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Review

A global snapshot on the prevalent macrolide-resistant *emm* types of Group A *Streptococcus* worldwide, their phenotypes and their resistance marker genotypes during the last two decades: A systematic review

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ABSTRACT

Watchful epidemiological surveillance of macrolide-resistant Group A *Streptococcus* (MRGAS) clones is important owing to the evolutionary and epidemiological dynamic of GAS. Meanwhile, data on the global distribution of MRGAS *emm* types according to macrolide resistance phenotypes and genotypes are scant and need to be updated. For this, the present systematic review analyses a global set of extensively characterized MRGAS isolates from patients of diverse ages and clinical presentations over approximately two decades (2000 to 2020) and recaps the peculiar epidemiological features of the dominant MRGAS clones. Based on the inclusion and exclusion criteria, 53 articles (3593 macrolide-resistant and 15,951 susceptible isolates) distributed over 23 countries were dissected with a predominance of high-income countries over low-income ones. Although macrolide resistance in GAS is highly variable in different countries, its within-GAS distribution seems not to be random. *emm* pattern E, 13 major *emm* types (*emm12, 4, 28, 77, 75, 11, 22, 92, 58, 60, 94, 63, 114*) and 4 *emm* clusters (A-C4, E1, E6, and E2) were significantly associated with macrolide resistance. *emm* patterns A-C and D, 14 major *emm* types (*emm89, 3, 6, 2, 44, 82, 87, 118, 5, 49, 81, 59, 227, 78*) and 3 well-defined *emm* clusters (A-C5, E3, and D4) were significantly associated with macrolide susceptibility. Scrutinizing the tendency of each MRGAS *emm* type to be significantly associated with specific macrolide resistance phenotype or genotype, interesting vignettes are also unveiled. The 30-valent vaccine covers ~95% of MRGAS isolates. The presented data urge the importance of comprehensive nationwide sustained surveillance of MRGAS circulating clones particularly in Low and Middle income countries where sampling bias is high and GAS epidemiology is obfuscated and needs to be demystified.

1. Introduction

Streptococcus pyogenes, or Group A *Streptococcus* (GAS), triggers a broad spectrum of diseases upon colonization of the throat or skin, from mild and non-invasive infections such as pyoderma and pharyngitis to severe invasive ones such as toxic shock syndrome and necrotizing fasciitis (Ijaz et al., 2020; Ralph and Carapetis, 2013). The global burden of severe GAS infections is substantial causing an annual death of 500,000 people and the suffering of at least 18.1 million people living with the effects of such diseases at any time (Carapetis et al., 2005).

The main virulence factor of GAS is the M protein, which forms fibrils on the surface of the bacteria (Ghosh, 2011). The M protein has many functions in promoting infection, for example, its involvement in the pathogens' adhesion to epithelial cells, penetration into tissues, and protection against phagocytosis allowing the bacteria thus to escape the innate and acquired immune systems (McMillan et al., 2013; Stewart et al., 2016). Besides, the M protein encoded by the *emm* gene is polymorphic with more than 80 distinct M types being identified (Bessen et al., 2018). Deciphering such polymorphism of the M protein between strains, an approach is known as M typing, seems useful in delineating the circulating clones and investigating the epidemiological relationships (Tewodros and Kronvall, 2005). Throughout the years, M typing has progressed from phenotypic methods using antisera to the sequencing of the *emm* gene notably the sequence encoding the N-

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terminal hypervariable region (Beall et al., 1996). Among the >250 *emm* types recognized to date, there are over 1900 distinct allelic forms (*emm* subtypes) of the *emm* type-specific region (Jespersen et al., 2020).

Additional typing methods based on M proteins have emerged, wherein the allocated types can be inferred directly from the *emm* types at ease (Baroux et al., 2014; Sanderson-Smith et al., 2014; Seale et al., 2016; Shulman et al., 2014; Smeesters et al., 2017). For instance, the *emm* pattern-based technique stratifies the isolates into three main groupings (A-C, D, E) based on the COOH-terminal peptidoglycan domain of the *emm* and flanking *emm*-like genes (*mrp*, *enn*) and the arrangement of these genes on the chromosome (Bessen et al., 2018; Frost et al., 2018). To date, the *emm* pattern genotype has been ascertained for 170 of the recognized *emm* types (Bessen et al., 2018). Another method is the *emm* cluster typing that distinguishes among >200 *emm* types 48 discernable *emm* clusters grouping closely related *emm* types based on the phylogeny of the entire surface-exposed portion of M proteins and also on their ability to bind six human serum proteins (Sanderson-Smith et al., 2014).

With regards to the treatment of GAS diseases, β-lactam especially penicillin remains the first antibiotic of choice for both noninvasive and invasive GAS infections (Shulman et al., 2012). Macrolides or lincomycin are the most notable alternatives in penicillin-allergic patients, and can also be used together with β-lactam in severe cases. In contrast to the ongoing susceptibility to penicillin, the resistance of GAS toward macrolides has emerged after <2 decades from the discovery of erythromycin (Kaplan and Cornaglia, 2005), with two essential macrolide resistance mechanisms associated with distinct phenotypes. Resistance, caused by the methylation of the ribosomal target of the antibiotics, leads to cross-resistance to macrolides, lincosamides, and streptogramins B, the so-called MLSb phenotype. This phenotype, which can be constitutive (cMLSb) or inducible (iMLSb), is caused by a variety of rRNA methylases encoded by *erm* genes as *ermB* genes, and *ermTR* genes (a subclass of the *ermA*) (Cattoir, 2016). The acquisition of active efflux, commonly encoded by *mefA* and infrequently by *mefE* along with *msrD*, is usually associated with M phenotype defined as resistance to 14- and 15- membered lactone ring macrolides, but not to 16-membered macrolides, lincosamides, or to streptogramin B antibiotics (Iannelli et al., 2018; Rafei et al., 2020a; Silva-Costa et al., 2015a; Tatsuno et al., 2018). Other macrolide resistance mechanisms have rarely been defined, such as mutations in the ribosomal target site either in the domain V of 23S rRNA or in the ribosomal proteins L4 and L22 (Bingen et al., 2002; Del Grosso et al., 2016).

Globally, there are large spatial asymmetries in the prevalence of macrolide resistance in GAS, ranging from as low as 2% in Europe to as high as 90% in China (Rafei et al., 2020a). At the temporal scale, whilst many countries like Belgium, Portugal, Greece, Spain, Taiwan, and Korea witnessed a decline in the macrolide resistance rate sometimes even without a concomitant reduction in drug consumption (Choi et al., 2015; Grivea et al., 2020; Huang et al., 2014; Montes et al., 2014; Silva-Costa et al., 2015b; Van Heirstraeten et al., 2012), others like Finland, and Serbia noticed an increase (Opavski et al., 2015; Smit et al., 2015). Such changes in the resistance rate had been tied in many instances to the turnovers of the predominant resistant clones (Smit et al., 2015). Besides, some epidemiological studies have also noted associations between *emm* types and macrolide resistance phenotypes and/or genotypes as between *ermB* and *emm28* (Ayer et al., 2007; Robinson et al., 2006; Silva-Costa et al., 2015a), leading some authors to suggest the potential usefulness of *emm* typing to infer antibiotic resistance (Metzgar et al., 2009). However, these local observations need to be validated on a global scale.

Although many eloquent reviews classified *emm* types according to regions, clinical specimens (invasive, noninvasive), and periods (Gherardi et al., 2018; Rafei et al., 2020a; Steer et al., 2009), data on the global distribution of *emm* types according to resistance phenotypes and genotypes are scant and need to be updated owing to the epidemiological and/or evolutionary dynamic nature of GAS (Silva-Costa et al., 2015a). For this, the present aims to unravel the identity of the most common *emm* types involved in macrolide resistance worldwide from a global collection of macrolide-resistant (MR) isolates with different spatiotemporal features. Gathering such global data on *emm* types of both MR- and macrolide-susceptible (MS) isolates can serve as baseline information to access the theoretical coverage of the proposed 30-valent *emm*-based vaccine (StreptAnova), and its performance if introduced into practice (Dale et al., 2011; Pastural et al., 2020). Also, the present intends to evidence the presence of any potential associations between specific *emm* types, patterns, or clusters with macrolide resistance either prevalence, phenotype (cMLSb and iMLSb) or genotypes (*mefA*, *ermA*, and *ermB*).

2. Methodology

2.1. Search strategy and study selection criteria

This review extracts from studies aimed to disclose the epidemiology of GAS in different countries over the world, data regarding the *emm* types involved in macrolide resistance regardless of their invasiveness along with their associated macrolide resistance phenotypes and genotypes. To limit analysis on relevant resources published in the last two decades, searches were done following the PRISMA methodology (Fig. 1) in PubMed and ScienceDirect using the term "(*S. pyogenes* OR group A *Streptococcus*) AND (macrolide OR erythromycin)". The search retrieved nearly 900 papers published between January 2000 and August 2020. Then, the articles written in English or French were individually reviewed by two authors RR and RI. All suitable studies held at either national, (mono, or multi) regional or monocentric studies in a country regardless of the isolates' source infection (invasive, noninvasive, or carriage) were examined if they had no overlapping investigated period from the same region. Papers analyzing isolates collected before the year 2000 or having a hybrid isolate collection before and after 2000 were excluded, except if they mentioned the MR-*emm* types isolated since 2000. Studies showing monocentric or regional outbreaks without evidence of multiclonality by typing techniques (pulsed field gel electrophoresis or Whole Genome Sequencing) or those analyzing one epidemic clone were precluded. Studies were defined as appropriate for analysis when MR and MS *emm* types could be extracted easily. Thus, articles profiling only the *emm* types for MR isolates not together with MS isolates were excluded. Considering that a large number of studies did not list all MR *emm* types and binned the less prevalent ones as others, those studies are enclosed but isolates with *emm* types denoted as others are not analyzed. Based on inclusion and exclusion criteria, we kept for analysis 53 articles distributed over 23 countries. The isolates with ambiguous *emm* types corresponding to species other than GAS (as *Streptococcus dysgalactiae*) are excluded from the studies. For articles stating the *emm* subtypes, only the *emm* types were garnered. In order to investigate the presence of significant linkages between some *emm* types and macrolide resistance, the *emm* types for MS isolates were also included. Of note, papers not meeting the inclusion criteria are discussed if containing relevant information.

For earlier studies carrying out M serotyping, *emm* types are deduced from serotypes using the published data (Facklam et al., 1999, 2002). Moreover, the *emm* patterns and clusters are deduced from *emm* types following the US Centers for Disease Control and Prevention (CDC) when applicable. The *emm* types designed as sequence types (ST) in the articles were converted into their numeric designation if available in CDC (CDC, n.d.). The 30-valent vaccine coverage for MR isolates was defined by the proportion of isolates covered by the vaccine *emm* types.

Excel sheet was created to record the country, the period (years) of completion of data collection, the geographic area involved (monocentric, mono or multi-regional, or a nationwide survey), the studies according to the continent (Europe, Asia, Africa, North America, and South America), the source of data (carriage, noninvasive, invasive or mix), the MR and MS *emm* types for each included article. For each *emm*

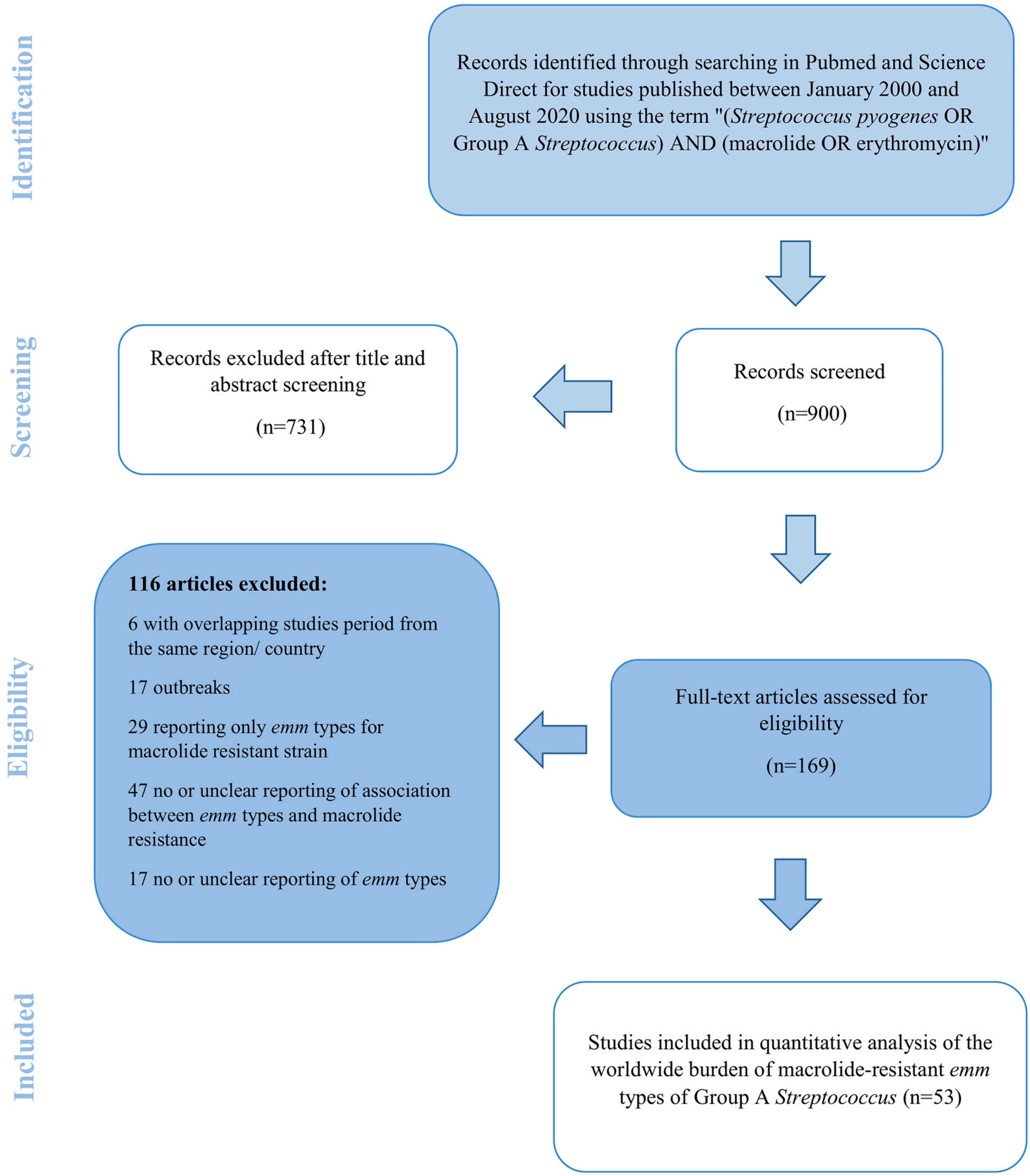

Fig. 1. Flow diagram presenting the followed PRISMA methodology for the selection and evaluation process of the screened papers.

type, the number of MR isolates belonging to this type from all studies was summed up. The same was held for MS isolates. Finally, the total number of both MR and MS isolates, for which the *emm* types are well defined in the articles, was also calculated. As studies doing sequencing for 23S rRNA and ribosomal proteins-encoding genes are very limited in number (Green et al., 2006; Richter et al., 2005), the analysis was restricted to the three macrolide resistance genes (*ermA, ermB,* and *mefA/E* genes). The results of subtyping the *ermA* and *mefA* gene from the analysis were omitted from the analysis, given that few articles are detailing the prevalence of the *ermA* subtypes (*ermT* and *ermTR*), as well as the subclass of *mefA* (*mefA* or *mefE*).

Statistical analyses were performed with GraphPad Prism 6.0 software (GraphPad Software, Inc., CA, USA). Univariate analyses of categorical variables are done using Fisher's exact test or chi-squared test. The results are expressed in terms of (odds ratios (OR); 95% confidence intervals (CIs); *p*-values). All the statistical tests are bilateral with a risk of type I error of 5%. The results of statistical analysis are presented in Tables 1 to 5 in the Supplementary file.

3. Results and discussion

3.1. Data extraction and analysis

Table 1 describes the characteristics of the 53 studies included in our analysis. As two articles from Tunisia tackled the same isolates collected from the same spatiotemporal frame, their data are merged and they

Table 1
Distribution of 53 studies according to the study year, the geographical scale, continent, and the analyzed specimens.

Study characteristics	Total* nb of isolates (% of resistant isolates)	Number of studies (%)	References
The period (years) of completion of data collection			
2000	195 (65%)	1 (1.89%)	(Dicuonzo et al., 2002)
2002	1123 (33%)	5 (9.43%)	(Chen et al., 2007; Kim and Lee, 2004; Kim and Yong Lee, 2004; Lorino et al., 2006; Yan et al., 2003)
2003	3031 (4%)	3 (5.66%)	(Eisner et al., 2006; McGregor and Spratt, 2005; Tanz et al., 2004)
2004	921 (8%)	4 (7.55%)	(Hotomi et al., 2009; Koh et al., 2008; Luca-Harari et al., 2008; Smeesters et al., 2010)
2005	643 (23%)	4 (7.55%)	(Creti et al., 2007; Krucsó et al., 2007; Stathi et al., 2008; Tanz et al., 2006)
2006	1280 (16%)	4 (7.55%)	(Hraoui et al., 2011a, 2011b; Jaggi et al., 2007; Michos et al., 2009; Wajima et al., 2008)
2007	396 (3%)	2 (3.77%)	(Meisal et al., 2010; Mijac et al., 2010)
2008	625 (83%)	2 (3.77%)	(Dundar et al., 2010; Liang et al., 2012)
2009	1229 (15%)	5 (9.43%)	(Bahnan et al., 2011; Friães et al., 2013; Koh and Kim, 2010; Malli et al., 2010; Pato et al., 2018)
2010	1435 (14%)	3 (5.66%)	(Huang et al., 2014; Plainvert et al., 2012; Shivekar and Menon, 2015)
2011	273 (12%)	2 (3.77%)	(Karaky et al., 2014; Ray et al., 2016)
2012	1065 (53%)	4 (7.55%)	(Arêas et al., 2014; Ikebe et al., 2015; Wajima et al., 2014, 2013)
2013	1608 (21%)	3 (5.66%)	(Gherardi et al., 2015; Michos et al., 2016; Olivieri et al., 2015)
2014	46 (26%)	1 (1.89%)	(Bocking et al., 2017)
2015	3452 (8%)	4 (7.55%)	(Chochua et al., 2017; Friães et al., 2019; Meehan et al., 2018; Park et al., 2017)
2016	233 (57%)	2 (3.77%)	(Lu et al., 2017; Sánchez-Encinales et al., 2019)
2017	1596 (9%)	3 (5.66%)	(Grivea et al., 2020; Kim et al., 2019; Sanson et al., 2019)
2018	393 (33%)	1 (1.89%)	(Ubukata et al., 2020)
total	19,544 (18%)	53	
The studies according to the involved geographical scale			
monocentric	4038 (19%)	17 (32.08%)	(Arêas et al., 2014; Bahnan et al., 2011; Bocking et al., 2017; Dicuonzo et al., 2002; Dundar et al., 2010; Eisner et al., 2006; Hraoui et al., 2011a, 2011b; Jaggi et al., 2007; Karaky et al., 2014; Kim and Yong Lee, 2004; McGregor and Spratt, 2005; Michos et al., 2016, 2009; Olivieri et al., 2015; Sanson et al., 2019; Shivekar and Menon, 2015; Yan et al., 2003)
mono-regional	3611 (17%)	10 (18.87%)	(Chen et al., 2007; Gherardi et al., 2015; Grivea et al., 2020; Kim and Lee, 2004; Koh and Kim, 2010; Koh et al., 2008; Lorino et al., 2006; Malli et al., 2010; Park et al., 2017; Ray et al., 2016)
multi-regional	4497 (21%)	7 (13.21%)	(Hotomi et al., 2009; Kim et al., 2019; Liang et al., 2012; Lu et al., 2017; Sánchez-Encinales et al., 2019; Tanz et al., 2006, 2004)
nationwide	7398 (18%)	19 (35.85%)	(Chochua et al., 2017; Creti et al., 2007; Friães et al., 2019, 2013; Huang et al., 2014; Ikebe et al., 2015; Krucsó et al., 2007; Luca-Harari et al., 2008; Meehan et al., 2018; Meisal et al., 2010; Mijac et al., 2010; Pato et al., 2018; Plainvert et al., 2012; Smeesters et al., 2010; Stathi et al., 2008; Ubukata et al., 2020; Wajima et al., 2014, 2013, 2008)
The studies according to the continent and country			
Europe			
Portugal	864 (7%)	3 (5.66%)	(Friães et al., 2019, 2013; Pato et al., 2018)
Spain	93 (2%)	1 (1.89%)	(Sánchez-Encinales et al., 2019)
Greece	3033 (20%)	5 (9.43%)	(Grivea et al., 2020; Malli et al., 2010; Michos et al., 2016, 2009; Stathi et al., 2008)
France	1220 (7%)	1 (1.89%)	(Plainvert et al., 2012)
Italy	807 (34%)	5 (9.43%)	(Creti et al., 2007; Dicuonzo et al., 2002; Gherardi et al., 2015; Lorino et al., 2006; Olivieri et al., 2015)
Serbia	134 (1%)	1 (1.89%)	(Mijac et al., 2010)
Norway	262 (3%)	1 (1.89%)	(Meisal et al., 2010)
Austria	69 (3%)	1 (1.89%)	(Eisner et al., 2006)
Denmark	278 (3%)	1 (1.89%)	(Luca-Harari et al., 2008)
Hungary	26 (8%)	1 (1.89%)	(Krucsó et al., 2007)
United kingdom	121 (7%)	1 (1.89%)	(McGregor and Spratt, 2005)
Ireland	973 (5%)	1 (1.89%)	(Meehan et al., 2018)
Asia			
Lebanon	220 (18%)	2 (3.77%)	(Bahnan et al., 2011; Karaky et al., 2014)
Japan	2073 (38%)	6 (11.32%)	(Hotomi et al., 2009; Ikebe et al., 2015; Ubukata et al., 2020; Wajima et al., 2014, 2013, 2008)
Korea	1493 (11%)	6 (11.32%)	(Kim and Lee, 2004; Kim and Yong Lee, 2004; Kim et al., 2019; Koh and Kim, 2010; Koh et al., 2008; Park et al., 2017)
India	218 (19%)	2 (3.77%)	(Ray et al., 2016; Shivekar and Menon, 2015)
China	674 (94%)	2 (3.77%)	(Liang et al., 2012; Lu et al., 2017)
Taiwan	950 (30%)	3 (5.66%)	(Chen et al., 2007; Huang et al., 2014; Yan et al., 2003)
Turkey	91 (12%)	1 (1.89%)	(Dundar et al., 2010)
Africa			
Tunisia#	102 (5%)	1 (1.89%)	(Hraoui et al., 2011a, 2011b)

(continued on next page)

Table 1 (*continued*)

Study characteristics	Total* nb of isolates (% of resistant isolates)	Number of studies (%)	References
North America			
USA	5204 (7%)	4 (7.55%)	(Chochua et al., 2017; Jaggi et al., 2007; Sanson et al., 2019; Tanz et al., 2004)
Canada	475 (27%)	2 (3.77%)	(Bocking et al., 2017; Tanz et al., 2006)
South America			
Brazil	164 (9%)	2 (3.77%)	(Arêas et al., 2014; Smeesters et al., 2010)
The studies according to the type of the investigated specimens			
non-invasive	8878 (21%)	23 (43.40%)	(Arêas et al., 2014; Bahnan et al., 2011; Chen et al., 2007; Dicuonzo et al., 2002; Gherardi et al., 2015; Karaky et al., 2014; Kim and Lee, 2004; Kim and Yong Lee, 2004; Kim et al., 2019, p. 4; Koh and Kim, 2010; Koh et al., 2008; Liang et al., 2012; Lorino et al., 2006; Malli et al., 2010; Park et al., 2017; Pato et al., 2018, p. 3; Ray et al., 2016; Smeesters et al., 2010; Tanz et al., 2006, 2004; Ubukata et al., 2020; Wajima et al., 2014; Yan et al., 2003)
invasive	4803 (16%)	14 (26.42%)	(Bocking et al., 2017; Chochua et al., 2017; Creti et al., 2007; Friães et al., 2019, 2013; Ikebe et al., 2015; Jaggi et al., 2007; Luca-Harari et al., 2008; Meisal et al., 2010; Plainvert et al., 2012; Sánchez-Encinales et al., 2019; Shivekar and Menon, 2015; Stathi et al., 2008, p. 1; Wajima et al., 2013)
mix	5863 (16%)	10 (30.19%)	(Dundar et al., 2010; Eisner et al., 2006; Grivea et al., 2020; Hotomi et al., 2009; Hraoui et al., 2011a, 2011b; Huang et al., 2014; Krucsó et al., 2007; Lu et al., 2017; McGregor and Spratt, 2005; Meehan et al., 2018; Michos et al., 2016, 2009; Mijac et al., 2010; Olivieri et al., 2015; Sanson et al., 2019; Wajima et al., 2008)

Mix: a combination of invasive and non-invasive isolates.
When calculating the percentage of resistant isolates, the denominator is considered the total of isolates of a given row, and the numerator is the number of resistant isolates in that row.

In Tunisia: the references (Hraoui et al., 2011a, 2011b) are merged into one study.

* total includes resistant and susceptible isolates.

were regarded as one article (Hraoui et al., 2011a, 2011b); the total number of enclosed papers is, thereby, set as 53 investigating 19,544 isolates and being originated from 23 countries mostly European ones (7880 isolates), then Asian (5719 isolates), North American (5679 isolates), African (102 isolates), and South American ones (164 isolates).

Approximately 32% of articles were regional either mono- (~19%) or multi-regional (~13%), while the proportion of nationwide and monocentric studies was ~36% and ~ 32% respectively. Regarding the type of sample, the majority of studies (~43%) investigated the epidemiology of noninvasive GAS isolates (Table 1).

3.1.1. *emm* patterns

Although the *emm* pattern E prevailed in all GAS isolates and constitutes ~49% of 15,951 MS isolates, it was more significantly associated with macrolide resistance (1.22; [1.13–1.31]; <0.0001) (Supplementary file, Table 1). Noteworthy, the *emm* pattern served as a genotypic marker for the preferred tissue tropism of GAS wherein pattern A-C strains are strongly associated with the throat and so-called "throat specialists", pattern D strains are denoted as "skin specialist", and pattern E strains are obtained from both throat and skin and called generalists (Bessen et al., 2018). The herein slight dominance of pattern E over pattern A-C regardless of the macrolide resistance status may be referred to as the heterogeneity of the infection source among the investigated isolates. The higher frequency of antimicrobial resistance in pattern E isolates was explained by their more readiness to acquire mobile genetic elements due to unique gene content (e.g. serum opacity factor, SOF) compared to pattern A-C strains (Sanson et al., 2019). Notably, *emm* patterns (A-C (0.87; [0.81–0.94]; 0.0003) and D (0.43; [0.31–0.58]; <0.0001) were significantly associated with macrolide susceptibility as revealed else (Rafei et al., 2020b).

3.1.2. *emm* clusters

emm clusters showed more amenability to surveil the trends of GAS infections than *emm* types owing to their stability and their limited number responsible for disease burden (Baroux et al., 2014). Nevertheless, the caveat restricting such a wide application in GAS surveillance is the existence of ~30% of *emm* types awaiting their assignment to *emm* clusters and patterns (Bessen et al., 2018).

A total of 12 well-defined *emm* clusters have been identified among MR *emm* types, where E4 (25.33%), A-C4 (21.26%), A-C3 (20.43%), E1 (13.97%), and E6 (9.88%) were the five most common clusters accounting for ~90% of total isolates. Whereas, MS isolates belonged to 15 well-defined *emm* clusters with slight variations regarding the prevalence and the type of dominant *emm* clusters; the four most common clusters were E4 (25.63%), A-C3 (20.83%), A-C4 (13.35%), and E1 (11.28%). Taken together that *emm* clustering epidemiology varies between regions, the predominance of E4 in both groups (MS and MR) cannot be attributed solely to its success but also to the herein abundance of the USA and Europe isolates as E4 prevailed among *emm* clusters in such landscapes (Muhtarova et al., 2019; Shulman et al., 2014). Intriguingly, A-C4 (1.75; [1.60–1.92 < 0.0001), E1 (1.55; [1.40–1.72]; <0.0001), E6 (1.70; [1.50–1.93]; <0.0001), and E2 (2.85; [2.22–3.67]; <0.0001) were significantly associated with macrolide resistance, and A-C5 (0.09; [0.06–0.14]; <0.0001), E3 (0.36; [0.29–0.45]; <0.0001), D4 (0.53; [0.35–0.80]; <0.0001) and singletons-Y (0.27; [0.21–0.34]; <0.0001) with macrolide susceptibility. Such associations of *emm* clusters reflect potential linkages between their corresponding *emm* members and macrolide resistance or susceptibility. However, some caution should be exhibited when interpreting these data. For example, the prevalence of A-C4 in MR isolates may be due to the over-representation of noninvasive isolates in this collection and the known linkage between this cluster and non-invasiveness (Chiang-Ni et al., 2016). E6 strains are denoted as "super-specialist" strains owing to their ability to shift the modes of transmission and GAS disease courses along with a hybrid virulence factor combination (Bessen et al., 2018). A systematic review and meta-analysis evidenced the preponderance of E6 over other *emm* clusters in Africa (Salie et al., 2020). Subsequently, such a high frequency of macrolide resistance in the E6 cluster is an alarming issue and needs ongoing surveillance.

3.1.3. *emm* types

MR isolates belonged to 70 different *emm* types with the first 10 dominant ones accounting for >88% of the total 3593 isolates: *emm12* (21.26%), *emm1* (20.40%), *emm4* (13.05%), *emm*28 (10.52%), *emm77* (7.18%), *emm75* (5.01%), *emm11* (3.84%), *emm22* (3.45%), *emm89*

(2.28%), and *emm92* (1.78%) (Supplementary file, Table 1). Despite the prevalence of some *emm* types, only *emm12* (1.76; [1.60–1.93]; <0.0001), *emm4* (1.22; [1.10–1.36]; 0.0003), *emm28* (1.20; [1.06–1.35]; 0.0034), *emm77* (2.97; [2.53–3.49]; <0.0001), *emm75* (1.64; [1.38–1.95]; <0.0001), *emm11* (2.84; [2.29–3.53]; <0.0001), *emm22* (2.00; [1.61–2.48]; <0.0001), *emm92* (17.0; [9.95–29.05]; <0.0001), *emm58* (3.12; [2.05–4.76]; <0.0001), *emm60* (18.47; [8.53–40.03]; <0.0001), *emm94* (3.71; [1.87–7.37]; <0.0001), *emm63* (4.45; [2.12–9.35]; <0.0001), and *emm114* (8.01; [2.68–23.91]; <0.0001) encompassed significantly more MR isolates. *emm1* (20.51%) was the dominant *emm* type in MS isolates, followed by *emm12* (13.33%), *emm4* (10.95%), *emm89* (9.44%), *emm28* (8.95%), *emm3* (6.78%), and *emm6* (5.27%), where these seven prevalent *emm* types accounted for approximately 75% of the total 15,951 isolates (Supplementary file, Table 1). Markedly, only the *emm89* (0.22; [0.18–0.28]; <0.0001), *emm3* (0.09; [0.06–0.14]; <0.0001), *emm6* (0.17; [0.12–0.24]; <0.0001), *emm2* (0.43; [0.31–0.60]; <0.0001), *emm44* (0.33; [0.21–0.51]; <0.0001), *emm82* (0.05; [0.01–0.20]; <0.0001), *emm87* (0.08; [0.02–0.24]; <0.0001), *emm118* (0.06; [0.02–0.26]; <0.0001), *emm5* (0.13; [0.05–0.36]; <0.0001), *emm49* (0.33; [0.15–0.70]; <0.0001), *emm81 (0.02; [0.001–0.38]; <0.0001)*, *emm59* (0.04; [0.002–0.62]; 0.0003), *emm227* (0.09; [0.01–0.68]; 0.0034), and *emm78* (0.06; [0.003–0.91]; 0.003) are significantly less resistant to erythromycin.

3.1.4. Phenotype and genotype of MRGAS

Among the 53 included articles, only 25 articles dissected the phenotype of MR isolates. Of 1002 MR isolates analyzed phenotypically, M phenotype and cMLSb were the dominant macrolide resistance phenotypes representing each 40.82% of MR isolates, followed by iMLSb (18.36%) (Supplementary file, Table 2). Besides phenotypic analysis, 33 out of 53 articles deciphered the genetic mechanisms behind the macrolide resistance giving a total of 2644 isolates. The results mirrored those obtained with the analysis of macrolide resistance phenotype where *mefA/E* and *ermB* genes were consistently responsible for about 39.71% and 39.07% of MRGAS isolates respectively, followed by *ermA* accounting for 19.7% of MRGAS (Supplementary file, Table 3). It is worth mentioning that the prevalence of macrolide resistance phenotypes fluctuate throughout the time, for instance, the M phenotype was dominant among the MRGAS during the 1990s in many European countries, but receded below the MLSb rates in the 2000s (Huang et al., 2014; Montes et al., 2014; Olivieri et al., 2015; Opavski et al., 2015). Notably, some phenotypes also maintained some degree of predominant stability in some countries as iMLSb in India and relatively in the USA (Abraham and Sistla, 2017; Chochua et al., 2017), cMLSb in France and China (Lu et al., 2017; Plainvert et al., 2012), and M phenotype in Japan and Lebanon (Ikebe et al., 2015; Rafei et al., 2020b).

Similarly, the distribution of *emm* types among the macrolide resistance phenotypes was almost consistent with that among macrolide resistance genotypes (Supplementary file, Table 2 and 3). The discrepancy can be ascribed by the fact that not all studies carried out a systematic genotypic and phenotypic analysis of *emm* types. Generally, the M phenotype was significantly more related to the MR-*emm4* (3.94; [2.70–5.75]; <0.0001), −*emm1* (4.30; [2.74–6.74]; <0.0001), −*emm75* (11.17; [6.25–19.97]; <0.0001), and -*emm2* (72.2; [4.37–1192]; <0.0001) lineages (Supplementary file, Table 4). Among MRGAS isolates, *mefA*/E genes are more present than *erm* genes in *emm1* (4.08; [3.40–4.91]; <0.0001), *emm4* (2.74; [2.11–3.54]; <0.0001), *emm75* (12.80; [7.88–20.80]; <0.0001), *emm2* (43.58; [6.49–349]; <0.0001), *emm3* (11.33; [2.59–49.64]; <0.0001), and *emm106* (4.13; [1.31–13.01]; 0.009).

Despite the high diversity of *emm* types within each macrolide resistance phenotype with 26 *emm* types being observed in cMLSb, 21 in M phenotype, and 16 in iMLSb, significant associations are extrapolated (Supplementary file, Table 2). The MR lineages significantly associated with cMLSb included the ones defined as *emm12* (8.40; [5.99–11.79]; <0.0001), *emm28* (5.74; [3.19–10.33];<0.0001), *emm11* (14.21; [5.02–40.25];<0.0001), whereas the MR *emm* types significantly connected to iMLSb were *emm77* (64.8; [29.04–144.6]; <0.0001), *emm89* (6.01; [3.20–11.29]; <0.0001), *emm94* (109.1; [6.40–1012]; <0.0001), and *emm58* (9.07; [1.65–49.88]; 0.0122) (Supplementary file, Table 4).

Among ERGAS isolates, *erm* genes were significantly more enriched in *emm12* (1.93; [1.55–2.40]; <0.0001), *emm28* (9.32; [5.99–14.51]; <0.0001), *emm77* (7.88; [4.89–12.71]; <0.0001), *emm11* (18.39; [6.75–50.09]; <0.0001), *emm22* (1.84; [1.18–2.85]; 0.006), *emm89* (3.83; [2.00–7.31]; <0.0001), *emm92* (74.24; [4.58–1204]; <0.0001), *emm58* (23.28; [3.18–170.3]; <0.0001). Comparing *ermA* and *ermB* among ERGAS isolates, *ermA* gene was significantly more represented than *ermB* in *emm77* (46.64; [25.12–86.61]; <0.0001), *emm4* (79.2; [24.97–251.0]; <0.0001), *emm92* (230.5; [14.20–3741]; <0.0001), *emm58* (16.48; [5.80–46.90]; <0.0001), *emm94* (49.74; [2.94–841.8]; <0.0001), *emm83* (7.89; [1.67–37.28]; 0.002), and *emm6* (5.90; [1.19–29.30]; 0.014), whereas *ermB* appeared significantly more than *ermA* in *emm12* (4.42; [3.16–6.18]; <0.0001), *emm1* (13.27; [7.18–24.53]; <0.0001), *emm28* (8.68; [5.31–14.19]; <0.0001), *emm11* (5.10; [2.72–9.60]; <0.0001), and *emm22* (2.12; [1.19–3.76]; 0.009) (Supplementary file, Table 4).

Asia contributed alone to 54.86% of MR isolates, Europe to 30.73%, North America to 13.89%, and Africa with Southern America to 0.53%. Regarding MS isolates, the majority originated from Europe (42.48%), then from North America (32.47%), Asia (23.5%), South America (0.94%), and Africa (0.61%) (Supplementary file, Table 5). Whilst ten *emm* types (*77*, *4*, *28*, *12*, *1*, *11*, *75*, *89*, *22*, and *2*) constituted 93.57% of the total MRGAS isolates in Europe, *emm77* (3.06; [2.59–3.60]; <0.0001), *emm28* (1.50; [1.36–1.65]; <0.0001), *emm6* (1.66 [1.12–2.45]; 0.0101) were significantly more overrepresented than outside European region (Supplementary file, Table 4). In Asia, six *emm* types (*1*, *12*, *4*, *28*, *75*, and *22*) accounted for 86.45% of MRGAS isolates, with a significant presence of *emm1* (1.65 [1.54–1.78]; <0.0001), *emm12* (1.47 [1.35–1.60]; <0.0001), and *emm58* (2.43 [1.61–3.68]; <0.0001) compared to outside Asia. Seven *emm* types (*4, 28, 92, 11, 12, 75, 77*) formed 88.42% of MRGAS isolates in North America, with a significant prevalence of *emm92* (14.2 [7.69–26.23]; <0.0001) in comparison to outside this continent.

3.2. 30-valent vaccine

Toward developing a GAS vaccine, one of the main active strategies is based on M protein with the 30-valent vaccine being a potential candidate. The 30-valent vaccine, currently undergoing clinical trials, is formulated from N-terminal fragments of M protein from 30 *emm* types that prevailed in Europe and the USA as well as the N-terminal fragment of the Spa18 antigen (Dale et al., 2011; Frost et al., 2018; Vekemans et al., 2019). Although MR isolates belonged to 70 different *emm* types, the 30-valent vaccine covers ~95% of 3593 isolates belonging to *emm12, 1, 4, 28, 77, 75, 11, 22, 89, 92, 2, 58, 6, 18, 3, 44, 83, 114, 49, 73, 5, 87, 82, 118, 29,* and *19* of 30 covered *emm* types (Table 2). Remarkably, *emm14*, *emm24, emm78,* and *emm81* are the only vaccine *emm* types without any noticeable macrolide resistance throughout studies. Alarmingly, five *emm* types (*emm60*, *94*, *106, 63, and 9*) that accounted for ~2.5% of the total of MR isolates, are absent in the 30-valent vaccine formulation. However, growing evidence indicates that the 30-valent vaccine does not only elicit specific immunity against vaccine *emm* types but also cross-reactive immunity against non-vaccine *emm* types likely present within the same clusters (Dale et al., 2013; Frost et al., 2017). Adding the *emm* types with positive or equivocal cross-opsonization status raises the vaccine coverage to ~98%, whereas incorporating all the vaccine *emm* clusters increases the coverage to 99.28%, highlighting thus the potential broad coverage of this vaccine (Table 2).

Table 2
Distribution of macrolide-resistant isolates according to 30 valent vaccine *emm* clusters and vaccine protection categories.

	Vaccine *emm* types (nb of isolates)	*emm* types with positive or equivocal cross-opsonization (nb of isolates)	*emm* types with negative cross-opsonization (nb of isolates)	*emm* types with unknown cross-opsonization (nb of isolates)	Total
Vaccine *emm* clusters					
A-C3	1 (733)			227 (1)	734
A-C4	12 (764)				764
A-C5	3 (24)				24
E1	4 (469), 78 (0)	60 (33)			502
E2	92 (64)	68 (1), 76 (12)		90 (1), 104 (4), 106 (15), 110 (3), 117 (1)	101
E3	44 (21), 49 (7), 58 (37), 82 (2), 87 (3), 118 (2)	9 (12), 79 (1), 183 (1)		113 (2)	88
E4	2 (38), 22 (124), 28 (378), 73 (7), 77 (258), 89 (82), 114 (9)	8 (4), 102 (7)	124 (1)	169 (2)	910
E6	11 (138), 75 (180), 81 (0)	42 (1), 48 (1), 63 (14), 65 (1), 85 (3), 94 (15)		99 (2)	355
D4	83 (10)	64 (1)	80 (7)	41 (1), 101 (1), 108 (1), 223 (3), 225 (1)	25
Clade Y	5 (4), 6 (33), 14 (0), 18 (24), 19 (1), 24 (0), 29 (2)				64
Total	**3414**	**107**	**8**	**38**	**3567**
Non Vaccine *emm* clusters					
A-C1				46 (1)	1
D2		71 (2), 100 (1)			
D5		97 (4)			4
Outliers		95 (5)			5
Singletons			17 (1)	57 (2)	3
Unclassified				st815 (4), 132 (1), 141 (1), 147 (1), 204 (2), 212 (1)	10
Total		**12**	**1**	**13**	**26**

Emm types present in the 30-valent vaccine formulation (*1, 2, 3.1, 4, 5.14, 6.4, 11, 12, 14.3, 18, 19, 22, 24, 28, 29, 44, 49, 58, 73, 75, 77, 78, 81, 82, 83.1, 87, 89, 92, 114 and 118*) are denoted as vaccine *emm* types. Non-vaccine *emm* types that were killed more than 50% in cross-opsonization in one or both cross-opsonization studies are categorized respectively as equivocal or positive.
vaccine *emm* types that were killed less than 50% in the cross-opsonization studies were classed as “cross-opsonization-negative”.
Non-cognate vaccine *emm* types that were untested in the cross opsonization studies were classed within “*emm* types with unknown cross-opsonization”.
References are (Dale et al., 2013; Frost et al., 2017; Giffard et al., 2019; Salie et al., 2020)

3.3. Insights into the molecular epidemiology of macrolide-resistant emm types

Here, we described and recapped thoroughly the peculiar epidemiological features of the ten most dominant MR *emm* types (*emm12*, *1*, *4*, *28*, *77*, *75*, *11*, *22*, *89*, *92*), and we shed light on the significant associations obtained through the statistical analysis.

3.3.1. emm12

This type was significantly associated with *ermB* and cMLSb and was more represented in Asia (Supplementary file, Table 4). During the 2011 outbreak of scarlet fever in Hong-Kong and Mailand, China, *emm12* was the main prevailing *emm* type, mostly driven by three distinct *emm12* lineages. In addition to *ssa*-carrying prophage (ΦHKU.vir), the acquisition of multi-drug resistance to macrolides (*ermB*) and tetracyclines (*tetM*) encoded by integrative and conjugative elements (ICE) has been hypothesized to play a major role in this resurgence of scarlet fever (Davies et al., 2015; You et al., 2018). Among the MR *emm12* strains, ST36 was the most prevalent clone, but other ST36 variants could thrive as ST467 in Japan (Tanaka et al., 2016). *emm12* was significantly associated with macrolide resistance in many countries like Spain (Montes et al., 2014), Taiwan (Chuang et al., 2015), and Japan (Hotomi et al., 2009). In Korea, the dramatic reduction of *ermB-emm12* from 28% in 2002 to 3.4% in 2009 paralleled the decrease of macrolide resistance from 44.8% to 4.6% in that period (Koh and Kim, 2010). However, the figure was different for *mefA-emm12*, wherein the progressive decline of *ermB-emm11* and *ermB-emm28*, and the initial increase of *mefA-emm12*, and *mefA-emm4* concurred with the drop of macrolide resistance from 11.7% in 2005 to 2.8% in 2012 in northern Spain (Montes et al., 2014). While in some countries almost *emm12* strains expressed one single macrolide resistance phenotype, many clones were simultaneously circulating in others. For example, in China, *emm12* ranked mostly first among MR *emm* types quintessentially carrying the *ermB* (Chang et al., 2010; Liang et al., 2012). In Japan, while *mefA-emm12* and *ermB-emm12* concomitantly circulated, high macrolide resistance mediated by the *ermB* gene was mainly found in *emm12* and *emm28* (Ikebe et al., 2015; Wajima et al., 2014). Regarding the USA, despite being a prevalent clone, the *mefA*-, *ermA*-, and *ermB-emm12* were reported with different percentages (Chochua et al., 2017; Richter et al., 2005). *mefA-emm12* prevailed in Ireland, Iceland, Spain, Belgium, Germany, and Portugal (Meehan et al., 2018; Montes et al., 2014; Pires et al., 2012; Reinert et al., 2004, 2003; Silva-Costa et al., 2015b; Southon et al., 2020; Van Heirstraeten et al., 2012). Of additional interest is the multidrug resistance proclivity in MR *emm12* isolates notably for tetracycline (Gherardi et al., 2015; Opavski et al., 2015). Quite pronounced is the identification of *emm12* isolates in Ireland resistant to macrolides (conferred by *mefA*) along with a decreased beta-lactam susceptibility (conferred by a single amino acid substitution Met593Thr in penicillin-binding protein (PBP2X)) (Southon et al., 2020).

3.3.2. emm1

Since 1980, *emm1* type has been emerging and was intriguingly correlated with the striking resurgence of severe GAS infections. The evolutionary pathways behind the success of the contemporary pandemic strain (the so-called M1T1) can be simplified by three separated events: acquisition of a prophage encoding DNase enzyme (Sda1, also called SdaD2), acquisition of SpeA2 superantigen, and recombination of a 36 kb of *emm12* region with increased production of NAD + -glycohydrolase (NAG) and streptolysin O (SLO) (Nasser et al., 2014). The main ST is ST28 but other ST are also described as ST661, 618, 647 (Silva-Costa et al., 2015b; Wajima et al., 2014, 2013). During the last two decades, *emm1* remains the leading invasive *emm* type in many countries such as some European ones "Norway, Portugal, and Greece" (Friães et al., 2019; Grivea et al., 2020; Luca-Harari et al., 2009; Naseer et al., 2016), as well as the USA (Chochua et al., 2017), Japan (Wajima et al., 2008) and China (Chan et al., 2009). Generally, *emm1* isolates appeared to be MS in many countries like France, Greece, Spain, and Turkey (Dundar et al., 2010; Grivea et al., 2020; Montes et al., 2014; Plainvert et al., 2012), but no significant association is observed here (Supplementary file, Table 4). In Taiwan, the decline in macrolide resistance during 2002–2003 in the community coincided with the major shift of the endemic clones to *emm1* type (Lin et al., 2008). Alarmingly, upward trends of MR *emm1* strains were also recorded. While *emm1* was MS during 2006–2008 in a monocentric study in Japan, it exhibited a high resistance rate in 2011–2013 (87.8%) compared to *emm28* and *emm12* (Sakata, 2015). Since 2011, the sharp increase in the number of STSS (streptococcal toxic shock syndrome) in Japan mirrored the escalation in the number of *mefA-emm1* (Ikebe et al., 2015). When *emm1* becomes MR, M phenotype seems to be the major macrolide resistance mechanism with *mefA* prevalence compared to *erm* genes (Supplementary file, Table 4) (Creti et al., 2007; Tanaka et al., 2016; Van Heirstraeten et al., 2012; Wajima et al., 2013). This *mefA*-dominance can be explained by a great fitness and low cost where *mefA-emm1*, *ermB-emm28*, and *ermA-emm77* were found to have lower fitness costs by experimental studies (Van Heirstraeten et al., 2012). Strikingly, *ermB*-positive *emm1* isolates with a high level of macrolide and clindamycin resistance were progressively described (Friães et al., 2013; Liang et al., 2012; Plainvert et al., 2015), and were involved in scarlet fever in China, Taiwan, and the United Kingdom (Lamagni et al., 2018; Yan et al., 2003; You et al., 2013). These data call for close surveillance of such a successful *emm1* clone, particularly with the description of rapid bacterial evolution of *emm1* to new clones during an outbreak of invasive infections in Brazil (Fernandes et al., 2017).

3.3.3. emm4

Despite being accused of invasive infections, *emm4* revealed significant associations with noninvasive ones particularly those of respiratory origin (d'Humières et al., 2015; Eisner et al., 2006; Kim et al., 2019; Meehan et al., 2018; Tamayo et al., 2014; Wajima et al., 2008). It was also one of the leading causes of scarlet fever in Taiwan, the United Kingdom, and Korea (Park et al., 2017; Turner et al., 2016; Yan et al., 2003). Similar to *emm89*, *emm4* was acapsular, a phenotype showing a prompted adhesion to surfaces (Turner et al., 2015). Nowadays, *emm4* is drawing different trend patterns over the world either decreasing (like in Spain (Montes et al., 2014), Japan (Ubukata et al., 2020; Wajima et al., 2014), China (Feng et al., 2010), Taiwan (Huang et al., 2014)), or increasing (as in Korea (Kim et al., 2019; Koh and Kim, 2010), Italy (Creti et al., 2007)) ones. Concurrently, *emm4* was one of the leading MR isolates in countries as Portugal, Greece, Canada, Taiwan with significant linkages with macrolide resistance (Huang et al., 2014; Michos et al., 2016; Silva-Costa et al., 2012; Syrogiannopoulos et al., 2013; Tanz et al., 2006) as was revealed herein (Supplementary file, Table 4). MS *emm4* isolates prevailed in others like Spain, Turkey, and Korea wherein minor MR *emm4* sub-clones were isolated (Dundar et al., 2010; Koh and Kim, 2010; Montes et al., 2014). Moreover, changes can be even noticed in the same country; wherein the proportion of MR *emm4* isolates within *emm4* showed significant changes over time in Portugal, while the ratio of macrolide resistance within other *emm* types remained stable (Silva-Costa et al., 2012). Noteworthy, such fluctuations may be referred to as the antibiotic selection pressure and as the ongoing declining trend for M phenotype in some countries like Portugal (Friães et al., 2019). Intriguingly, MR *emm4* isolates tended to be mono-resistant in several countries and carrying essentially the *mefA* gene with M phenotype, consequently reflecting a high fitness for *mefA-emm4* (Supplementary file, Table 4). Regarding *emm4* genetic lineages, ST39 is the main one carrying essentially *mefA*, but recent associations with *ermTR* are also described in Italy and the USA (Chochua et al., 2017; Grivea et al., 2020). ST38 (Single locus variant of ST39) is the second prevalent *emm4* genetic lineage harboring either *mefA* (Takahashi et al., 2016; Wajima et al., 2014) or *ermA* (Chang et al., 2010) when being MR. In this line, large investigations are needed to conclude any potential associations between genetic lineage and resistant determinants.

3.3.4. emm28

In addition to the wide range of triggered infections, *emm28* showed a noticeable tropism for genital and perianal regions being significantly associated with postpartum infections (Luca-Harari et al., 2008; Plainvert et al., 2012). The vaginal tissue tropism is explained by the closeness of the surface protein (R protein) to the adhesin of group B streptococci (Chochua et al., 2017; Luca-Harari et al., 2008). Besides, *emm28* has been ranked among the main MR isolates in Europe, Japan, Korea, and Canada (Montes et al., 2014; Plainvert et al., 2012; Silva-Costa et al., 2012; Tanz et al., 2006; Wajima et al., 2014), wherein significant junctions with macrolide resistance were disclosed along with a high resistance rate (Grivea et al., 2020; Montes et al., 2014; Park et al., 2017; Plainvert et al., 2012; Silva-Costa et al., 2012; Tanz et al., 2006) (Supplementary file, Table 4). Moreover, *emm28* strains were significantly over-represented among *ermB*-positive MRGAS expressing usually cMLSb (Supplementary file, Table 4). Unlike the situation in Canada, MR *emm28* isolates were reported sporadically in the USA despite being one of the most common *emm* (Chochua et al., 2017; Tanz et al., 2006, 2004). While countries like Japan, France, and Spain have recorded increasing values of *emm28* associated with increases in gynaeco-obstetric infections or macrolide resistance (Ardanuy et al., 2010; Plainvert et al., 2012; Wajima et al., 2014, 2013), recent reports thereof outlined downtrends in *emm28* incidence (Montes et al., 2014; Plainvert et al., 2015; Ubukata et al., 2020). The genetic background of *emm28* showed homogeneity; wherein almost *emm28* belonged to ST52, along with the identification of its Double Locus variant (DLV) ST1117 with the *mefA* gene (Grivea et al., 2020). Multi-resistance is one of the peculiar characteristics of *emm28* (Pérez-Trallero et al., 2011; Ksia et al., 2017). Since 2000, an epidemic *emm28* clone has been standing out in Europe and beyond with main characteristics: cMLSb phenotype, *ermB* gene, and bacitracin resistance, thereby rising problems for laboratories that relied on bacitracin for GAS identification (Friães et al., 2019, 2013; Malhotra-Kumar et al., 2003; Mihaila-Amrouche et al., 2004; Montes et al., 2014; Perez-Trallero et al., 2004). Besides this clone, *emm28* strains expressing tetracycline resistance disseminated worldwide, thus a deeper investigation is required to verify their belonging (or not) to the same global lineage as well as their susceptibility to bacitracin as that revealed in Spain (Meehan et al., 2018; Montes et al., 2014; Pérez-Trallero et al., 2007; de Torres et al., 2011).

3.3.5. emm77

The prevalence of *emm77* either MS or MR differed widely between countries from being elevated in Europe (Michos et al., 2016; Syrogiannopoulos et al., 2013) (Supplementary file, Table 4) to negligible in Japan, China, and Taiwan (Hotomi et al., 2009; Huang et al., 2014; Lu et al., 2017; Wajima et al., 2013). Moreover, this prevalence looked to be unstable over time (Grivea et al., 2020; Syrogiannopoulos et al., 2013). For example, MR *emm77* disappeared completely between 2011 and 2012 in Serbia after ranking third among MRGAS isolates in 2008 with a percentage of 14.6%; a decline in macrolide resistance was, thereby, noticed (Gajic et al., 2018; Opavski et al., 2015). In Belgium, the steady rise of low-level resistant *ermA-emm77* proportions from 2006 onward is linked to the reduced use of antimicrobial agents (macrolide, lincosamides, streptogramin B, and tetracycline) below the critical threshold (0.62 value of packages/1000 inhabitants/day) (Van Heirstraeten et al., 2012). Although *emm77* was recovered mainly from MS isolates in some publications (Tanz et al., 2004; Montes et al., 2014), it was significantly associated with macrolide resistance in others (Grivea et al., 2020; Michos et al., 2016), as revealed herein (Supplementary file, Table 4). Besides, iMLSb and *ermA* are the major macrolide resistance phenotype and genotype respectively for *emm77* isolates (Supplementary file,

Table 4), stressing again the Belgian findings on the high fitness benefit of *ermA* in this type (Van Heirstraeten et al., 2012). Noteworthy, *ermB-emm77* are mainly isolated from the East-Asia (Koh et al., 2008; Lu et al., 2017; Wajima et al., 2013), and alarmingly even from healthy Korean elementary school children (Koh et al., 2008). Resistance to tetracycline with *tetO* as a resistant gene determinant is widely disseminated in *emm77* isolates either with or without macrolide co-resistance (Chochua et al., 2017; Dundar et al., 2010; Gherardi et al., 2015; McGregor and Spratt, 2005; Meehan et al., 2018; Opavski et al., 2015; Plainvert et al., 2012). Regarding genetic lineages, ST63 is the main one where *ermA-tetO/emm77* clone seems to ravage globally (Grivea et al., 2020; Lu et al., 2017; Meehan et al., 2018; Opavski et al., 2015). Otherwise, other STs were also identified but at a lesser and unsteady rate as *ermA-tetO/emm77*/ST369 in Norway, Italy (Palmieri et al., 2006), *emm77*/ST550 in Greece (Grivea et al., 2020), and *ermB-emm77*/ST347 and ST35 in Japan (Wajima et al., 2013). In the USA, the genetic diversity of *emm77* is considerable wherein three distinct ST were identified: ST63 with *tetO* and *ermTR* associations, ST399 with *tetM* and *ermT* or *ermB* associations, and ST133 with *tetM* associations (Chochua et al., 2017).

3.3.6. *emm75*

emm75 is a prevalent MR clone in North America, Serbia, and Japan with a high within-*emm75* type macrolide resistance (Gajic et al., 2018; Hotomi et al., 2009; Opavski et al., 2015; Sanson et al., 2019; Tanz et al., 2004). Moreover, *emm75* is widely overrepresented among the MRGAS with M-phenotype (Supplementary file, Table 4), but *ermB-emm75* isolates were also commonly described in China (Lu et al., 2017). Regarding genetic lineages, considerable diversity was observed in *emm75*. ST49 and ST150 (DLV of ST49) were the widespread lineages co-circulating sometimes together in the same country as in Japan, the USA, Spain (Chochua et al., 2017; Montes et al., 2014; Wajima et al., 2014). Besides, resistance to fluoroquinolones in *emm75* appears to be on the rise and perhaps replacing resistance to macrolide as stated in Norway (Meisal et al., 2010; Plainvert et al., 2012).

3.3.7. *emm11*

Even though that *emm11* is considered uncommon associated only with <5% of cases in invasive infections in Europe, and the USA (Martinaud et al., 2010), a marked association with macrolide resistance notably with cMLSb and *ermB* was widely observed as retrieved herein (Supplementary file, Table 4) (Chochua et al., 2017; Gherardi et al., 2015; Montes et al., 2014; Naseer et al., 2016; Plainvert et al., 2012; Silva-Costa et al., 2015b; Van Heirstraeten et al., 2012). *emm11* was ranked as among the three top MR *emm* types in many European countries (Gherardi et al., 2015; Meehan et al., 2018; Montes et al., 2014; Plainvert et al., 2012; Silva-Costa et al., 2015b). However, countries like Spain and Portugal are witnessing a decreasing trend of MR *emm11* after a noticeable increase (Friães et al., 2019; Montes et al., 2014; Silva-Costa et al., 2015b). In East Asia, MS *emm11* isolates were more common than resistant ones (Huang et al., 2014; Wajima et al., 2013). Most remarkable of this type is its propensity to be multi-resistant especially for tetracycline along with erythromycin and clindamycin (Meehan et al., 2018; Montes et al., 2014; Silva-Costa et al., 2015b). For example, in the USA, *emm11*, *75*, *77*, and *92* accounted for 72.7% of the strains resistant to any antimicrobial in the invasive group (Sanson et al., 2019). Furthermore, in Spain, nearly 80% of erythromycin- and tetracycline-resistant strains were of type *emm11* (Montes et al., 2014). As for lineages, MR *emm11* isolates were often homogenous genetically belonging essentially to ST403, but also, even to a lesser degree, to ST403 single locus variants (SLV) as ST20, ST21, ST562 (Chochua et al., 2017; Grivea et al., 2020; Montes et al., 2014; Sanson et al., 2019; Silva-Costa et al., 2015b; Wajima et al., 2013).

3.3.8. *emm22*

In addition to being ranked among the ten top common MR *emm* types, *emm22* showed significant associations with macrolide resistance in Taiwan, Greece, Portugal, and China (Supplementary file, Table 1 and 4) (Chan et al., 2009; Huang et al., 2014; Michos et al., 2016; Silva-Costa et al., 2012). These findings contrast Korean and American ones where *emm22* was commonly found with macrolide susceptibility (Chochua et al., 2017; Koh and Kim, 2010; Tanz et al., 2006). In Europe, MR *emm22* has not been considered currently a leading MR type and was witnessing decreasing numbers, even though it was ranked first among MRGAS in Portugal and Second in Belgium in the early 2000s (Friães et al., 2019; Malhotra-Kumar et al., 2005; Michos et al., 2016; Silva-Costa et al., 2006). Otherwise, in East Asia, MR *emm22* emerged in China (notably between 2005 and 2008), and Taiwan (after 2000, particularly from 2006 to 2010) (Chan et al., 2009; Huang et al., 2014). Generally, *ermB* was more enriched in MR *emm22* (Supplementary file, Table 4). Whilst circulating MR *emm22* strains were found almost homogenous in terms of their phenotypes and/or their genotypes as those present in Portugal, France, and Italy (*ermB-emm22*); Greece, and Norway (*ermA-emm22*); and Taiwan (*mefA-emm22*) (Dicuonzo et al., 2002; Huang et al., 2014; Littauer et al., 2006; Michos et al., 2016; Pires et al., 2012; Plainvert et al., 2012), others were retrieved heterogeneous where three distinct *emm22* clones (*ermA*-, *mefA*-, and *ermB-emm22*) co-circulated as in Brazil or Spain (Montes et al., 2014; de Torres et al., 2011). Besides, co-resistance to both tetracyclines and macrolides was frequently observed in *emm22* (Huang et al., 2014; Littauer et al., 2006; Naseer et al., 2016; Silva-Costa et al., 2015b). ST46 as genetic lineage prevailed globally, but unrelated STs have also been described (Silva-Costa et al., 2006).

3.3.9. *emm89*

Since 2000, this type has been increasingly reported in GAS infections in many countries worldwide; an increasing linked by in-depth genomic studies to clade shift from predecessors (clades 1, 2, and O) to a genetically distinct clone designated “clade 3” (Beres et al., 2017; Chochua et al., 2017; Friães et al., 2015; Grivea et al., 2020; Latronico et al., 2016; Meehan et al., 2018; Pato et al., 2018; Teatero et al., 2017; Turner et al., 2015). This last clade is characterized by its virulence and two marked genetic events: an upregulated *nga* operon (as described in the contemporary epidemic *emm1* clone), and the loss of *hasABC* gene region encoding the hyaluronic acid capsule (an unusual feature shared by *emm4* and *emm22* strains) (Turner et al., 2015; Zhu et al., 2015). In Finland, there is also a description for a virulent subclade D of *emm89* clade III with the highest 30-day estimated case-fatality rate among bacteremic cases (Latronico et al., 2016). ST101 appeared to be the main genetic background of the *emm89*-new clade, albeit SLVs of ST101 were also described hinting thus for ongoing diversification and possible increases in transmissibility or virulence of this lineage (Friães et al., 2015). Regarding macrolide resistance, *emm89* strains tended to be susceptible (Supplementary file, Table 1 and 4) (Dundar et al., 2010; Montes et al., 2014; Silva-Costa et al., 2012), although an upward trend for *emm89*-clade 3 was recorded in Greece (Grivea et al., 2020). Besides, MR *emm89* strains are almost described with heterogeneous resistance genes expressing primarily iMLSb phenotype (Supplementary file, Table 3 and 4). Of note, *ermB-emm89* clones are described as epidemic before 2000 (Creti et al., 2007). The paucity of antibiotic resistance among the *emm89* isolates (notably those belonging to clade 3) is explained by the absence of mobile genetic elements, which confer a vigorous selective advantage in the emanation of the epidemic clade (Beres et al., 2017). It is noteworthy to mention that many studies did not perform subtyping for *emm89* strains, hence the difficulty of assessing accurately the level of macrolide resistance of the emerging clade.

3.3.10. *emm92*

emm92 was essentially reported in the USA from invasive isolates, but also, even rarely, in India and Spain (Abraham and Sistla, 2017; Chochua et al., 2017; Montes et al., 2014; Richter et al., 2005), with *erm* (particularly *ermA*) being significantly associated with MR forms

(Supplementary file, Table 4). In the USA, *ermB-emm92* isolates present in the early 2000's studies are replaced in the last decade by *ermT-emm92*/ST82 (Chochua et al., 2017; Richter et al., 2005), wherein *ermT* was borne on a broad-host-range plasmid (pRW35), and responsible for iMLSb phenotype (Chochua et al., 2017; Sanson et al., 2019). Indeed, in-depth genomic studies in the USA demonstrated a highly clonal *emm92* showing an elevated frequency to be multi-resistant to antibiotics, including macrolide, tetracyclines, and aminoglycosides, thus suggesting a recent alarming emergence (Chochua et al., 2017; Sanson et al., 2019).

3.4. General considerations and limitations

This study reveals for the first time on a global collection the involvement of a small subset of *emm* types in the whole burden of macrolide resistance. Moreover, it depicts significant associations found between *emm* types and macrolide resistance phenotype and/or genotype. The non-random distribution of macrolide resistance, including the determinants thereof among *emm* types, could either indicate 1) the circulation of a restricted number of successful MRGAS clones in the population; or 2) the existence of ancestral *emm* types with stable antibiotic resistance signatures possibly in order to harness the power of such resistance determinants under strong selective antibiotic pressure; or even 3) the potential direct or indirect role of the M protein as barriers for horizontal genetic transfer (HGT) limiting thereby the transfer of macrolide resistance among GAS (Creti et al., 2005; Gherardi et al., 2015). Nevertheless, this last aspect of M protein remains speculative for HGT of transmissible macrolide resistance determinants; even that it has been recognized but still understood and debatable for prophages mediated-HGT carrying notably virulence factors (Creti et al., 2005; Vojtek et al., 2008). However, despite these associations, some MR *emm* types can be found with many phenotypes and/or genotypes hinting for independent acquisitions of macrolide resistance, local expansions, and active selection of resistance. Such subclones must be surveilled tightly for possible emergence. It is trustworthy to mention, that multiple factors can also affect these conclusions. First, *emm* types were spatiotemporally dynamic even inside the same country, such dynamicity could be explained in part by the acquired type-specific herd immunity, particularly when no changes of macrolide consumption can be noted (Montes et al., 2014). Second, the extent of antibiotic use can also favor the emergence of the fittest clones able to sprout in stressful conditions and the removal of less fit existing clones (Van Heirstraeten et al., 2012). Third, even though circulated *emm* types from the African and South American landscapes differed from the European and American ones and were far more diverse (Smeesters et al., 2006; Steer et al., 2009), the particular richness and diversity of MR *emm* types in Europe, Asia, and North America regions compared to other regions (supplementary file, Table 5) can be explained by the paucity of data especially from the African and Middle Eastern ones, and subsequent the under-coverage bias of the total population of MRGAS isolates. Fourth, studies from many countries as Lebanon are monocentric or regional ones with limited (or no) nationwide studies, which can obfuscate the real figure of MRGAS epidemiology. It is noteworthy to mention that although nationwide studies are of high importance, small-scale studies could also give an insightful snapshot to understand the circulated MR strains in a country and to look for potential linkages between *emm* types and resistance determinants. Fifth, many studies did not type all their GAS isolates or listed only prevalent MR *emm* types without detailing the minor ones, which can create some bias in our data, but not in the whole conclusions. Indeed, the aim of the present was not to build diametrically strongest significant statistical associations, but rather to provide insights into the global MRGAS epidemiology and verify previously encountered local relationships between phenotype and serotype but herein at a global scale. For this, the authors appeal to fully characterize and list their MRGAS isolates in terms of *emm*, phenotype, and genotype; more robust systematic reviews and meta-analysis can be, thereby, conducted. Sixth, our collection was heterogeneous in terms of demographic patients, and the invasiveness of the origin, which raises some difficulty to glean significant junctions. However, while some associations were revealed between macrolide resistance and either the origin of isolates (invasive and noninvasive) or the age of patients (younger or older) through literature, they were contradicting reflecting perhaps differences in the epidemiology of circulating GAS clones (Huang et al., 2014; Montes et al., 2014; Sanson et al., 2019; de Torres et al., 2011). Seventh, exploring the temporal context of macrolide resistance within the different geographical regions is utterly important to explain *emm* dynamicity in light of such spatiotemporal contexts. Nevertheless, the retained studies are insufficient to inspect such contexts as articles discussing only the macrolide resistance without profiling the *emm* types are excluded from the present analysis. We acknowledge that the temporal component may also confound our conclusions. We have, however, framed the selection of articles published within two decades and without overlapping periods if originated from the same country or region (to avoid having duplicate isolates). Eighth, increased vigilance must be paid to the potential drawn conclusions for the observed unique combinations between *emm* types and macrolide resistance status because they are based on retained articles according to our adopted criteria. Taken as an example the *emm33* identified in the present only in MS strains, it was described in Finland as MR carrying the *ermTR* and expressing cMLSb resistance phenotype but not included herein as it was involved in a local epidemic of skin and soft tissue infections with also invasive cases in Finland (Pesola et al., 2015). Therefore, even MS *emm* types can be evolved into resistant ones which contribute to outbreaks. Quite intriguing is the abundant description of multi-resistant *emm* clones for both macrolides and tetracyclines where tetracycline abuse in the human or animal sector has been suggested to drive the emergence of macrolide resistance (Chang et al., 2010; Friães et al., 2012; Silva-Costa et al., 2008). This convergent evolution can be tied to resistance genetic determinants as the transposons of the Tn*916* family carrying both *ermB* and *tetM*, integrative conjugative elements ICE*Sp2905* harboring both *ermTR* and *tetO*, or prophages ϕm46.1 where *mefA* was along with *tetO* (Cattoir, 2016). Lastly, while *emm* type remains a useful epidemiological marker for GAS, it is not considered based on WGS a suitable one for inferring evolutionary genotypes wherein very few of the genotypic clusters belonged to a single *emm* type (Jespersen et al., 2020). In the light of such global dis-concordance between *emm* and genotypic clusters, future investigations of larger datasets are paramount to figure out potential relationships between refined core genome clusters and macrolide resistance. Meanwhile, although genomic data are continuously trickling out from developed countries, their dearth from developing countries adds value for *emm* typing. Pending the systematic WGS integration in GAS surveillance, *emm* sequencing is seemingly a more amenable and affordable technique to be used worldwide along with assuring compatibility with developed countries adopting WGS as a surveillance GAS technique.

Regarding the 30-valent vaccine, even not covering all MR *emm* types (Castro and Dorfmueller, 2021; Davies et al., 2019), it protects against the most prevalent ones with potentially a high coverage rate if considering the vaccine *emm* clusters or the *emm* types with cross-opsonization status. Noting that the vaccine coverage rate against all GAS isolates regardless of their macrolide susceptibility varied between countries according to the type, frequency, and dynamicity of circulating clones (Rafei et al., 2020a).

4. Conclusion and perspectives

This study analyses a global set of extensively characterized MRGAS isolates from patients of diverse ages and clinical presentations over approximately two decades. Although macrolide resistance in GAS is highly variable in different countries, its within-GAS distribution seems not to be random. Significant associations were found between macrolide resistance and either *emm* pattern, cluster, and type, as well as between macrolide resistance phenotype with gene markers and *emm* type. While relationships are concluded between a continent and an *emm* type, they remain fragile due to the unfairly distributed studies among different countries. These primary findings urge the importance of comprehensive nationwide sustained surveillance of MR circulating clones especially in developing countries where data are limited and sampling bias is high particularly in landscapes battered by economic, sanitary, and humanitarian crises. Such data are seminal for refined meta-analysis to evidence associations between macrolide resistance frequency and both geo-temporal context and clones, to pinpoint any drift related to *emm* type or resistance gene determinants in a global context and refine continuously the vaccine formulations. Finally, taken together that macrolide resistance is not the sole factor drawing the epidemiology of GAS clones, other molecular determinants should be jointly pursued as the repertory of virulence encoding genes.

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Declaration of Competing Interest

None to declare.

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