MAJOR ARTICLE

The *emm*-Cluster Typing System for Group A *Streptococcus* Identifies Epidemiologic Similarities Across the Pacific Region

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Background. Group A *Streptococcus* (GAS)–related disease is responsible for high mortality and morbidity in the Pacific region. The high diversity of circulating strains in this region has hindered vaccine development due to apparently low vaccine coverage of type-specific vaccines.

Method. Prospective passive surveillance of all GAS isolates in New Caledonia was undertaken in 2012 using *emm* typing and *emm*-cluster typing. Molecular data were compared with the results from a prior study undertaken in the same country and with data from 2 other Pacific countries, Fiji and Australia.

Results. A high incidence of invasive infection was demonstrated at 43 cases per 100 000 inhabitants (95% confidence interval, 35–52 cases per 100 000 inhabitants). Three hundred eighteen GAS isolates belonging to 47 different *emm* types were collected. In Noumea, only 30% of the isolates recovered in 2012 belonged to an *emm* type that was present in the same city in 2006, whereas 69% of the isolates collected in 2012 belonged to an *emm* cluster present in 2006. When comparing New Caledonian, Australian, and Fijian data, very few common *emm* types were found, but 79%–86% of the isolates from each country belonged to an *emm* cluster present in all 3 countries. A vaccine that could protect against the 10 most frequent *emm* clusters in the Pacific region would potentially provide coverage ranging from 83% to 92%.

Conclusions. This study confirms the high disease burden of GAS infection in New Caledonia and supports the added value of the *emm*-cluster typing system to analyze GAS epidemiology and to help inform global GAS vaccine formulation.

Keywords. *emm* cluster; invasive diseases; *Streptococcus pyogenes*; typing; vaccine.

Streptococcus pyogenes (group A *Streptococcus* [GAS]) is responsible for both mild and severe disease, ranging from pharyngitis and cutaneous infections to invasive infections including streptococcal toxic shock syndrome (STSS), and other complications such as acute rheumatic fever and rheumatic heart disease [1]. Globally, this bacterium is responsible for a mortality of >500 000 deaths per annum, particularly in low-income countries and in the Pacific region [2, 3].

In New Caledonia (NC), GAS diseases are a major public health concern. The prevalence of rheumatic heart disease was estimated at 9 per 1000 children in 2008–2010 [4]. A previous hospital-based surveillance study of invasive GAS infection conducted in the hospital in Noumea in 2006 observed an incidence of 38

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cases per 100 000 inhabitants [5]. This study found a low case fatality rate (CFR) of 3.3%, possibly reflecting the inclusion of cases of mild severity. We therefore decided in this study to use more stringent criteria to define definite and probable GAS invasive infections.

Molecular typing of GAS relies on the sequence of the gene encoding for a surface protein called the M protein [6]. This M protein, encoded by the *emm* gene, is a major virulence factor of GAS, mainly due to its antiphagocytic properties [7], and is the only GAS vaccine antigen that has reached phase 2 clinical trials so far [8, 9]. The N-terminal part of the M protein has a variable nucleotide and amino acid sequence, resulting in antigenic diversity, and is the basis for the widely used, nucleotide-based *emm*-typing scheme [10]. There have been 223 different *emm* types reported worldwide [11]. Molecular epidemiology studies have shown considerable variation in *emm*-type distribution at both a country and regional level [12, 13]. The diversity of strains circulating in low-income settings far exceeds that in high-income settings, resulting in the prediction of low coverage of type-specific vaccines. Moreover, the profile of the many *emm* types recovered from low-income countries differ considerably from one country to another, thereby hindering vaccine development [14–16]. Pioneering work in the 1950s showed that the presence of type-specific antibodies is responsible for immunity against the homologous *emm* type [17, 18]. In contrast, no effect on infection by heterologous GAS types was observed with the strains tested in these studies. However, several lines of evidence suggest that the type-specific paradigm might not be directly applicable to the many strains circulating in low-income countries. The preclinical development of a 30-valent vaccine has demonstrated in vitro cross-protection against isolates expressing M proteins not included in the vaccine [19, 20]. This hypothesis of a cross-protection phenomenon was previously proposed for the many *emm* types circulating in Brazil based on predictive data of M protein complete sequences [21, 22]. Finally, a new *emm*-cluster typing system that classifies the many GAS *emm* types into 48 discrete *emm* clusters containing closely related M proteins that share binding and structural properties has been recently proposed [23]. This *emm*-cluster system predicts the M protein vaccine antigen content and serves as a framework to investigate the cross-protection phenomenon. Importantly, the *emm*-cluster system is not in contradiction with the type-specific paradigm, which was essentially based on the small proportion of variants circulating in high-income countries, but proposes a complementary hypothesis for the many variants from low-income settings [23].

The present study aimed to characterize the clinical and molecular epidemiology of GAS infections in NC using both the *emm*-typing and *emm*-cluster systems to evaluate the implications of these data for vaccine coverage.

METHODS

Patient Population

New Caledonia is a French overseas territory in the Pacific. The indigenous Melanesian Kanak community represents 44.6% of the 252 000 inhabitants [24]. Half of the population lives in the capital city of Noumea. There are only 2 hospitals: the hospital in Noumea, which is the major hospital in NC (482 beds), and the hospital in the Northern province (78 beds).

Study Design

Prospective passive surveillance of GAS infections was undertaken from 1 January to 31 December 2012, at the 2 NC hospitals. We identified GAS isolates through 2 laboratories: the laboratory of Insitut Pasteur for the hospital in Noumea and the laboratory of the Northern hospital. There is no other hospital in the island, so our strain collection is likely to be representative of all GAS infections occuring in the hospital where a microbiological sample was collected. Standard demographic data including age, sex, and residence district were recorded along with with clinical information including clinical presentation, comorbid health conditions, site of isolation, complications, and outcome. A single isolate was included per infection.

Case Definitions

Definite invasive disease was defined by the isolation of GAS from a normally sterile site (eg, blood; cerebrospinal, pleural, or peritoneal fluid). Probable invasive disease was defined as an unwell patient with GAS isolated from a nonsterile site who required 1 or more of the following: hospitalization for intravenous antibiotics; surgery; or admission to the intensive care unit (ICU). Streptococcal toxic shock syndrome was defined using previously published criteria [25]. Noninvasive GAS disease was defined as isolation of GAS from a nonsterile site with a clinical syndrome consistent with GAS infection but that did not meet the probable invasive GAS disease case definition.

Microbiology

Identification of GAS was based on β-hemolysis on blood agar, colony morphology, Gram stain, catalase reaction, and positive latex agglutination test (streptococcal grouping kit, Oxoid). All *emm* typing was performed according to the protocol described by the US Centers for Disease Control and Prevention (CDC) with minor modifications; primers MF2 and MR1 were used when primer 1 and 2 were not successful, as previously described [16]. One new *emm* sequence was submitted to the CDC streptococcal database and to GenBank (accession number *emm* 17.3, GenBank KJ191123). The *emm* clusters were deduced based on the *emm*-typing results as recently described [23]. M protein 30-valent vaccine coverage data were deduced using previous studies [19, 20].

Statistical Analysis

Statistical analyses were performed using Stata version 11 software (StataCorp, College Station, Texas). Categorical variables were described as a median and interquartile range (IQR). Incidence rates were calculated using data from the last census in NC [24]. The Simpson reciprocal index (SRI) was used to measure GAS strain diversity [22], with confidence intervals (CIs) calculated as previously described [26]. The value of this index ranges from 1 to 223 (total number of *emm* types described so far)—the higher the value, the greater the diversity.

Comparison of Molecular Epidemiology to Previous Studies

The *emm*-typing and *emm*-cluster profiles of the present study were compared with those of a prior epidemiological survey of GAS invasive infection conducted in NC 6 years prior [5]. We only included data from the hospital in Noumea because the previous study was restricted to cases from this hospital; both definite and probable invasive infections were included in this comparison. Because the Pacific region is well known to be associated with a high burden of GAS disease and a high number of circulating strains [12, 13, 27–29], our data were compared with data obtained from 2 other Pacific countries, Fiji and Australia. The Fijian study included 535 isolates (67 *emm* types) associated with invasive disease and noninvasive throat and skin GAS infections in 2006 [29]. The Australian study included 334 isolates (38 *emm* types) recovered from noninvasive throat and skin infection in the Northern Territory in 2007 [28].

Ethical Approval

The study was approved by the French ethical research committee (Comite de Protection des Personnes Sud-Ouest et Outre mer III; DC 2012/90). Oral consent for participation in the study was obtained from all adult participants and from parents of the included children.

RESULTS

During the 12-month study period, 318 cases of GAS infection were detected through the microbiology laboratories of the 2 hospitals. The majority of the cases were noninvasive (n = 205), followed by definitely invasive (n = 57) and probably invasive (n = 49) (Table 1). The clinical manifestation was not known for 7 patients. The median age of patients with noninvasive infection was 24 years (IQR, 16–39), whereas patients with invasive infections (both definitive and probable) were older (median, 39.5 years; IQR, 21–61). The sex ratio (male: female) was 2:1 in both noninvasive and invasive cases (137/68 and 73/33, respectively). Seventy-eight percent (n = 248) of the infections were identifed at the main hospital in Noumea, but no significant difference could be observed between the study sites. Among the noninvasive cases, skin and soft tissue infections (SSTIs) were the most common clinical manifestations (90%) (Table 1). The all-ages incidence of noninvasive GAS infection was 83 cases per 100 000, with a peak incidence in patients aged 15–24 years of 145 cases per 100 000 (Figure 1).

Table 1. Clinical Manifestations of Group A Streptococcal Diseases by Age

Clinical Manifestation	No. of Patients by Age Group			Total No. (%)
	0–14 y	15–49 y	≥50 y	
In patients with definite invasive GAS infection (n = 57)				
Septicemia	4	5	20	29 (51)
Necrotizing fasciitis	1	4	4	9 (16)
Septic arthritis	0	3	1	4 (7)
Cellulitis	0	2	0	2 (4)
Pneumonia	1	0	1	2 (4)
Osteomyelitis	0	2	0	2 (4)
Streptococcal toxic shock syndrome	0	1	1	2 (4)
Erysipelas	0	0	2	2 (4)
Peritonitis	0	1	0	1 (2)
Bacteremia with no clinical focus	0	0	2	1 (2)
Pleuropericarditis	0	1	0	1 (2)
Hygroma	0	1	0	1 (2)
In patients with probable invasive GAS infection (n = 49)				
Erysipelas	2	14	6	22 (45)
Cellulitis	6	15	2	23 (47)
Pneumonia	1	1	0	2 (4)
Endometritis	0	2	0	2 (4)
In patients with noninvasive GAS infection (n = 205)				
Superficial infection				
Erysipelas	1	5	4	10 (5)
Cellulitis	2	1	1	4 (2)
Abscess	18	65	7	90 (44)
Wound infection	13	32	9	54 (26)
Phlegmon	1	14	2	17 (8)
Vaginitis	0	7	0	7 (3)
Pustular lesion	2	2	1	5 (2)
Otitis	3	0	1	4 (2)
Impetigo/pyoderma	3	1	0	4 (2)
Pharyngitis/angina	2	0	0	2 (1)
Scarlet fever	1	0	0	1 (0)
Other	1	2	0	3 (1)
Asymptomatic colonization				
Vagina	0	2	0	2 (1)
Multiple orifices	1	0	0	1 (0)
Postinfectious sequelae				
Acute rheumatic fever[a]	1	0	0	1 (0)

Abbreviation: GAS, group A *Streptococcus*.

[a] The case of acute rheumatic fever was in a 13-year-old boy with antecedent of rheumatic heart disease.

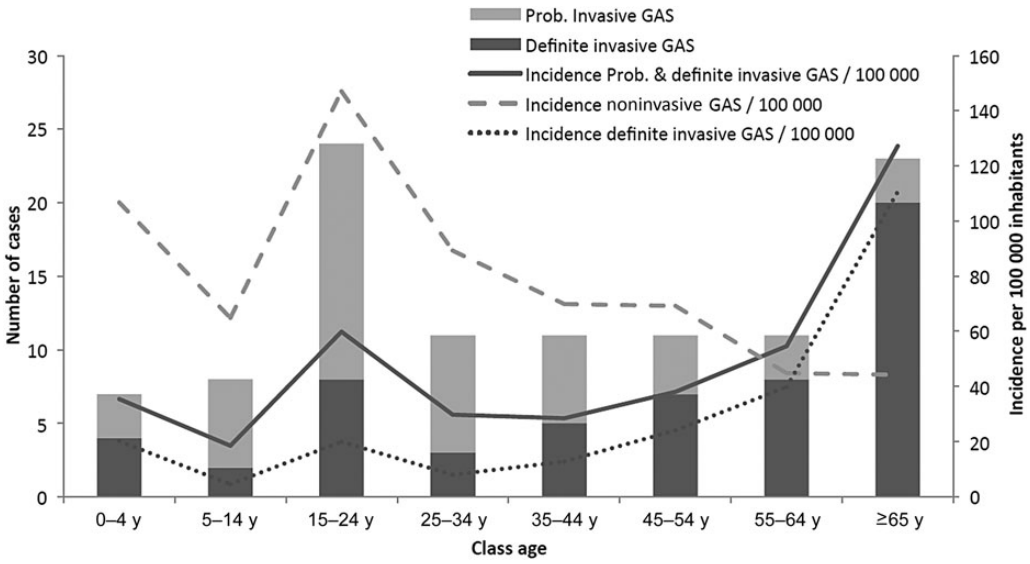

Figure 1. Age distribution and incidence of invasive and noninvasive group A streptococcal diseases, New Caledonia (n = 311), 2012. Abbreviation: GAS, group A *Streptococcus*.

Invasive GAS Infection

The all-ages incidence of definite invasive GAS infection was 23 cases per 100 000 population (95% CI, 18–30 cases per 100 000 population), with a peak incidence of 111 per 100 000 in patients aged >65 years (Figure 1). The median age was 54 years (IQR, 27–67 years), and the sex ratio was 1.7:1. Septicemia was the most frequent clinical manifestation (51%), followed by necrotizing fasciitis (16%) and septic arthritis (7%) (Table 1). Two cases of STSS were reported. Two cases (4%) were in children aged <1 year (7 months and 10 months, respectively). Of the 57 patients with invasive GAS disease, the outcome was known for 56, and of these, 8 patients died, corresponding to a CFR of 14% (2 septicemia, 2 necrotizing fasciitis, 2 STSS, 1 pneumonia, 1 cellulitis). The median age of patients who died was 61.5 years (IQR, 54–71.5). All patients who died from invasive disease suffered from comorbidities including diabetes, ischemic heart disease, renal disease, and hypertension (Supplementary Table 1). Of the 48 surviving patients, 20 required a surgical drainage procedure (43%), 9 were admitted to the ICU (19%), 2 underwent an amputation (4%), and 1 had STSS (2%).

The all-ages incidence of probable invasive infection was 20 cases per 100 000 population (95% CI, 15–26), meaning the total incidence of definite and probable invasive GAS disease was 43 per 100 000 (95% CI, 35–52 per 100 000). The peak incidence of probable disease was 40 per 100 000 in those aged 15–24 years. The majority of patients had an SSTI, with 23 patients (47%) diagnosed with cellulitis and a further 22 diagnosed with erysipelas (Table 1); of these 45 patients, 32 required surgical drainage and 3 required admission to the ICU. The median age of patients with probable invasive infection was lower than those with definite disease (24 years; IQR, 20–40 years).

Molecular Epidemiology

Forty-seven different *emm* types were identified among the 318 GAS strains (Table 2). The 5 most frequent *emm* types (*emm*76, *emm*95, *emm*25, *emm*1, and *emm*93) were responsible for 51% of the cases. The diversity index in this strain population was 14.3 (95% CI, 12.2–17.2). Sixteen *emm* clusters were identified in this collection, with 5 of these *emm* clusters (E2, E3, M95, D4, and E4) accounting for 73% of the GAS infections (Supplementary Table 2).

Table 3 shows that the sample size, strain inclusion criteria, number of *emm* types and *emm* clusters, and diversity index were highly similar between the 2 NC studies conducted in 2006 and 2012. However, only 30% of the isolates recovered in Noumea in 2012 belonged to an *emm* type that was present in the same city in 2006 (Supplementary Table 3). In contrast, more than two-thirds of the 2012 isolates belonged to an *emm* cluster present in 2006.

Figure 2 shows that less than a third of the isolates (14%–30%) associated with skin infections in 3 Pacific countries (NC, Fiji, and Australia) belonged to an *emm* type common to all 3 locations, suggesting major differences between these epidemiologic landscapes. However, the analysis of the *emm* cluster distribution from the same skin infections demonstrated that 70%–84% of the isolates belonged to an *emm* cluster

Table 2. Molecular Epidemiology Data and 30-Valent Theoretical Coverage

emm Type	*emm* Cluster	30-Valent Theoretical Coverage	Invasive (n = 57)	Probably Invasive (n = 49)	Noninvasive (n = 205)	Unclassified (n = 7)	Total (N = 318)
*emm*1	A-C3	VA	4 (7)	5 (10)	12 (6)		21 (6)
*emm*2	E4	VA			2 (1)		2 (1)
*emm*3	A-C5	VA			2 (1)		2 (1)
*emm*11	E6	VA		2 (4)			2 (1)
*emm*17	M17	Not opsonized	1 (2)		1 (0)		2 (1)
*emm*22	E4	VA	1 (2)	3 (6)	2 (1)		6 (2)
*emm*25	E3	Cross-opsonized	4 (7)	4 (8)	27 (13)		35 (10)
*emm*27	E2	ND			1 (0)		1 (0)
*emm*28	E4	VA			1 (0)	1 (14)	2 (1)
*emm*33	D4	Cross-opsonized				1 (14)	1 (0)
*emm*36	D1	Cross-opsonized	1 (2)		2 (1)		3 (1)
*emm*41	D4	ND			1 (0)		1 (0)
*emm*44	E3	VA	2 (4)		4 (2)		6 (2)
*emm*46	A-C1	ND			1 (0)		1 (0)
*emm*49	E3	VA	1 (2)	1 (2)	3 (1)		5 (1)
*emm*53	D4	Cross-opsonized	1 (2)		3 (1)		4 (1)
*emm*56	D4	ND			1 (0)		1 (0)
*emm*58	E3	VA		1 (2)			1 (0)
*emm*60	E1	Cross-opsonized	1 (2)	1 (2)			2 (1)
*emm*65	E6	Cross-opsonized			2 (1)		2 (1)
*emm*66	E2	Cross-opsonized			8 (4)		8 (3)
*emm*68	E2	Cross-opsonized		1 (2)	2 (1)		3 (1)
*emm*70	D4	Not opsonized	1 (2)				1 (0)
*emm*75	E6	VA			1 (0)		1 (0)
*emm*76	E2	Cross-opsonized	11 (19)	4 (8)	27 (13)	3 (43)	45 (14)
*emm*77	E4	VA	1 (2)	2 (4)	7 (3)		10 (3)
*emm*81	E6	VA			1 (0)	2 (29)	3 (1)
*emm*86	D4	ND			1 (0)		1 (0)
*emm*88	E4	ND			1 (0)		1 (0)
*emm*89	E4	VA	3 (5)	2 (4)	6 (3)		11 (3)
*emm*92	E2	VA	1 (2)	1 (2)	3 (1)		5 (1)
*emm*93	D4	ND	1 (2)	3 (6)	14 (7)		18 (5)
*emm*95	M95	Cross-opsonized	6 (11)	10 (20)	29 (14)		45 (14)
*emm*100	D2	Cross-opsonized		3 (6)	6 (3)		9 (3)
*emm*101	D4	ND	3 (5)	1 (2)	2 (1)		6 (2)
*emm*102	E4	Cross-opsonized			1 (0)		1 (0)
*emm*103	E3	ND	1 (2)		1 (0)		2 (1)
*emm*104	E2	ND	3 (5)		2 (1)		5 (2)
*emm*105	M105	Cross-opsonized	1 (2)				1 (0)
*emm*108	D4	ND			2 (1)		2 (1)
*emm*109	E4	Cross-opsonized			1 (0)		1 (0)
*emm*111	M111	Cross-opsonized	1 (2)	1 (2)	3 (1)		5 (2)
*emm*178	D4	ND			1 (0)		1 (0)
*emm*187	ND	ND			1 (0)		1 (0)
*emm*207	D1	ND	4 (7)		4 (2)		8 (2)
*emm*229	A-C4	ND	1 (2)	3 (6)	11 (5)		15 (5)
*emm*230	D4	ND			1 (0)		1 (0)
Nontypable	ND	ND	3 (5)	1 (2)	4 (2)		8 (3)

Data are presented as No. (%).

Abbreviations: ND, not determined; VA, vaccine antigens.

Table 3. Comparison of 2 Epidemiological Prospective Surveys in New Caledonia

Characteristic	Le Hello [5]	Current Study
Year	2006	2012
No. of invasive strains	88	90[a]
No. of *emm* types	29	27
No. of *emm* clusters	11	14
Simpson index of diversity (95% CI)	14.3 (11–20.5)	14.7 (11.5–20.4)
Common strains (*emm* types)	34% (30/88)	30% (27/90)
Common strains (*emm* clusters)	88% (77/88)	69% (62/90)

Nontypable stains were excluded from this analysis.

Abbreviation: CI, confidence interval.

[a] To allow for the most accurate comparison with the study performed by Le Hello [5], only the definitive and probable invasive isolates recovered from the main hospital in Noumea are included in this comparison.

common to all 3 countries. The same analysis was undertaken with all isolates (skin, throat, and invasive disease) included in the 3 locations (Supplementary Figure 1) and provided similar results. The *emm*-cluster analysis therefore allows finding a common point between what previously appeared to be highly different epidemiology in these 3 countries.

M Protein Vaccine Coverage

Based on the *emm* types included in the 30-valent vaccine, the theoretical protective coverage of this vaccine would be 24.2% (95% CI, 19.5%–28.9%). When including the *emm* types that have been shown to be cross-opsonized in a rabbit model [19, 20, 23], the theoretical protective coverage rises to 76.1% (95% CI, 71.4%–80.8%; Table 2). Of note, theoretical coverage of the 30-valent vaccine is unknown for 16 *emm* types because cross-opsonization of these *emm* types by the vaccine has not yet been tested; these 16 *emm* types accounted for 65 isolates, suggesting that the potential efficacy of the 30-valent vaccine could be higher than 76.1% if some of those *emm* types were cross-opsonized.

Independent of any current vaccine candidate, our analysis has facilitated the identification of potential vaccine target priorities in the Pacific region. Figure 3 shows that a vaccine that could demonstrate protection against the 10 most frequent *emm* clusters recovered from these 3 Pacific countries could provide coverage ranging from 83% to 92%.

DISCUSSION

The incidence of invasive GAS disease in New Caledonia is high, with an all-ages incidence of definite disease of 23 cases per 100 000 population and of definite and probable disease of 43 per 100 000. The incidence of definite disease is several-fold higher than that found in North America and Europe (1–6 per 100 000), more than double that of neighboring Fiji (9.9 per 100 000), and equivalent to that observed in Maori and Pacific Islanders in New Zealand [25, 27, 30–35]. The reason for the high incidence is not entirely clear, but the addition of noninvasive disease data in our report, along with other Pacific data, support the contention that endemic bacterial SSTI contributes to the high burden in younger age groups

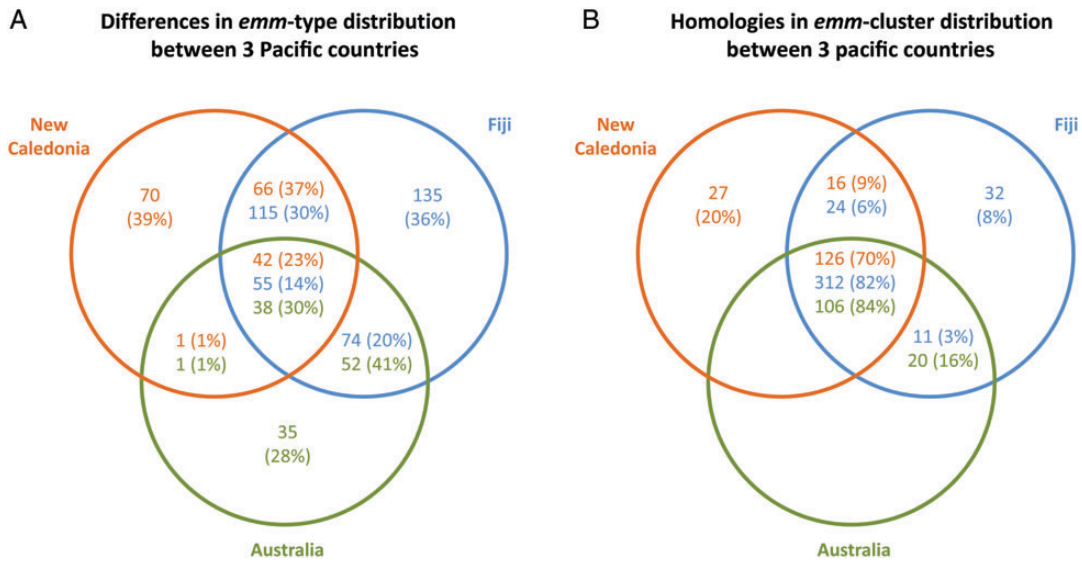

Figure 2. Distribution of *emm* types and *emm* clusters among skin infections recovered from 3 Pacific countries. The number of isolates (%) associated with skin infections and belonging to specific and common *emm* types (*A*) and *emm* clusters (*B*) is shown for each country.

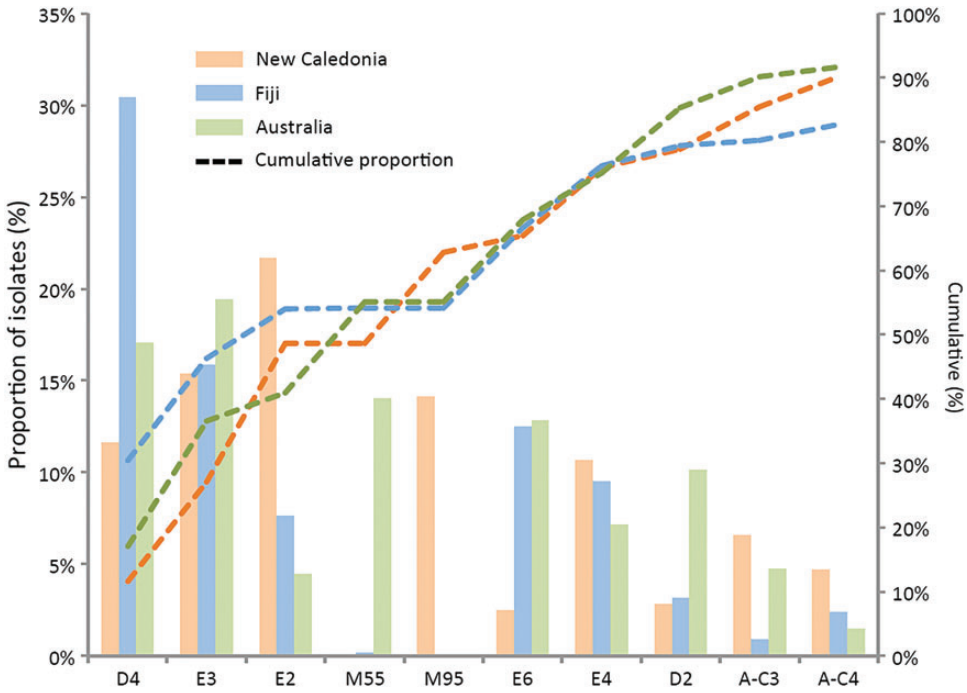

Figure 3. Ten most common *emm* clusters as proportions of all isolates in 3 countries from the Pacific region.

(<25 years). Bacterial skin infection in these younger age groups also likely contributes to the very high burden of disease in older age groups by favoring transmission of bacteria to vulnerable patients with comorbid medical disease. These findings warrant further investigation into the effect that public health control of bacterial skin disease may have in reducing invasive GAS disease across all ages. The contribution of comorbid conditions such as diabetes to the high incidence and high CFR of invasive GAS disease is well described in both developing and developed country settings [27, 33]. Poorly controlled diabetes is an important public health problem in NC [36].

Although the incidence of definite invasive GAS disease in 2012 (23 per 100 000) was lower than the overall rate found in 2006 (38 per 100 000), the incidence of definite and probable invasive disease combined in 2012 (43 per 100 000) was comparable to the overall 2006 figure [5]. Although this difference may be due to a real reduction in disease incidence, it is more likely due to differences in case definitions; that is, the earlier study likely included cases of probable invasive disease within their total estimate.

It has been nearly 10 years since the circulation of a high diversity of GAS strains in developing countries was first described, initially in India and in Ethiopia [14, 15]. The question of GAS strain diversity has since been assessed in many other countries [16, 20, 28, 29, 37, 38], has been reviewed systematically [12, 13], and has stimulated the development of a new type-specific vaccine formulation [19] in an attempt to overcome the issue of poor coverage in low-income settings [8, 39]. The diversity of GAS strains in NC (SRI 14.3) is higher than in the United States, Canada, and Europe but lower than in Ethiopia, India, and Fiji, for which SRI ranged from 27 to 50 [12].

Importantly, our results show that, based on *emm*-typing results, 70% of the strains recovered in New Caledonia in 2012 were absent in the same country 6 years prior. This result is clearly different from what is observed in North America where, although some variation occurs on a year-to-year basis, the overall *emm* type distribution remains stable through short periods of time, with only a limited number of strains responsible for the majority of infections over the last 10 years [34, 37]. The large change in *emm*-type distribution in NC indicates that vaccine coverage predictions based on *emm*-typing results must be interpreted with caution in the Pacific region. Such a transformation in *emm*-type distribution in a relatively short period of time cannot easily be explained by the minimal changes in socioeconomic, political, or medical climate in NC over these 6 years. An alternative hypothesis could be that the high discriminating power of *emm* typing might result in detecting differences that, in current times and in specific geographic locations, do not have clinical relevance [40].

When analyzing the NC data, we found that the *emm* clusters varied little during the same period of time. We previously

demonstrated that the *emm*-cluster typing system correlates with the binding abilities of the many *emm* types described so far [23]. Importantly, this capacity to bind host ligands is related with the virulence potential of any GAS isolate [7]. Moreover, in comparison with previous typing methods for GAS, the *emm*-cluster typing provides complementary information in terms of M protein sequence homology, structure conservation, and theoretical efficacy of M protein vaccine candidates [23]. It is therefore likely that this typing identifies clinically relevant variations in GAS epidemiology in the Pacific region. Importantly, this new molecular analysis allowed us to identify a common point between the *emm* types present in Australia, Fiji, and NC; whereas very few similarities could be found among the *emm* types in these 3 countries, only a limited number of *emm* clusters were responsible for most of the disease burden. The *emm*-cluster system could therefore be an important typing tool to identify vaccine antigen priorities. Of note, the *emm*-cluster allocation is automatically deduced from the *emm*-typing results [23]. This new typing system does not replace *emm* typing but rather adds meaningful information to this broadly used typing scheme.

In conclusion, this study confirmed the high disease burden of GAS infections in NC and supports the added value of the *emm*-cluster typing system to analyze the epidemiology of GAS and to contribute to global GAS vaccine development efforts by informing vaccine formulation.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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