taken to limit

the spread of SARS-CoV-2. However, the overall cyclic pattern with alternating high- and low-incidence years was apparent in pre-pandemic years already. The underlying cause of this general GAS incidence oscillation remains uncertain, although decreased population immunity has often been proposed as an important contributing factor [3]. An alternative explanation is the emergence of clones with enhanced immune evasion capabilities, allowing more efficient spread in the population.

Our results demonstrate that the observed increased incidence of notifiable GAS with *emm12* during the 2022/23 season was not caused by a closely related group of isolates but rather by diverse lineages that were already present before the 2022/23 season. The distribution pattern presented in Fig. 2A, where the 2022/23 genomes are scattered throughout the tree together with genomes from several previous seasons, is consistent with the high genetic diversity reported in previous studies investigating the increase in *emm12* iGAS [18, 20, 21]. The comparison of the cgMLST profiles of our *emm12* isolates with those of isolates recovered internationally (Fig. 3) showed that isolates from Sweden were in most cases closely related to *emm12* isolates recovered in Denmark. This was not entirely unexpected, since our region in the

Table 2 Focus and outcome of infection of 44 patients with *emm12* isolates selected for WGS

	No. patients (%) ¹
Focus of infection	
SSTI ⁴	20 (45)
Female genital tract	8 (18)
RTI	8 (18)
Joint infection	4 (9)
Shunt infection	1 (2)
Unknown	3 (7)
Severity of infection ²	
Sepsis	23 (52)
Septic shock	12 (27)
Site of acquisition, <i>n</i> =43 ³	
Community-acquired	43 (100)
Nosocomial	0 (0)
Course of disease	
Admitted to hospital	43 (98)
Admitted to ICU	8 (18)
Days of hospitalization, median (IQR)	8 (4–17)
Source control surgery	14 (32)
In hospital death	2 (5)
Empirical antibiotic treatment	
Cefotaxime	14 (32)
Benzylpenicillin	5 (11)
Piperacillin/Tazobactam	5 (11)
Cloxacillin	4 (9)
Carbapenem + Clindamycin	4 (9)
Other	12 (27)

¹Except where indicated otherwise²In accordance with sepsis-3 and The Phoenix Sepsis Score³One patient record could not be evaluated with respect to the site of acquisition⁴Abbreviations used were; *SSTI* Skin and soft tissue infection, *RTI* Upper and lower respiratory tract infection, *ICU* Intensive care unit, *IQR* Interquartile range

south of Sweden is geographically very close to Denmark, and there is a significant volume of work commuting and tourism between the countries. Still, there were also isolates from Sweden that were genetically closer to isolates recovered in more distant countries, including from other continents.

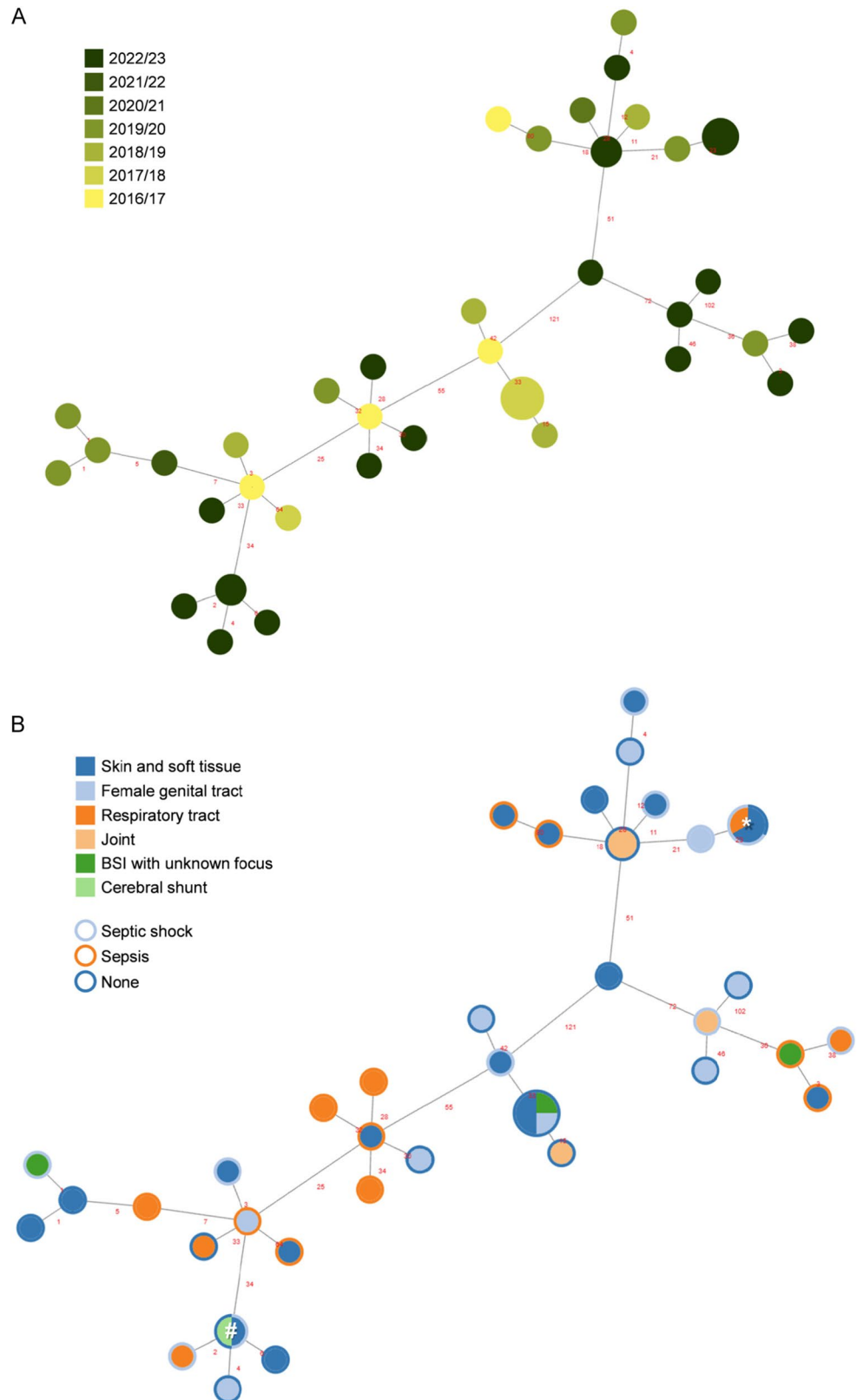
In our study cohort, the severe infections caused by *emm12* did not affect any particular age group and only a minority of our cases were children. This is in contrast to some previous studies [22, 23]. We found no association between the focus of infection and specific bacterial clusters (Fig. 2B), suggesting that host factors such as immunity and genetics likely played a larger role in determining the clinical presentation than bacterial characteristics.

This study has several limitations, mostly due to its retrospective design. Not all isolates had been *emm*-typed, and these are indicated as “ND” in Fig. 1. In some cases,

the infections were diagnosed through sequencing of the 16 S rRNA gene only, and no *emm*-type determination was therefore obtained. In addition, since the *emm*-typing was not performed within this research project but rather as a part of laboratory routine, data on *emm*-type of some isolates were missing for reasons unknown to us. The distribution of *emm*-types presented in Fig. 1 is thus not complete. Another limitation is that only a temporal subset of the *emm12* isolates was selected for WGS. In total, 44 of the 66 *emm12* isolates were included in the genomic analysis and the subsequent chart review. Nevertheless, we consider this subset sufficient to address the scientific questions outlined in the study aims.

In conclusion, our study suggests that the increase of *emm12* cases in the 2022/23 season was caused by several different clones and that host factors likely played a major role in determining the clinical outcome, possibly being more relevant than bacterial characteristics.

Fig. 2 Minimum spanning tree generated with the cgMLST profiles of *emm12* GAS isolates recovered in Sweden, 2016–2023 (n=44). The size of each node is proportional to the number of isolates with that particular cgMLST profile. Links are labelled with the number of allelic differences between nodes (from a total of 1,385 compared loci). **(A)** Nodes coloured according to isolation season (running from November 1st through April 31st). **(B)** Nodes coloured according to primary infection focus, with the outer ring coloured according to the presence of septic shock or sepsis. BSI, bloodstream infection. * Septic shock in one patient with respiratory tract infection and one patient with skin and soft tissue infection. # Septic shock in one patient with skin and soft tissue infection



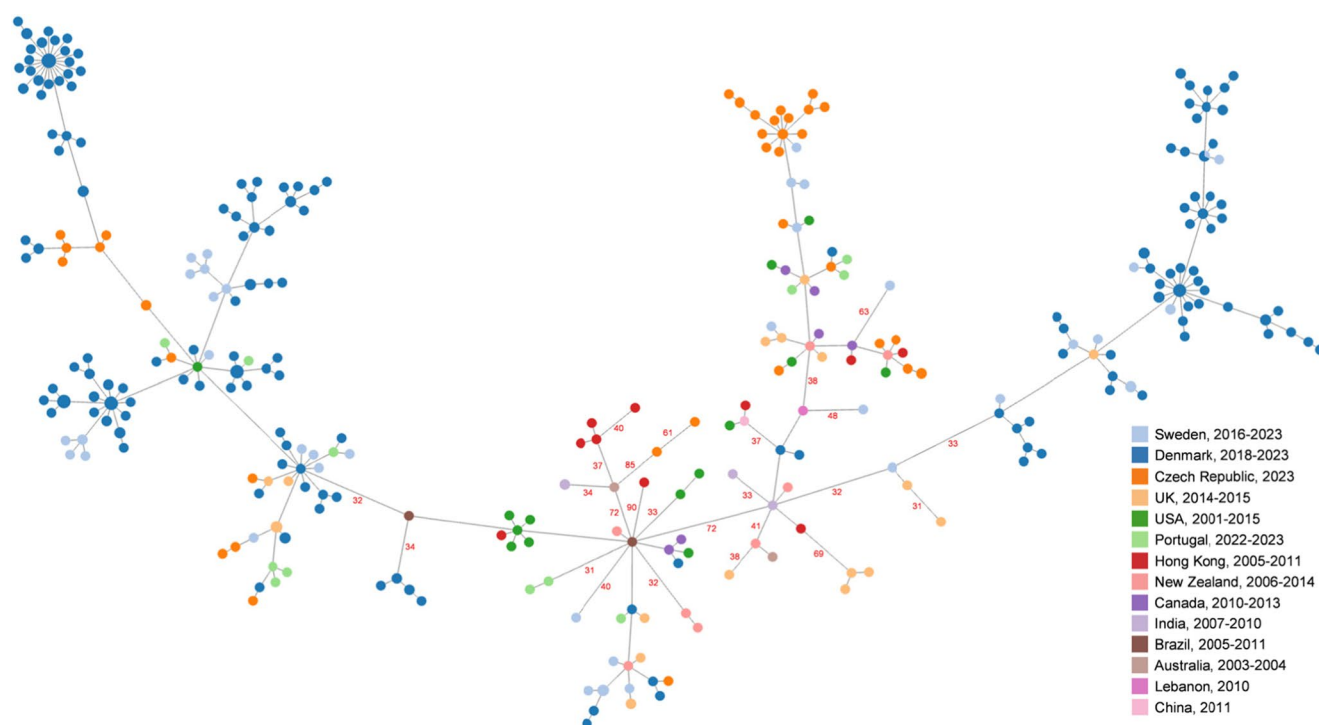


Fig. 3 Minimum spanning tree generated with the cgMLST profiles of *emm12* GAS isolates from Sweden, 2016–2023 ($n = 44$) (this study), Denmark, 2018–2023 ($n = 239$) [21], Portugal, 2022–2023 ($n = 12$) [18], Czech Republic, 2023 [20] and diverse international *emm12* isolates 2001–2015 ($n = 69$) [35]. The size of each node is proportional to

the number of isolates with that particular cgMLST profile on a logarithmic scale. Nodes are coloured according to the country of isolation. Link distances > 30 allelic differences are labelled in red (from a total of 1,104 compared loci)

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Author contributions Erik Senneby and Magnus Rasmussen planned, performed and designed the study and drafted the manuscript. Zakarias Thorin extracted and analysed information from the medical records. Eva Gustafsson provided the information on the notifiable *S. pyogenes* infections. Torgny Sunnerhagen provided microbiological expertise. Ana Friães, Rafael Mamede and Mario Ramirez performed the genomic analyses. All authors provided both critical comments to the manuscript and approved to the submission.

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Data availability Pseudonymized data will be shared upon reasonable request.

Declarations

Competing interests The authors declare no competing interests.

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