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# Differences in the epidemiology between paediatric and adult invasive *Streptococcus pyogenes* infections

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## SUMMARY

In order to investigate for possible differences between paediatric and adult invasive *Streptococcus pyogenes* (iGAS) infections, a total of 142 cases were identified in 17 Greek hospitals during 2003–2007, of which 96 were children and 46 adults. Bacteraemia, soft tissue infections, streptococcal toxic shock syndrome (STSS), and necrotizing fasciitis were the main clinical presentations (67·6%, 45·1%, 13·4%, and 12·0% of cases, respectively). Bacteraemia and lymphadenitis were significantly more frequent in children ($P = 0{\cdot}019$ and 0·021, respectively), whereas STSS was more frequent in adults ($P = 0{\cdot}017$). The main predisposing factors in children were varicella and streptococcal pharyngotonsillitis (25% and 19·8%, respectively), as opposed to malignancy, intravenous drug abuse and diabetes mellitus in adults (19·6%, 15·2% and 10·9%, respectively). Of the two dominant *emm*-types, 1 and 12 (28·2% and 8·5%, respectively), the proportion of *emm*-type 12 remained stable during the study period, whereas *emm*-type 1 rates fluctuated considerably. Strains of *emm*-type 1 from children were associated with erythromycin susceptibility, STSS and intensive-care-unit admission, whereas *emm*-type 12 isolates from adults were associated with erythromycin and clindamycin resistance. Finally, specific *emm*-types were detected exclusively in adults or in children. In conclusion, several clinical and epidemiological differences were detected, that could prove useful in designing age-focused strategies for prevention and treatment of iGAS infections.

**Key words**: *emm*-type, invasive diseases, necrotizing fasciitis, streptococcal toxic shock syndrome, *Streptococcus pyogenes*, varicella.

## INTRODUCTION

During the first 3 years (2003–2005) of enhanced surveillance for invasive *Streptococcus pyogenes* (iGAS) disease in Greece, we observed erythromycin resistance – primarily *mef*(A)-mediated – at a rate of 11·9%, and a high prevalence of *emm*-type 1 strains (fully susceptible to erythromycin) and *emm*-type 12 strains [1]. This surveillance covered both adult and paediatric cases and presented for the first time data

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from Greece, as part of the Strep-EURO initiative [1]. Preliminary observations regarding the epidemiology within each age group led us to further investigate possible epidemiological and clinical differences of iGAS infections between the two groups, during the extended period of 2003–2007, as similar comparable data are scarce in the literature and the majority of previous studies simply presented results on overall iGAS infections, or compared invasive and superficial infections [2–17]. In addition, typing of the isolates using *emm*-gene sequencing was performed, in order to assess strain variation.

## MATERIALS AND METHODS

The study was conducted prospectively from 2003 to 2007; during 2003–2005, it was part of the Strep-EURO initiative [1]. All enrolled cases were hospitalized in 17 general hospitals, 13 of which were in the Athens metropolitan area, two in northern, one in southern and one in western Greece. Reporting was on a voluntary basis. The study area covered about 40% of the total Greek population (2001 census: 10 964 020) (http://www.statistics.gr/portal/page/portal/ESYE/PAGE-themes?p_param=A1604).

Cases were identified as patients with *S. pyogenes* isolated from a normally sterile site, and diagnosed with streptococcal toxic shock syndrome (STSS), as defined previously by the Working Group on Severe Streptococcal Infections [18], necrotizing fasciitis (NF), cellulitis/soft tissue infections (CSTI), osteomyelitis, arthritis, meningitis, primary bacteraemia with and without an apparent focus, empyema, pneumonia, and lymphadenitis. Only one isolate (the first) per patient was included in the study, except where putatively different strains [based on different minimum inhibitory concentrations (MICs)] were isolated from repeat specimens or different body sites.

Isolates were identified as *S. pyogenes* using standard methodology [1]. Susceptibility testing to penicillin, erythromycin, clindamycin, tetracycline and vancomycin was performed using the disk diffusion method according to CLSI guidelines [19]. MICs to erythromycin, clindamycin and tetracycline were determined by a gradient strip method (Etest, bioMérieux, France) according to the manufacturer's instructions. All results were interpreted using CLSI breakpoints [20]. Erythromycin-resistant isolates were screened for macrolide-lincosamide-streptogramin B ($MLS_B$) resistance phenotypes as described previously [21].

Crude DNA extracts were prepared using a previously published protocol [1]. Assignment of *emm*-types was performed with PCR and DNA sequencing according to the protocols and the Blast-*emm* search engine of the CDC website (http://www.cdc.gov/ncidod/biotech/strep/strepindex.htm). Presence of *spe*A, *spe*B and *spe*C genes was investigated as described previously [1].

The following data were collected prospectively, using the same standardized questionnaire throughout the study period, from patients' charts and the attending physician: clinical presentation (as described above), treatment [surgical intervention, intensive-care unit (ICU) admission, ventilatory assistance], outcome within the first 7 days after onset of the symptoms (successful treatment, improvement, or death), and risk factors present at least 4 weeks prior to infection (trauma/skin lesion, prior surgical operation, pharyngotonsillitis, varicella infection, immunosuppression, malignancy, steroid use, intravenous drug abuse, diabetes mellitus, impetigo, alcohol abuse).

Statistical analysis was performed using SPSS v. 16.0 statistical software (SPSS Inc., USA). The patients were divided in two age groups for comparison: paediatric cases (<18 years) and adult cases ($\geqslant$18 years).

For qualitative variables, absolute and relative frequencies were computed; mean (standard deviation; S.D.) and median (interquartile range) for quantitative variables. Mann–Whitney tests were used for age comparisons between the two groups. For comparison of proportions, $\chi^2$ and Fisher's exact tests were used, as appropriate. $\chi^2$ tests for homogeneity were computed in order to evaluate differences in the monthly or yearly distribution of isolates. In case of a significant association in the total sample, adjustments were made for age group (children or adults) using logistic regression models. All $P$ values reported are two-tailed and statistical significance was set at 0·05.

## RESULTS

A total of 142 cases of invasive *S. pyogenes* infections were enrolled in the study. The basic microbiological data of the first 101 cases (period 2003–2005) have been presented previously [1]. Isolates were derived from blood (48% of cases), deep soft tissue (sampling performed during surgery, 37%), synovial fluid (7%), pleural fluid (4%), cerebrospinal fluid (2%) and

Table 1. *Significant differences in children and adults with respect to clinical and epidemiological characteristics*

| | Adult cases ($N=46$) | | Paediatric cases ($N=96$) | | |
|---|---|---|---|---|---|
| Characteristics | *n* | % | *n* | % | *P* |
| Clinical presentation | | | | | |
| STSS | 11 | 23·9 | 8 | 8·3 | **0·017*** |
| Bacteraemia | 25 | 54·3 | 71 | 74·0 | **0·019*** |
| Lymphadenitis | 1 | 2·2 | 15 | 15·6 | **0·021*** |
| Risk factors | | | | | |
| Varicella infection | 0 | 0·0 | 24 | 25·0 | **<0·001*** |
| Diabetes mellitus | 5 | 10·9 | 0 | 0·0 | 0·003 |
| Malignancy | 9 | 19·6 | 2 | 2·1 | 0·001 |
| Intravenous drug abuse | 7 | 15·2 | 0 | 0·0 | <0·001 |
| Alcohol abuse | 3 | 6·5 | 0 | 0·0 | 0·032 |
| Surgical operation | 10 | 21·7 | 5 | 5·2 | 0·006 |
| Immunosupression | 7 | 15·2 | 1 | 1·0 | 0·002 |
| Pharyngotonsillitis | 1 | 2·2 | 19 | 19·8 | **0·005*** |
| Treatment | | | | | |
| Surgical intervention | 11 | 23·9 | 51 | 53·1 | **0·001*** |

STSS, Streptococcal toxic shock syndrome.
* All *P* values were calculated using Fisher's exact test, except those indicated by an asterisk, which were calculated using $\chi^2$.
Bold values indicate significant differences that were confirmed with logistic regression analysis.

bronchoalveolar secretions (1%). Only the first isolate for each case was included.

Patients' age ranged from 6 months to 90 years (mean 20 years). A total of 96 (68%) cases were paediatric (mean age 5·4 years, S.D. = 3·27) and 46 (32%) cases were adults (mean age 50 years, S.D. = 19·65). Of the paediatric cases, 52 (54%) were boys, and 44 (46%) girls; of the adult cases, 32 (70%) were men and 14 (30%) women.

Clinical manifestations included bacteraemia with or without focus (96 cases, 67·6%) of which primary bacteraemia (without any apparent focus) was detected in 20 cases, CSTI (64, 45·1%), STSS (19, 13·4%), NF (17, 12·0%), lymphadenitis (16, 11·3%), arthritis (12, 8·5%), pneumonia (11, 7·7%), osteomyelitis (8, 5·6%), empyema (7, 4·9%), myositis (4, 2·8%) and meningitis (3, 2·1%). A total of 104 patients presented with two or more clinical conditions.

All isolates were fully susceptible to penicillin or vancomycin. A total of 22 (15·5%) isolates were resistant to erythromycin (EryR; MIC range 1 to >256 mg/l), of which six were additionally resistant to clindamycin (MIC >256 mg/l), expressing the constitutive resistant ($cMLS_B$) phenotype. Of the remaining 17 EryR isolates, six belonged to the M phenotype, and 11 to the inducible resistant ($iMLS_B$) phenotype. Most (7/11) of the $iMLS_B$ strains were isolated during 2006 and 2007, with a parallel disappearance of the M phenotype during the same period (data not shown). Forty-three (30·3%) isolates were non-susceptible to tetracycline (TetR), of which eight were intermediately resistant (MIC = 4 mg/l) and 35 fully resistant (MIC $\geqslant$ 8 mg/l). No significant differences were recorded regarding antibiotic resistance between the adult and paediatric age groups.

Varicella and streptococcal pharyngotonsillitis, were the main predisposing factors in the paediatric group (Table 1), whereas in adults, malignancy, diabetes mellitus, and intravenous drug or alcohol abuse were detected more often.

While bacteraemia was the major clinical presentation in both age groups, it was significantly more frequent in children, as was lymphadenitis. On the other hand, STSS was more frequent in adults (Table 1); nevertheless, it proved more fatal in children (Table 2), as those that presented with STSS were more likely to die within 7 days, compared to non-STSS cases, a difference not detected in adults.

A total of 138 strains were *emm*-typed successfully and assigned to 31 different *emm*-types. Overall, the most common *emm*-types (with a predominance of $\geqslant$5%) were *emm*-types 1 and 12 (28·2 and 8·5%, respectively), together comprising over a third of all isolates. As shown in Figure 1, the proportion of

Table 2. *Significant differences between paediatric and adult patients, regarding the correlation of specific clinical and microbiological characteristics with clinical severity, outcome and predisposing risk factors*

| | | Adult cases ($N=46$) | | | | | Paediatric cases ($N=96$) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Non-ICU admission ($n=39$) | | ICU admission ($n=7$) | | | Non-ICU admission ($n=83$) | | ICU admission ($n=13$) | | |
| | | *n* | % | *n* | % | *P* | *n* | % | *n* | % | *P* |
| Renal impairment | Yes | 6 | 54·5 | 5 | 45·5 | 0·005 | 1 | 100·0 | 0 | 0·0 | n.s. |
| | No | 33 | 94·3 | 2 | 5·7 | | 82 | 86·3 | 13 | 13·7 | |
| Liver abnormalities | Yes | 4 | 50·0 | 4 | 50·0 | 0·012 | 5 | 71·4 | 2 | 28·6 | n.s. |
| | No | 35 | 92·1 | 3 | 7·9 | | 78 | 87·6 | 11 | 12·4 | |
| Respiratory distress syndrome | Yes | 5 | 62·5 | 3 | 37·5 | n.s. | 4 | 33·3 | 8 | 66·7 | <0·001 |
| | No | 34 | 89·5 | 4 | 10·5 | | 79 | 94·0 | 5 | 6·0 | |
| Erysipelas rash | Yes | 3 | 75·0 | 1 | 25·0 | n.s. | 11 | 61·1 | 7 | 38·9 | 0·002 |
| | No | 36 | 85·7 | 6 | 14·3 | | 72 | 92·3 | 6 | 7·7 | |
| *emm*-type 1 | Yes | 9 | 75·0 | 3 | 25·0 | n.s. | 20 | 71·4 | 8 | 28·6 | **0·004*** |
| | No | 30 | 88·2 | 4 | 11·8 | | 63 | 92·6 | 5 | 7·4 | |

| | | Adult cases ($N=46$) | | | | | Paediatric cases ($N=96$) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Non-STSS ($n=35$) | | STSS ($n=11$) | | | Non-STSS ($n=88$) | | STSS ($n=8$) | | |
| | | *n* | % | *n* | % | *P* | *n* | % | *n* | % | *P* |
| Outcome within 7 days | Death | 0 | 0·0 | 2 | 18·2 | n.s | 0 | 0·0 | 3 | 37·5 | <0·001 |
| | Survival | 35 | 100·0 | 9 | 81·8 | | 88 | 100·0 | 5 | 62·5 | |

| | | Adult cases ($N=46$) | | | | | Paediatric cases ($N=96$) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Non-NF ($n=42$) | | NF ($n=4$) | | | Non-NF ($n=83$) | | NF ($n=13$) | | |
| | | *n* | % | *n* | % | *P* | *n* | % | *n* | % | *P* |
| Trauma | Yes | 13 | 31·0 | 3 | 75·0 | 0·005 | 17 | 20·5 | 10 | 76·9 | <0·001 |
| | No | 29 | 69·0 | 1 | 25·0 | | 66 | 79·5 | 3 | 23·1 | |

ICU, Intensive care unit; n.s., not significant; STSS, streptococcal toxic shock syndrome; NF, necrotizing fasciitis.
* All *P* values were calculated using Fisher's exact test except that indicated by an asterisk, which was calculated using $\chi^2$.
Bold values indicate significant differences that were confirmed with logistic regression analysis.

infections due to *emm*-type 12 remained relatively stable during the whole study period. In contrast, that of *emm*-type 1 fell sharply ($P=0·026$) in 2005, rising gradually to reach its 2003 levels, by 2007.

In contrast to adults, where *emm*-type 1 was the only predominant type (12/46, 26·1%), a great variety was observed in children: *emm*-types 1 (28/96, 29·2%), 12 (10/96, 10·4%), 22 (7/96, 7·3%), 4 (5/96, 5·2%), and 77 (5/96, 5·2%). Furthermore, *emm*-types 22, 28, 75, 78, 83, 84 and 115 were detected exclusively in paediatric isolates, whereas *emm*-types 19, 44, 80, 87, 101, 113, and 117 were detected exclusively in isolates from adults. Nevertheless, these *emm*-types were represented by only a few isolates each, thus rendering statistical evaluation impossible.

However, even for the two types common to both age groups, age-related differences could be observed, as shown in Tables 2–4, although these differences were not always confirmed by logistic regression analysis. For example, when comparing erythromycin or tetracycline susceptibility, STSS, empyema and lymphadenitis in relation to *emm*-type (the predominant *emm*-type 1, or other *emm*-types) within the two age groups, a statistical difference was detected

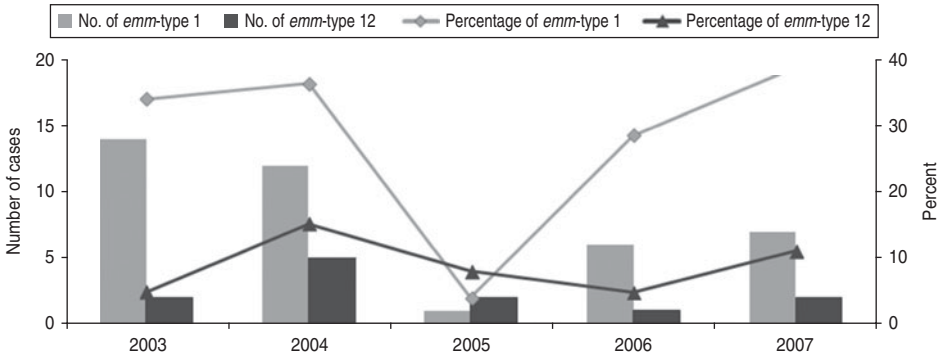


**Fig. 1.** Time fluctuation of invasive diseases due to *emm*-types 1 and 12. The percentage values refer to the proportion of all invasive disease attributable to *emm*-types 1 and 12. The number of *emm*-type 1 and *emm*-type 12 cases per year is plotted on the primary y-axis and the percentage on the secondary y-axis.

within the paediatric group but not within the adult group (Table 3). In addition, a serious clinical condition, using ICU admission as an indicator, was more likely to be due to an *emm*-type 1 strain infection, and related to rash and respiratory distress syndrome (RDS) in children (Table 2). Finally, an association between the presence of the *spe*A gene and *emm*-type 1 was detected within all age groups, as well as between the presence of *spe*C gene and *emm*-type 1, but only within the paediatric group (Table 4).

Regarding all other microbiological, clinical or epidemiological parameters, no significant differences were detected between the age groups.

## DISCUSSION

Since the early 1990s, different studies [2–17], including those of the multi-centre European initiative Strep-EURO [6–9], have attempted to address the problem of increasing invasive *S. pyogenes* (iGAS) diseases. Nevertheless, only in a few of these studies was a direct and thorough comparison of putative epidemiological and clinical differences between adult and paediatric iGAS disease attempted [13, 17]. Therefore, our study focused on investigating possible differences between adults and children, with respect to the *emm*-types, risk factors, clinical presentation, treatment, and outcome.

The study was prospective and on a voluntary basis for participating hospitals. Therefore, underreporting cannot be ruled out. In addition, the extrapolation of the data presented here to the total of the Greek territory should be made with caution, as no previous comparable study exists. Nevertheless, it should be noted that the areas mentioned above were simultaneously covered with respect to both their adult and paediatric populations, rendering patient samples comparable.

Some of the age-specific differences we observed, such as lower STSS rates and higher varicella zoster incidence in paediatric infections, have been described previously [11], as has the fluctuation in the *emm*-type 1 isolation rate [4–6, 10], which has been suggested to peak periodically every few years. Nevertheless, we were not able to confirm all the differences using logistic regression analysis, possibly due to the limited number of cases represented in each category. It is of interest that specific *emm*-types were detected only in paediatric or adult cases, to our knowledge an observation reported for the first time, although their limited number made statistical evaluation difficult.

Despite the importance of varicella infection and pharyngotonsillitis as risk factors, about half of paediatric cases occurred in previously healthy children, in contrast to adult cases where numerous risk factors were present in >90% of cases, which is similar to previous observations [12, 13]. Varicella infections in healthy children have been associated with increased risk of iGAS infections, including clinical presentations not directly related to skin. Possible immunosupression of the T-cell-mediated immunity [11, 14, 22] has been suggested as an explanation.

Regarding clinical presentation, STSS in paediatric cases was associated with *emm*-type 1 (leading also to higher mortality, as indicated by the increased number of deaths within the first week), whereas, in adult cases, it was not associated with a specific *emm*-type – a difference, to our knowledge, not hitherto reported. The immaturity of the paediatric immunological system, coupled with the epidemiological differences in the *emm*-types detected between the age groups may explain the differences. This observation,

Table 3. *Significant differences between* emm-*type 1 and* emm-*type 12 cases compared to all other* emm-*type cases within each of the two age groups*

| | | Adult cases ($N=46$) | | | | | Paediatric cases ($N=96$) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Other *emm*-types ($n=34$) | | *emm*-type 1 ($n=12$) | | | Other *emm*-types ($n=68$) | | *emm*-type 1 ($n=28$) | | |
| | | *n* | % | *n* | % | *P* | *n* | % | *n* | % | *P* |
| Trauma | Yes | 12 | 75·0 | 4 | 25·0 | n.s. | 24 | 88·9 | 3 | 11·1 | 0·015* |
| | No | 22 | 73·3 | 8 | 26·7 | | 44 | 63·8 | 25 | 36·2 | |
| Erythromycin | Resistant | 5 | 83·3 | 1 | 16·7 | n.s. | 16 | 100·0 | 0 | 0·0 | 0·005 |
| | Susceptible | 29 | 72·5 | 11 | 27·5 | | 52 | 65·0 | 28 | 35·0 | |
| Tetracycline | Resistant | 16 | 88·9 | 2 | 11·1 | n.s. | 25 | 100·0 | 0 | 0·0 | <0·001* |
| | Susceptible | 18 | 64·3 | 10 | 35·7 | | 43 | 60·6 | 28 | 39·4 | |
| STSS | Yes | 7 | 63·6 | 4 | 36·4 | n.s. | 2 | 25·0 | 6 | 75·0 | 0·007 |
| | No | 27 | 77·1 | 8 | 22·9 | | 66 | 75·0 | 22 | 25·0 | |
| Empyema | Yes | 0 | 0·0 | 1 | 100·0 | n.s. | 1 | 16·7 | 5 | 83·3 | 0·008 |
| | No | 34 | 75·6 | 11 | 24·4 | | 67 | 74·4 | 23 | 25·6 | |
| Lymphadenitis | Yes | 1 | 100·0 | 0 | 0·0 | n.s. | 6 | 40·0 | 9 | 60·0 | 0·010 |
| | No | 33 | 73·3 | 12 | 26·7 | | 62 | 76·5 | 19 | 23·5 | |
| Outcome within 7 days | Death | 1 | 50·0 | 1 | 50·0 | n.s. | 0 | 0·0 | 3 | 100·0 | 0·023 |
| | Survival | 33 | 75·0 | 11 | 25·0 | | 68 | 73·1 | 25 | 26·9 | |

| | | Adult cases ($N=46$) | | | | | Paediatric cases ($N=96$) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Other *emm*-types ($n=44$) | | *emm*-type 12 ($n=2$) | | | Other *emm*-types ($n=86$) | | *emm*-type 12 ($n=10$) | | |
| | | *n* | % | *n* | % | *P* | *n* | % | *n* | % | *P* |
| Erythromycin | Resistant | 4 | 66·7 | 2 | 33·3 | 0·014 | 12 | 75·0 | 4 | 25·0 | n.s. |
| | Susceptible | 40 | 100·0 | 0 | 0·0 | | 74 | 92·5 | 6 | 7·5 | |
| Clindamycin | Resistant | 0 | 0·0 | 2 | 100·0 | 0·001 | 3 | 75·0 | 1 | 25·0 | n.s. |
| | Susceptible | 44 | 100·0 | 0 | 0·0 | | 83 | 90·2 | 9 | 9·8 | |
| CSTI | Yes | 16 | 88·9 | 2 | 11·1 | n.s. | 45 | 97·8 | 1 | 2·2 | 0·016 |
| | No | 28 | 100·0 | 0 | 0·0 | | 41 | 82·0 | 9 | 18·0 | |
| Osteomyelitis | Yes | 1 | 100·0 | 0 | 0·0 | n.s. | 4 | 57·1 | 3 | 42·9 | 0·023 |
| | No | 43 | 95·6 | 2 | 4·4 | | 82 | 92·1 | 7 | 7·9 | |

n.s., Not significant; STSS, streptococcal toxic shock syndrome; CSTI, cellulitis/soft tissue infections.
* All *P* values were calculated using Fisher's exact test except those indicated by an asterisk, which were calculated using $\chi^2$.

if confirmed to be of clinical importance in further studies with higher patient enrolment, could be used to design age-focused prevention strategies. In contrast to STSS, we detected no clear association between other serious clinical conditions (e.g. NF or CSTI) and a risk factor within any specific age group. An exception was trauma as a risk factor for NF within the paediatric group and for CSTI in all cases, an observation also reported previously [11, 13, 15].

The other dominant *emm*-type, 12, was associated with varicella as a risk factor. The literature on this is conflicting, as one study [16] reported that varicella was associated with *emm*-types 1 and 3, whereas in another study [11] no association was detected. Differences in the epidemiology of skin *vs.* throat isolates and the specific study population may offer a possible explanation.

Finally, the presence of the *spe*A gene (its expression not having been assessed) was associated with *emm*-type 1 in both age groups, and with *emm*-type 12 isolates, STSS and death during the first week only within the paediatric population. As STSS is usually mediated by the SpeA pyrogenic exotoxin, this association between the *spe*A gene, *emm*-type

Table 4. *Significant differences between the presence and absence of* spe*A and* spe*C toxin genes,* emm*-types 1 and 12, STSS and outcome within the two age groups*

| | | Adult cases ($N=46$) | | | | | Paediatric cases ($N=96$) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *spe*A presence ($n=13$) | | *spe*A absence ($n=33$) | | | *spe*A presence ($n=32$) | | *spe*A absence ($n=64$) | | |
| | | *n* | % | *n* | % | *P* | *n* | % | *n* | % | *P* |
| *emm*-type 1 | Yes | 11 | 84·6 | 1 | 3·0 | <0·001* | 27 | 84·4 | 1 | 1·6 | <0·001* |
| | No | 2 | 15·4 | 32 | 97·0 | | 5 | 15·6 | 63 | 98·4 | |
| *emm*-type 12 | Yes | 0 | 0·0 | 2 | 6·1 | n.s. | 0 | 0·0 | 10 | 15·6 | 0·028 |
| | No | 13 | 100·0 | 31 | 93·9 | | 32 | 100·0 | 54 | 84·4 | |
| STSS | Yes | 4 | 30·8 | 7 | 21·2 | n.s. | 7 | 21·9 | 1 | 1·6 | 0·002 |
| | No | 9 | 69·2 | 26 | 78·8 | | 25 | 78·1 | 63 | 98·4 | |
| Outcome within 7 days | Death | 1 | 50·0 | 1 | 50·0 | n.s. | 3 | 100·0 | 0 | 0·0 | 0·035 |
| | Survival | 12 | 27·3 | 32 | 72·7 | | 29 | 31·2 | 64 | 68·8 | |
| | | Adult cases ($N=46$) | | | | | Paediatric cases ($N=96$) | | | | |
| | | *spe*C presence ($n=12$) | | *spe*C absence ($n=34$) | | | *spe*C presence ($n=43$) | | *spe*C absence ($n=53$) | | |
| | | *n* | % | *n* | % | *P* | *n* | % | *n* | % | *P* |
| *emm*-type 1 | Yes | 1 | 8·3 | 11 | 32·4 | n.s. | 2 | 4·7 | 26 | 49·1 | <0·001* |
| | No | 11 | 91·7 | 23 | 67·6 | | 41 | 95·3 | 27 | 50·9 | |

n.s., Not significant; STSS, streptococcal toxic shock syndrome.
* All *P* values were calculated using Fisher's exact test except those indicated by an asterisk, which were calculated using $\chi^2$.

1 and STSS may indicate that these strains actually expressed the gene. In addition, the association within the paediatric population may be explained by the fact that this population has been exposed to the pathogen to a lesser extent than adults, resulting in limited herd immunity and lower anti-SpeA antibody titres, which offer some protection against the toxin [23–25].

In conclusion, apart from a major fluctuation with time of the predominant *emm*-type 1, responsible for invasive disease of particularly high severity in children, we also observed several significant clinical and epidemiological differences in the two age groups with invasive *S. pyogenes* disease. These differences could prove useful in designing age-focused strategies for intervention and prevention, empirical antimicrobial chemotherapy, or vaccine candidates.

## APPENDIX. The Hellenic Strep-EURO Study Group

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## DECLARATION OF INTEREST

None.

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