

Rapid review of Global Strep A *emm* types

Taariq Salie, BSc (Hons), Mark E Engel, MPH, PhD

AFROStrep Research Initiative, Department of Medicine,
Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa.

DOI: 10.25375/uct.13056074

Overview

This study employed rigorous methods drawn from the scientific techniques and guidelines offered by the Cochrane Collaboration (1) and by reviews published previously (2, 3).

Search methods for the identification of studies

A comprehensive search strategy was developed in order to search electronic databases so as to maximize sensitivity (Table 1-Appendix I). The search strategies incorporated both free term text that are controlled to suit specific databases individually and Medical Subject Headings (MeSH) adapted to suit each individual database. A combination of terms relating to “*emm* typing”, “*emm* clusters”, “*emm*/M protein” and “Streptococcal diseases” were employed. The following electronic databases were searched: PubMed, Scopus and Google Scholar for grey literature. The search was not restricted to publication date or language; however, abstracts must be clearly written in English for the study to be considered). Published and unpublished data, such as grey literature including theses and conference proceedings, were also considered for inclusion.

Selection of studies for inclusion

Studies describing the prevalence of *emm* clusters or *emm*-types within a given population were included in the review. Participants were not discriminated by country of residence, clinical manifestation of Strep A or site of Strep A isolation. All laboratory-confirmed GAS isolates were molecularly characterized by the *emm* typing method as developed by Beall (4) and in alignment with the Centers for Disease Control and Prevention (5), to classify GAS according to sequence analysis of the 5' hypervariable region of the M protein gene.

Two reviewers independently applied the search strategy to the relevant databases; titles and abstracts were evaluated to exclude studies that did not describe the prevalence of GAS. Thereafter, full texts of the included titles and abstracts were retrieved and further evaluated against the inclusion criteria (Table S2-Appendix). Discrepancies, where found between reviewers, were discussed and an arbitrator (third reviewer) resolved any disagreements.

Quality assessment

The risk of bias assessment established by Hoy (6) and modified by Werfalli (3), was adapted in questions specific for use in this review. Using a quantitative scoring system, studies were characterized as being of a low, moderate or high risk of bias. A study with a low risk of bias is deemed to be of high-quality and a low-quality study is associated with a higher risk of bias. Assessing the risk of bias informs the evaluation of heterogeneity in the pooled analyses.

Overview of Results:

The literature search for articles were reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) Statement (7). Figure 1 details the search results with the retrieval of 1,394 articles for consideration from the respective electronic databases. After title and abstract screening, we excluded 1,107 articles, including those that were duplicates and required access. One-hundred seventy-nine articles required full-text evaluation in order to meet the predefined inclusion criteria. Finally, 117 articles met the inclusion criteria and were included into the review with details provided in *Table ## (Spreadsheet tab_ "Study details")*. A list of the excluded studies (n=62) with reasons are detailed in *Table ## (Spreadsheet tab_ "Excluded studies")*. The risk of bias assessment is portrayed in the *Table ## (Spreadsheet tab_ "Risk of bias")*.

Characteristics of included studies

The included articles (n=117) were published between 1998 and 2020 with an average sample size of ~651 (ranging between 24 and 9,557). The studies were conducted throughout the world as the current review was not restricted to any geographical area. The country of each article was recorded and thereafter grouped into regions, with the most articles obtained from Europe (n=41), followed by Asia & Pacific (n=30), Oceania (n=17), North America (n=14) and the remainder of articles were obtained from Africa (n=8), South America (n=6) and Arab States (n=2). The studies were conducted in 34 countries across the globe with the countries contributing the most epidemiological data were from India and Australia (n=10) followed by Taiwan and USA (n=7) (Figure 2).

The risk of bias assessment criteria established by D. Hoy et al. (6) and modified by M. Werfalli et al. (3) was adjusted in this review to better suit the study articles. Fifty-six studies had a low risk of bias, 58 studies had a moderate risk of bias and only 3 studies (8-10) were deemed as having a high risk of bias (*Spreadsheet tab_ "Risk of bias"*).

The final dataset included a total of 77,068 isolates representing 193 heterologous *emm* types (*Spreadsheet tab_ "Global emm types_ Overall"*). The most predominant *emm* type globally is *emm1* (n=13,298), followed by *emm12* (n=9,806) and *emm4* (5,912). (*This could then be separated into different regions/countries, etc*). The most isolates were obtained from the North American region (n=36,176) with very little isolated from the African (n=1,595) and South America (n=786), where the burden of disease is greatest.

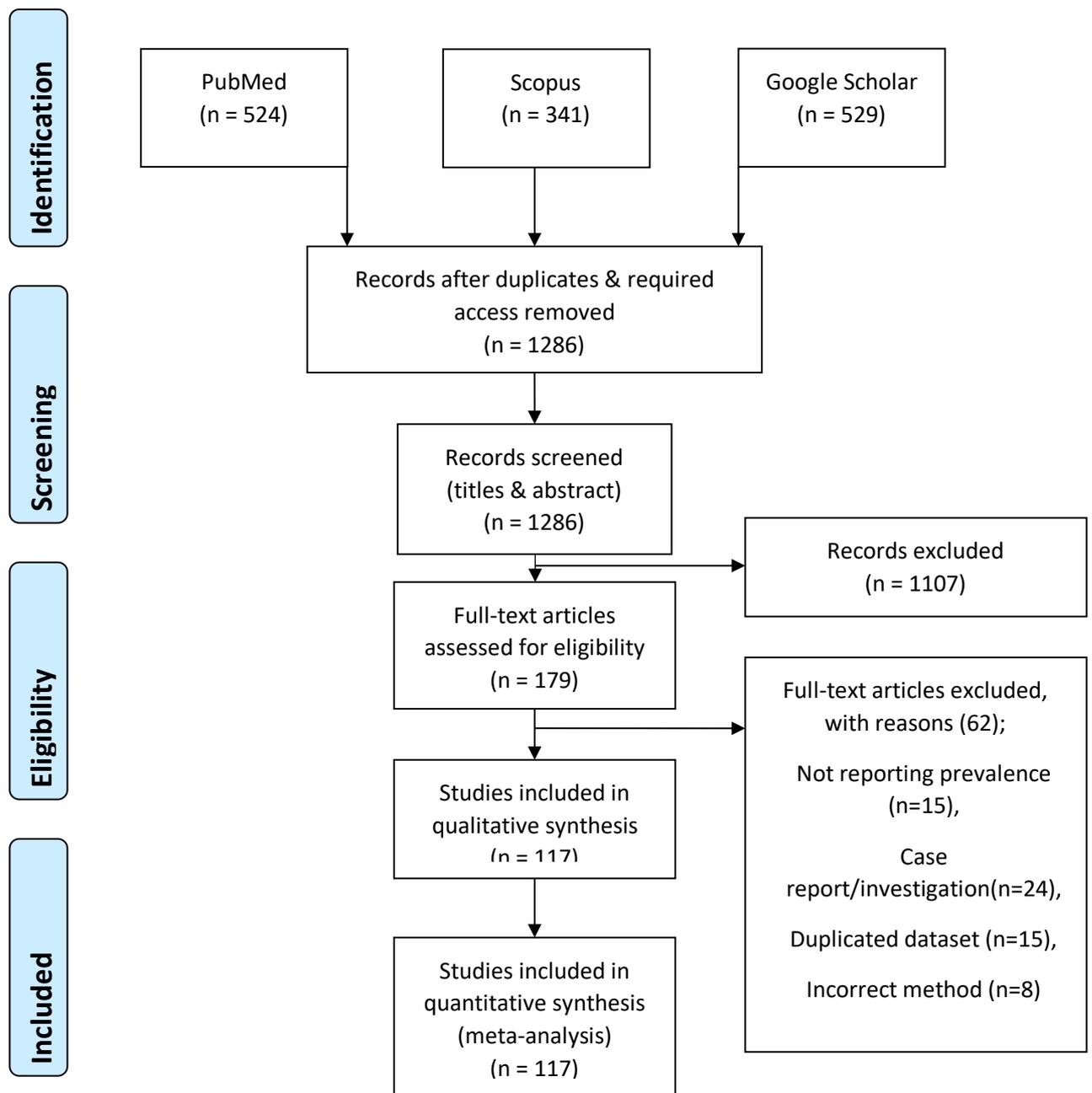


Figure 1. PRISMA diagram

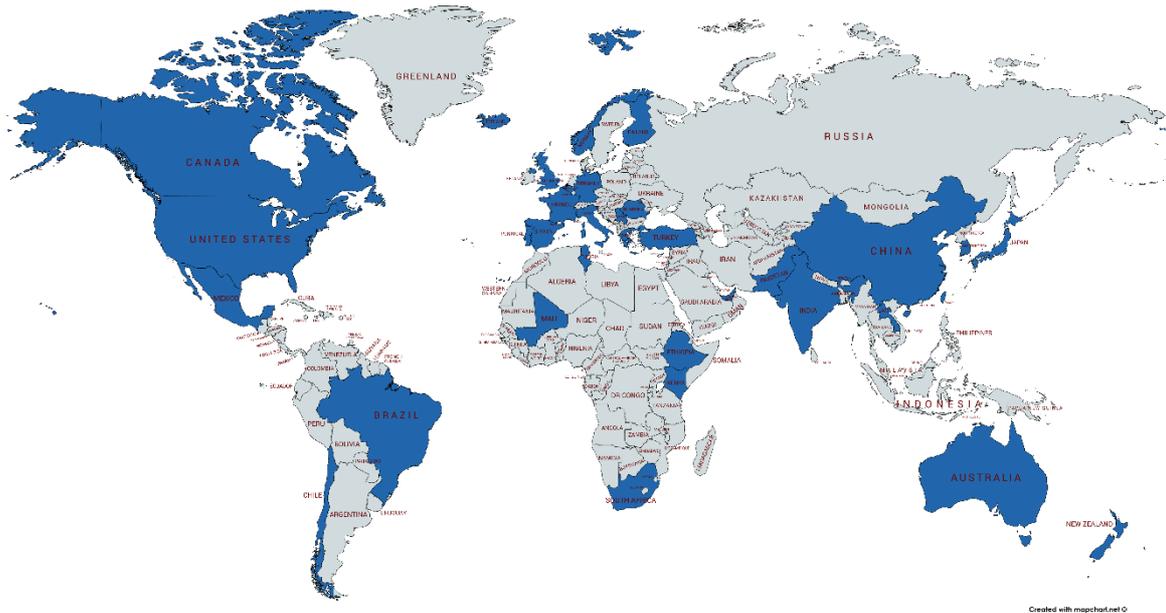


Figure 2. Worldwide map of countries contributing to the data included in the review.

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Appendix I - Figures and Tables

Table 1. Search Strategy with MeSH terms used for databases

Subject	MeSH terms
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Organism	
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Group A Streptococcus	"Group A Streptococcus" OR "Group A β -haemolytic Streptococcus" OR "Streptococcus pyogenes" OR "GAS"
Emm type/cluster	"Streptococcus pyogenes gene" OR "Group A Streptococcus typing" OR "GAS strains" OR "sequence types" OR "emm cluster typing system" OR "emm cluster" OR "emm typing" OR "emm sequences" OR "M protein" OR "M protein gene" OR "emm"
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Infections	
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Superficial Infections	"Non-invasive GAS infections" OR "Pharyngitis" OR "sore throat" OR "strep throat" OR "Impetigo" OR "Group A Strep skin infections" OR "Scarlet fever" OR "scarlatina"
Invasive Infections	"Invasive GAS" OR "iGAS" OR "sepsis" OR "septicaemia" OR "Streptococcal toxic shock syndrome" OR "Necrotizing fasciitis" OR "Strep bacteremia" OR "GAS blood infections" or Group A Streptococcal postpartum metritis" OR "Streptococcal postpartum infections"