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Review Article

Systematic Review of Group A Streptococcal *emm* Types Associated with Acute Post-Streptococcal Glomerulonephritis

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Abstract. Acute post-streptococcal glomerulonephritis (APSGN) is a postinfectious immune-mediated kidney disease associated with group A *Streptococcus* (GAS). The prevalence of APSGN varies within and between countries and is influenced by socioeconomic, host, and bacterial factors. The disease is more prevalent in developing countries and resource-poor settings of developed countries, such as the Indigenous populations residing in tropical Australia. The M-protein is a universally present GAS surface antigen that is the focus of molecular typing and vaccine research. Early reports suggested that some M-proteins (*emm* types) are more likely to cause APSGN than others. Here, we present the first systematic review of the global distribution of APSGN-associated GAS *emm* types. There were 46 *emm* types among the 676 cases described in 15 reviewed articles. Only 43% APSGN cases would have had theoretical coverage from the experimental M protein-based GAS vaccine. Vaccine coverage was higher in regions such as North America (97%) and the United Kingdom (98%) than Africa (67%) and Australia (38%). Variable vaccine coverage against APSGN- associated *emm* types highlights the need for further research into this disease, particularly in settings of poverty, where APSGN prevalence is higher. Three GAS *emm* types (*emm*49, *emm*60, and *emm*55) consistently occur in APSGN cases around the world. Future studies would therefore benefit from examining the genomic epidemiology of these *emm* types to unravel potential markers of APSGN.

INTRODUCTION

Streptococcus pyogenes, also known as Group A *Streptococcus* (GAS) or *Streptococcus* A, causes a wide spectrum of disease ranging from pharyngitis and impetigo to severe invasive disease and postinfectious sequelae such as rheumatic heart disease and acute post-streptococcal glomerulonephritis (APSGN). Acute post-streptococcal glomerulonephritis is a postinfectious immune-mediated kidney disease, where GAS antigens are purportedly deposited on the glomerular membrane and subsequently induce glomerulonephritis.[1] Echoing the prevalence of other GAS diseases such as impetigo and rheumatic heart disease, the estimated prevalence of APSGN is higher in countries with a low Human Development Index (HDI) (9.3–28.5 cases per 100,000 people) [2,3] than in high HDI countries (0.3–2 cases per 100,000 people).[3] Acute post-streptococcal glomerulonephritis can also occur in resource-poor settings within high HDI countries. For example, the prevalence of APSGN among Indigenous Australians in the tropical north of the country, where poor housing infrastructure[4] and reduced access to health care[5] are common, is the highest in the world (239 per 100,000 people), even though Australia is classified as a high HDI country.[6] This indicates that APSGN prevalence varies both within and between countries and is influenced by socioeconomic and possibly genetic host factors.[2]

In addition to investigating the host factors contributing to APSGN, researchers have also sought to identify bacterial factors that may lead to the development of this disease. The M-protein is a universally present surface antigen among GAS that has been the focus of most typing and vaccine research because of its reliable presence, molecular diversity, and immunogenicity. Early reports of APSGN outbreaks found that certain M-proteins (*emm* types) were overrepresented among APSGN cases, suggesting that some M-proteins are more "nephritogenic," that is, more likely to cause APSGN, than others.[7,8] However, just as APSGN incidence varies with the development index of a country, so too does the diversity of *emm* types within a country.[9] Studies which examine the relationship between the *emm* type and APSGN within a single geographic region will therefore be confounded by the *emm* type diversity within that region. Whereas in 2018 the 71st World Health Assembly adopted a resolution calling for greater action on GAS-associated rheumatic heart disease,[10] APSGN has not received the same attention despite continued outbreaks in geographical regions where rates of rheumatic heart disease are also elevated.[11–13] Research into APSGN also trails significantly behind research into acute rheumatic fever (ARF), another GAS sequela. A review of population-based studies identified 38 articles documenting the incidence of ARF compared with just 11 studies of APSGN, despite similar estimates of the global prevalence of each disease (471,000 cases per year in ARF and 472,000 cases of APSGN).[3] Given APSGN is a leading risk factor for the development of chronic kidney disease, particularly in resource-poor settings,[14] a deeper understanding of the molecular mechanisms and clinical epidemiology of GAS-associated APSGN is required so that effective preventative measures can be developed. We therefore conducted the first systematic review to examine the global distribution of APSGN-associated GAS *emm* types.

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METHODS

A literature search was conducted based on the PRISMA guidelines for conducting reviews.[15] The PubMed and Web of Science databases were searched using the terms: (pyogenes OR streptococc*) AND (*nephritis OR ((renal OR kidney) AND (disease)) OR nephropathy) AND (emm OR M). An English language limit was placed on the search. No date limits were used. The abstract and full text screening process are summarized in Figure 1. Abstracts that did not mention the aforementioned search terms were excluded. Full texts were excluded if they were review articles that did not contain primary data, contained overlapping data with previous studies, did not separate APSGN cases from other diseases in their dataset, or did not give numbers for each *emm* type in their dataset. Articles that did not provide an acceptable clinical definition of APSGN and studies that did not clearly differentiate APSGN cases from APSGN contacts were also excluded. An APSGN case was defined as having at least two of the following clinical signs: hematuria, hypertension, and facial or peripheral edema; laboratory evidence of hematuria and/or proteinuria; evidence of streptococcal infection by serology or culture; and a reduced complement C3 level.[12,16] Studies that described patients with at least one of the aforementioned clinical signs as well as positive streptococcal culture and histopathological evidence of glomerulonephritis were also included in the review.[16] Screening of abstracts and full texts and tabulation of data were performed by a single investigator (K. A. W.). As there is very good concordance between M-protein serotyping and *emm* gene sequencing results,[17] both methods of *emm* typing were included in the review. *emm* subtypes (e.g., *emm*55.3) were reported in some newer studies that had used sequence typing; these were regrouped into their broader parent *emm* types (e.g., *emm*55) to align with older studies that used M-protein serotyping (https://www.cdc.gov/streplab/assigning.html). The *emm* type of isolates listed as "sequence type" was inferred using the CDC *emm* database (https://www.cdc.gov/streplab/types-emm103-124.html). As previously described,[9] the geographic origin of studies was classified based on regions described in the United Nations Populations Prospects 2017 documentation (https://esa.un.org/unpd/wpp/Download/Standard/Population/). The Simpson's index of diversity was used to calculate *emm* variation among APSGN cases per region.[18] The diversity index was calculated as a percentage, which indicated the likelihood that two random isolates from the same geographic area would be a different *emm* type; higher percentages indicated higher levels of *emm* type diversity in a particular region.[9] CIs were calculated for diversity indices.[19] As a conservative approach, 95% CIs that did not overlap were considered to be significantly different at the 5% significance level. To indicate whether *emm* types were under- or over-represented in APSGN cases, we evaluated the equivalent to a "residual" in a χ^2 test [(observed frequency – expected frequency)/observed frequency]. The relative frequencies of each *emm* type observed in APSGN cases were compared with the expected frequency of *emm* types in each region, based on data from a large review of *emm* types associated with all diseases.[9] Formal hypothesis testing was not performed because of the small number of APSGN cases in some geographic regions and because of the nonrandom way in which data were collected.

RESULTS AND DISCUSSION

A total of 15 articles (from a starting set of 186 records) were included in the final review, encompassing studies from 12 countries in six regions around the world (Figure 1). A total of 676 APSGN cases were included in the review, originating from the United Kingdom (n = 47), the United States (n = 117), Latin America and the Caribbean (n = 322), Asia (n = 109), Africa (n = 60), and Australia (n = 21). Forty-six *emm* types were present among the 676 APSGN-associated GAS isolates (Table 1). The average number of confirmed APSGN cases reported in each study with *emm* typing performed was 43 (range 3–264).

Most studies featured data collected over several years, with data collected during the periods of 1964–1969

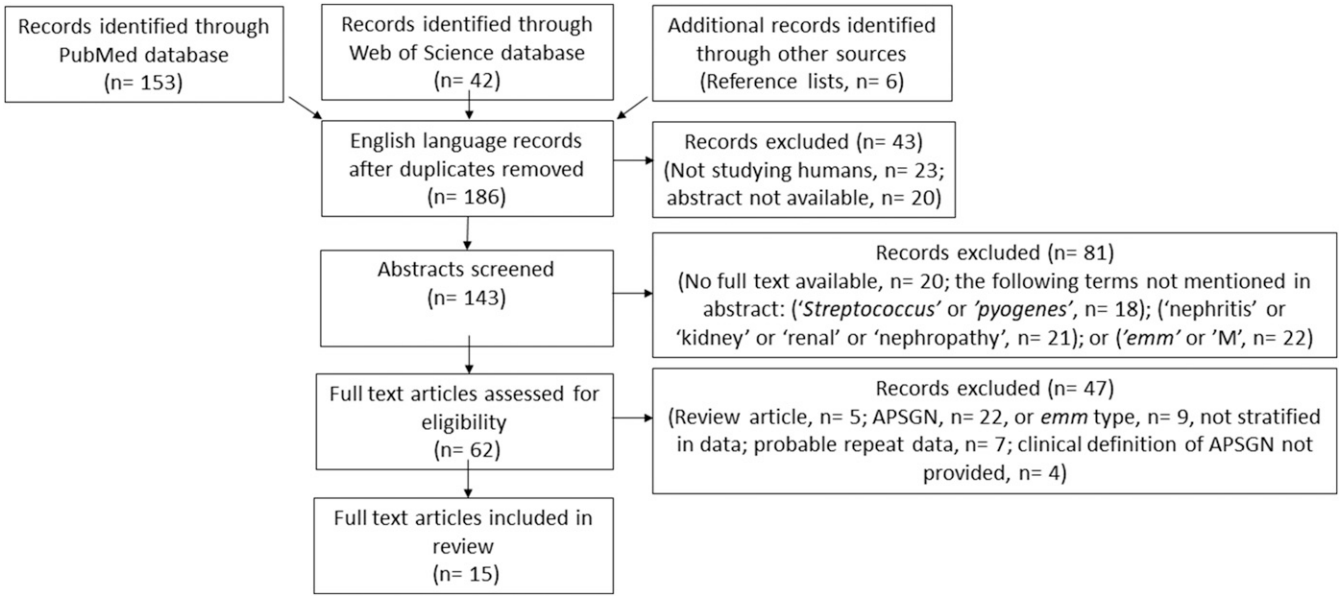

FIGURE 1. Summary of the selection process and reasons for study exclusion.

TABLE 1
emm types of group A *Streptococcus* isolated from patients with acute post-streptococcal glomerulonephritis

emm type	United Kingdom[24]*	North America[7,16,20]	Latin America and Caribbean[8,22,25,30]	Asia[23,27,28,29]	Africa[21,26]	Australia[12]	Total no. of specimens
55	1 (2%)	0	283 (87.9%)	0	12 (20%)	5 (23%)	301
49	7 (15%)	37 (32%)	0	8 (7%)	22 (36%)	1 (5%)	75
2	0	51 (44%)	10 (3.1%)	4 (4%)	0	0	65
12	11 (23%)	10 (8%)	0	34 (31%)	0	0	55
60	0	14 (12.0%)	0	10 (9%)	13 (22%)	0	37
1	8 (17.0%)	0	7 (2.2%)	13 (12%)	1 (2%)	0	29
73	1 (2%)	0	11 (3.4%)	0	0	0	12
4	4 (9%)	0	2 (0.62%)	12 (11.0%)	0	0	18
63	0	0	1 (0.31%)	7 (6%)	0	0	8
3	3 (6%)	0	0	0	0	3 (14%)	6
81	2 (4%)	0	0	3 (3%)	0	0	5
6	1 (2%)	0	2 (0.62%)	1 (1%)	0	0	4
18	0	0	0	3 (3%)	1 (2%)	0	4
61	0	4 (3%)	0	0	0	0	4
78	4 (9%)	0	0	0	0	0	4
11	0	0	3 (0.93%)	0	0	0	3
14	0	0	0	3 (2%)	0	0	3
28	0	0	0	3 (3%)	0	0	3
48	0	0	3 (0.93%)	0	0	0	3
57	0	0	0	0	0	3 (14%)	3
95	0	0	0	2 (2%)	1 (2%)	0	3
58	0	0	0	2 (2%)	0	0	2
9	2 (4%)	0	0	0	0	0	2
22	2 (4%)	0	0	0	0	0	2
25	0	0	0	1 (1%)	1 (2%)	0	2
85	0	0	0	0	0	2 (9%)	2
175	0	0	0	0	2 (3%)	0	2
Singletons†	1 (2%)	1(1%)	0	3 (3%)	7 (12%)	7 (32%)	19
Total	47	117	322	109	60	21	676

emm types highlighted in gray are those included in the experimental 30-valent M protein-based vaccine.[31]
* Numbers outside parentheses indicate the total number of isolates of that *emm* type. Parentheses indicate the proportion of each *emm* type as a percentage of total isolates from each region.
† Singletons = *emm* types that were represented by only one isolate. Includes *emm*5, 15, 19, 23, 33, 68, 70, 74, 88, 89, 91, 98, 105, 173, 179, 192, 208, 209, and 239.

($n = 3$),[7,16,20] 1970–1979 ($n = 3$),[8,21,22] 1980–1989 ($n = 3$),[23–25] 1990–1999 ($n = 3$),[26–28] and 2000–2009 ($n = 1$).[29] Two studies collected data over more than a 10-year period: one study from Chile collected data between 1980 and 1999[30] and a second study from Australia featured data from 1991 to 2008.[12] Seven of the 15 studies featured longitudinally collected data and did not mention an outbreak.[7,20–24,26] Six studies specifically defined their case collection as one or two outbreaks,[8,16,25,27–29] and all but one[25] of these reports attributed the outbreaks to a single *emm* type. The two studies that collected data over more than a 10-year period contained both small outbreaks and sporadic cases.[12,30] Several methods of *emm* typing were reported in the studies, including diffusion or precipitation M-protein serotyping ($n = 11$) and *emm* gene sequencing ($n = 3$). Two studies used both serotyping and precipitation methods of *emm* typing.[7,21] One study did not specify the method of *emm* typing used.[27] Most studies included APSGN cases that were M non-typeable.

The most common APSGN-associated GAS *emm* types were 55, 49, 2, 12, 60, 1, and 73. These seven *emm* types accounted for 85% of the reported APSGN cases. The majority (88%) of *emm*55 cases came from a single large outbreak of APSGN in 429 patients in Trinidad in 1971, 264 of whom had *emm*55 isolated from their skin or throat.[8] The large Trinidad outbreak met our inclusion criteria for this review, but its inclusion admittedly skewed the data such that *emm*55 was greatly overrepresented. Excluding this outbreak, *emm*55 still accounted for 37 (9%) remaining APSGN cases. Although *emm*55 was the most common APSGN-associated *emm* type, *emm*49 was the most widely dispersed, being reported in five of six regions. *emm*49 was overrepresented among APSGN cases in the United Kingdom and North America (44/161 [27%] cases) compared with *emm*49 among all diseases from the United Kingdom and the United States (306/24,055 [1.3%] cases).[9] *emm*60 was also overrepresented in APSGN cases, with its observed frequency in the United States and the United Kingdom (14/161 [8.7%] cases) being higher than its expected frequency among all GAS infections (48/24,055 [0.2%] cases).[9] *emm*1, the most commonly reported *emm* type across all GAS studies (18% of all samples, $n = 30,081$),[9] accounted for only 5% of APSGN-associated samples worldwide.

Figure 2 shows the distribution of APSGN-associated *emm* types around the world. Calculation of the Simpson's diversity index showed that *emm* type diversity varied across geographic regions: *emm* type diversity was higher in Australia (88%; CI = 87–88%), the United Kingdom (87%; CI = 83–91%), and Asia (85%; 81–90%) compared with North America (69%; CI = 64–74%) and Latin America (22%; CI = 16–29%). The low diversity seen in Latin America was largely influenced by the large *emm*55 APSGN outbreak of 1971, which accounted for 82% of APSGN cases from this region.[8] This is similar to the findings of the review by Steer et al.,[9] which found higher *emm* type diversity among GAS disease of all types in the Pacific and Africa and lower diversity in the United Kingdom and North America.

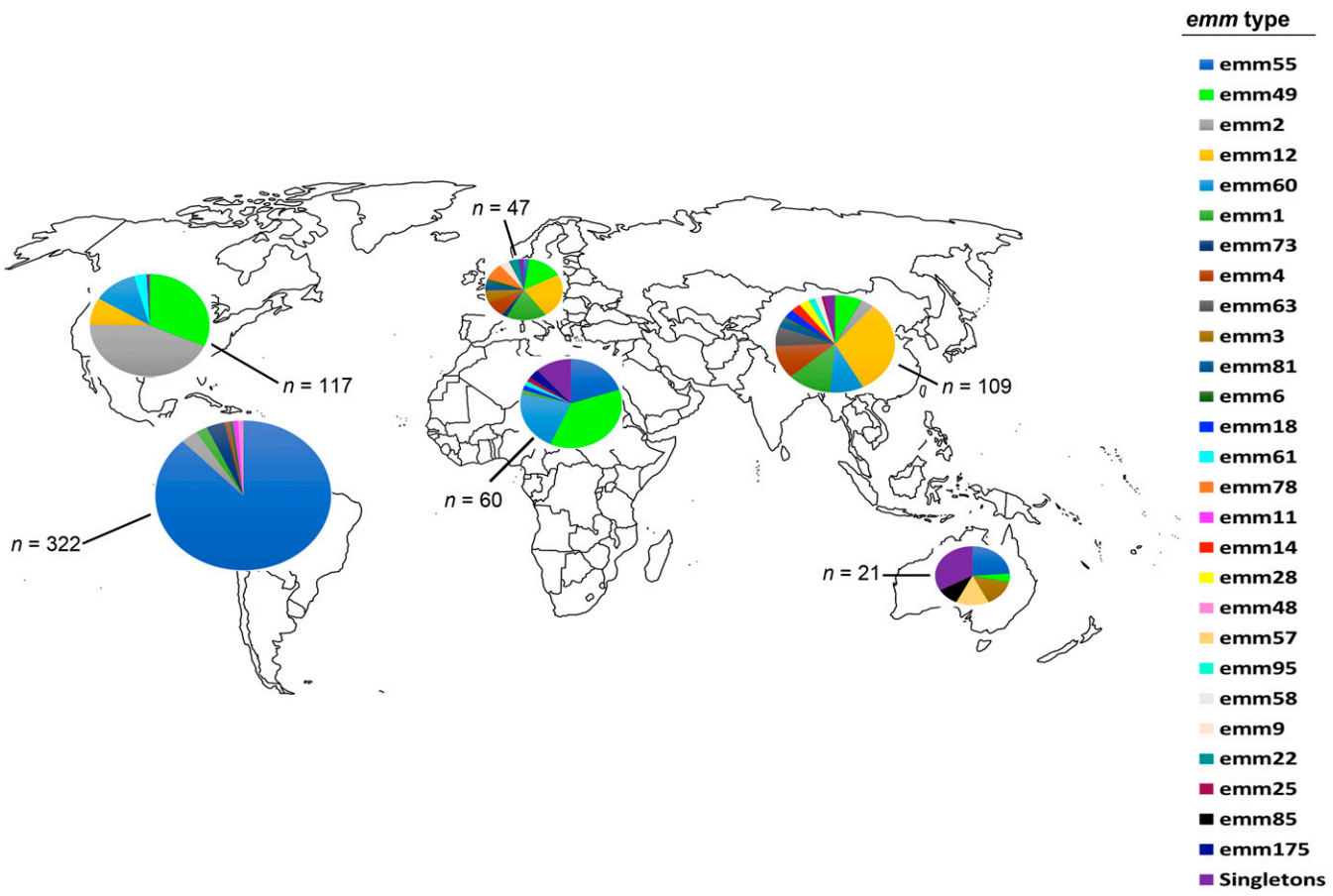

FIGURE 2. Global distribution of *emm* types associated with acute post-streptococcal glomerulonephritis.

Overall, 294 of 676 (43%) APSGN cases would have had theoretical protective coverage from the experimental 30-valent M-protein–based GAS vaccine,[31] although this would increase to 352/676 (52%) if non-vaccinal M-proteins with demonstrated protection by cross-opsonization were considered.[31,32] Because of the absence of *emm*55 in the 30-valent vaccine, only 11% of Latin American and Caribbean APSGN cases would have been covered. In Australia and Africa, 24% and 42% of cases would have been covered, respectively, increasing to 38% and 67% if non-vaccinal M-proteins with demonstrated protection by cross-opsonization were considered.[31,32] This is in contrast to North America, Asia, and the United Kingdom, where 84–97%, 80–98%, and 93–98% of cases, respectively, would have had theoretical protection from the M-proteins and cross-protection demonstrated by the experimental 30-valent GAS vaccine.[31,32] A similar pattern of vaccine coverage was seen in the review of *emm* types associated with all diseases, which found higher vaccine coverage in high-income countries such as the United Kingdom and the United States and lower coverage in Africa and the Pacific.[9] It is noteworthy that fewer APSGN cases were protected by the extended coverage of the 30-valent vaccine (52%) than the proportion of all GAS cases that would have had theoretical coverage by the narrower 26-valent vaccine (69.7%).[9]

Despite the strict inclusion criteria we imposed in this review, our report is limited by heterogeneity among the studies we examined. Studies varied in their design, sample size, typing methods, and whether GAS was isolated from the nose or throat of APSGN patients. The results would therefore be affected by bias, most notably in the inclusion of large outbreaks that skewed some of the data such as the overrepresentation of *emm*55 among APSGN cases from Latin America and the Caribbean.[8] Data on the site of isolation were not included in this review because some studies did not describe the site from which GAS was isolated. A study from Australia[13] and another from Ethiopia[26] noted that APSGN cases were more commonly associated with skin disease than pharyngitis; future investigations into the relationship between the GAS *emm* type, underlying disease, and APSGN are therefore indicated. We compared the observed proportions of APSGN-related *emm* types with expected proportions from previous reports of all GAS diseases,[9] but the studies we examined were not necessarily representative of the broader population from which they came. General trends were observed in APSGN data that nevertheless mirrored the trends found in worldwide *emm* type diversity and vaccine coverage, indicating that comparison of our dataset with the broader dataset from a previous review[9] was useful for assessing when the *emm* type frequency among APSGN cases diverged from the expected frequency for each region.

We observed a higher than expected occurrence of *emm*49 and *emm*60 among APSGN cases in particular regions and the underrepresentation of *emm*1 compared with its predominance as a cause of invasive disease. Monitoring of these nephritogenic *emm* types in susceptible populations such as Indigenous Australians in the tropical north is recommended for APSGN disease management. Future studies would benefit from

examining the molecular epidemiology of *emm*49, *emm*60, and *emm*55 to determine if the M-proteins themselves are particularly nephritogenic or whether *emm* acts as a marker for other characteristics of these lineages that have led to their apparent overrepresentation in APSGN cases around the world.

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