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High burden of invasive β-haemolytic streptococcal infections in Fiji

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SUMMARY

We undertook a 5-year retrospective study of group A streptococcal (GAS) bacteraemia in Fiji, supplemented by a 9-month detailed retrospective study of β-haemolytic streptococcal (BHS) infections. The all-age incidence of GAS bacteraemia over 5 years was 11·6/100 000. Indigenous Fijians were 4·7 times more likely to present with invasive BHS disease than people of other ethnicities, and 6·4 times more likely than Indo-Fijians. The case-fatality rate for invasive BHS infections was 28%. *emm*-typing was performed on 23 isolates: 17 different *emm*-types were found, and the *emm*-type profile was different from that found in industrialized nations. These data support the contentions that elevated rates of invasive BHS and GAS infections are widespread in developing countries, and that the profile of invasive organisms in these settings reflects a wide diversity of *emm*-types and a paucity of types typically found in industrialized countries.

INTRODUCTION

Recent studies have identified an increasing incidence of invasive group A streptococcal (GAS) infections worldwide [1, 2]; there has also been a growing number of reports of invasive disease caused by Lancefield group C and group G streptococci (GCS and GGS), also known as *Streptococcus dysgalactiae* subsp. *Equisimilis* [3, 4]. The incidence of invasive GAS infections in industrialized nations from well-established population-based studies ranges from 1·9 to 3·8/100 000 with a case-fatality rate of 10–13% [5–7]. However, the epidemiological picture is not clear in less-developed nations. From the limited published data available it is probable that invasive GAS disease is more common in these regions [8]. For example, in a recent study in Kenya, the incidence of GAS bacteraemia in children aged <1 year was 96/100 000 and in children aged <15 years the incidence was 13/100 000 [9]. Studies in indigenous populations in otherwise wealthy nations have also shown a high incidence of invasive GAS disease; 82/100 000 in Australian Aboriginals in Queensland and 46/100 000 in Native Americans in Arizona [10, 11].

The most common clinical presentation of invasive GAS infection is soft-tissue infection, including necrotizing fasciitis. Other presentations include pneumonia, septic arthritis and bacteraemia without

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focus. Invasive GAS infection is complicated by the development of streptococcal toxic shock syndrome in about 10% of cases [12]. The clinical presentation of invasive GCS and GGS disease appears to be similar to invasive GAS disease and toxic shock syndrome can also occur [13].

The molecular epidemiology of invasive GAS disease has been carefully recorded in some industrialized nations over the past several years particularly under the auspices of strep-EURO in Europe and the Centers for Disease Control and Prevention in the United States [1, 5, 14]. These surveillance systems have identified a wide variety of *emm*-types but with a clear predominance for a smaller number of dominant *emm*-types including *emm*-types 1, 3, 12 and 28 [5]. In contrast, available molecular data from indigenous populations such as the Aboriginal population in Northern Queensland and the Northern Territory of Australia demonstrate no apparent dominant *emm*-types [11, 15].

There are no published data on the incidence of invasive BHS or GAS infections in Pacific Island Countries, where there is a demonstrated high burden of other GAS diseases such as rheumatic fever and post-streptococcal glomerulonephritis [16, 17]. We aimed to document the epidemiology of invasive β-haemolytic streptococcal (BHS) infections in a developing country in the Pacific.

Setting

Fiji is an independent republic of some 300 islands in the Western Pacific north of the Tropic of Capricorn. It has an estimated current population of 832 000 people comprising of two major racial groups of Indigenous Fijians (over 50%) and Indo-Fijians ($\sim$40%). Fiji is ranked 90 out of 177 nations on the United Nations Development Programme Human Development Index and has a GDP *per capita* of US$ 6066 and an infant mortality rate of 16/1000 [18]. The overall crude mortality rate in Fiji is 5·3/1000, and life expectancy at birth is 64·5 years for males and 68·7 years for females [19]. More than 53% of the population live in rural areas. The major hospital, the Colonial War Memorial Hospital (CWMH), is located in the capital, Suva, in the Central Division of Fiji, on the main island of Viti Levu. This hospital predominantly serves the Central Division of Fiji, although patients from other divisions of Fiji may be referred to the hospital. We used the population of the Central Division from the most recent complete census in 1996 as the denominator for incidence calculations; the total population of the Central Division at this time was 297 607 with 175 878 being Indigenous Fijian (59·1%) and 98 660 being Indo-Fijian (33·2%).

Table 1. *Group A streptococcal bacteraemia in the Central Division of Fiji, January 2000 to February 2005*

Age group (years)	No. of cases	Population	Annual incidence per 100 000 (95% CI)
0–4	48	35 759	26 (19·2–34·4)
5–14	3	65 890	0·9 (0·2–2·6)
15–34	13	109 966	2·3 (1·2–3·9)
35–64	64	76 880	16·1 (12·4–20·6)
>64	40	9112	85 (60·7–115·7)
Unknown	11	—	—
Total	179	297 607	11·6 (10–13·5)

METHODS

We performed a retrospective review of positive GAS blood cultures at CWMH from people living in the Central Division during the period January 2000 to February 2005. GAS isolates and detailed clinical data were not available for most of these cases, so we supplemented these data with a more comprehensive review of cases of sterile site (blood culture, CSF and sterile site aspirates) BHS isolates during the 9-month period from June 2004 to February 2005. Clinical and demographic data were collected from the hospital electronic database and where available medical charts were reviewed for clinical information. In almost half of the cases the corresponding sterile site isolates were available for *emm*-typing, which was performed using the current technique devised by the Centers for Disease Control and Prevention (CDC, Atlanta, GA, USA) [20]. In addition, these isolates were all tested for the presence of conserved epitopes in the C-repeat region of the M protein, as described previously [21, 22]. Relative risks were calculated as incidence rate ratios with 95% confidence intervals (95% CI). This work was approved by the Fiji National Research Ethics Review Committee.

RESULTS

GAS bacteraemia, 2000–2005

The annual all-age incidence of positive GAS blood cultures in the Central Division for the 5-year period

January 2000 to February 2005 was 11·6/100 000 (95% CI 10·0–13·5), with the highest rates in children (<5 years) and the elderly (>64 years, Table 1). There were no seasonal peaks observed.

Invasive BHS infections, 2004–2005

During the 9-month period there were 49 cases of invasive BHS disease (39 GAS, 6 GGS and 4 GCS, Tables 2 and 3). Thirty-nine of these occurred in residents of the Central Division (all-age annual incidence of invasive BHS disease 17·5/100 000, 95%CI 12·4–23·9; Table 3). Thirty-one cases of invasive GAS infection occurred in residents of the Central Division (all-age incidence 13·9/100 000, 95% CI 9·4–19·7), similar to the incidence for the 2000–2005 period). The age distribution paralleled the bimodal distribution seen in the 2000–2005 period, with peaks occurring in children aged <5 years (44·7/100 000, 95% CI 23·1–78·2) and adults aged >64 years (146·3/100 000, 95% CI 70·2–269).

Ethnicity data were available in 48 cases, of which 42 (88%) were Indigenous Fijians. The incidence rate ratio for invasive BHS infections in the Central Division in Indigenous Fijians was 4·7 (95% CI 1·8–15·4) compared to other races, and 6·4 (95% CI 2·0–32·4) compared to Indo-Fijians (Table 3).

Of the 43 cases of invasive BHS disease with outcome information available there were 12 deaths (case-fatality rate 28%). Two of these occurred in children aged <5 years of age. Of the 34 cases of GAS disease with outcome information available there were 10 deaths (case-fatality rate 29%).

BHS were isolated from blood culture alone in 43 cases, from joint aspirate alone in four cases, from both blood culture and joint aspirate in one case, and from CSF in one case. We were able to ascertain a clinical diagnosis in 42 of these 49 cases. Soft-tissue infections were the most common clinical infection (12 cases, 29%), followed by pneumonia (10, 24%), and septic arthritis (8, 19%). Meningitis occurred in three patients. Accurate data to assess the proportion of cases complicated by streptococcal toxic shock syndrome were not available. The only reliable risk factor data were for diabetes and pyoderma. Of the 22 cases of BHS disease with risk factor information available, 10 (45%) had co-existing diabetes and eight (36%) had had pyoderma in the preceding 28 days.

Twenty-three BHS isolates were available for *emm*-typing. There were 17 different *emm*-types, including 12 different *emm*-types among the 16 GAS isolates. There were four cases with *emm*-type STN5554, three cases with *emm*-type STC74A and two cases with *emm*-type 18, otherwise all other cases were unique *emm*-types. STC74A was shared between GCS and GGS cases. *emm*-subtype 12·8, normally associated with GAS, was seen in a GGS isolate. All 23 isolates tested contained a conserved region epitope that is recognized by antisera to the vaccine candidate J8.

DISCUSSION

These data confirm that invasive BHS and GAS infections occur at elevated rates in Fiji compared to industrialized countries, and suggest that previous findings of high rates in Kenya and indigenous populations of Australia and the United States may reflect a general tendency for these diseases to occur more frequently in developing countries. Together with the high case-fatality rate documented here, this study supports our previous contention that the global burden of invasive GAS infections has been considerably underestimated [8].

We found a significantly elevated rate of invasive BHS infections in the Indigenous Fijian population compared with people of other racial backgrounds in Fiji. We did not have sufficient data to determine if this reflects an ethnic susceptibility or other factors (e.g. increased exposure to organisms because of overcrowded living conditions). Other studies have found higher rates of bacterial infections in Indigenous Fijians: one study found that Indigenous Fijian children were 29 times more likely than Indo-Fijian to present with chest X-ray-confirmed pneumonia [23]. It is our observation that the socio-economic status of Indigenous Fijians is not significantly worse than Indo-Fijians; a survey of household income and expenditure in 2002 found that 29·7% of Indigenous Fijian adults and 33·4% of Indo-Fijian adults were in full-time employment [24]. This raises the possibility that Indigenous Fijians may have an increased susceptibility to particular infections and this deserves further study.

The case-fatality rate in this study for invasive BHS and GAS infections was higher than in industrialized nations. Whilst this high rate probably represents late presentation and reduced availability of medical care such as access to intensive care and intravenous immunoglobulin, even under ideal conditions a substantial proportion of cases can be expected to die.

Table 2. *Detail of cases of β-haemolytic streptococcal (BHS) invasive disease at the Colonial War Memorial Hospital June 2004 to February 2005, by Lancefield group and by age*

Patient no.	BHS group	Age	Gender	Ethnicity	Clinical infection	Risk factors	Residence by division	Culture site	Outcome	*emm*-subtype
1	A	2 mo.	F	Indo-Fijian	Sepsis	n.a.	Central	BC	Deceased	68
2	A	2 mo.	F	Fijian	Pneumonia	n.a.	Central	BC	Recovered	n.a.
3	A	2 mo.	M	Fijian	Sepsis	n.a.	Central	BC	Recovered	n.a.
4	A	3 mo.	F	Fijian	Skin sepsis	Pyoderma*	Central	BC	Recovered	n.a.
5	A	5 mo.	F	Fijian	Sepsis	n.a.	Central	BC	Recovered	n.a.
6	A	7 mo.	F	Fijian	Meningitis	n.a.	Central	CSF	Recovered	n.a.
7	A	8 mo.	F	Fijian	Pneumonia	Pyoderma*	Central	BC	Recovered	81.3
8	A	10 mo.	F	Fijian	n.a.	n.a.	Northern	BC	n.a.	n.a.
9	A	1 yr 3 mo.	M	Fijian	Pneumonia	n.a.	Central	BC	Recovered	n.a.
10	A	1 yr 9 mo.	M	Indo-Fijian	Sepsis	No risk factor identified	Central	BC	Recovered	25
11	A	2 yr 1 mo.	M	Fijian	Meningitis	n.a.	Central	BC	Deceased	STN5554
12	A	2 yr 10 mo.	F	Fijian	Septic arthritis	Pyoderma*	Central	Joint aspirate	Recovered	18.12
13	A	4	M	Fijian	Meningitis	n.a.	Northern	BC	n.a.	n.a.
14	A	24	F	Fijian	Gynaecological	n.a.	Eastern	BC	Recovered	n.a.
15	A	25	M	Fijian	Endocarditis	n.a.	Central	BC	Recovered	n.a.
16	A	27	M	Fijian	Septic arthritis	n.a.	Central	Joint aspirate	Recovered	n.a.
17	A	32	M	Fijian	Pyomyositis/septic arthritis	n.a.	Central	Joint aspirate	Recovered	n.a.
18	A	36	F	Fijian	Cellulitis	Diabetes	Central	BC	Recovered	18.2
19	A	42	M	Fijian	Septic arthritis	n.a.	Eastern	Joint aspirate	Recovered	n.a.
20	A	43	M	Other	Peritonitis	n.a.	Central	BC	Deceased	n.a.
21	A	52	M	Fijian	n.a.	n.a.	Central	BC	Recovered	n.a.
22	A	54	F	Fijian	Soft tissue	Diabetes/Pyoderma*	Central	BC	Amputation	104
23	A	54	F	Fijian	Sepsis	Diabetes	Central	BC	Deceased	n.a.
24	A	55	F	Fijian	Neck abscess	Diabetes	Central	BC	Deceased	116·1
25	A	58	F	Fijian	Wound infection	Diabetes	Central	BC	Deceased	STN5554.1
26	A	58	M	Fijian	Pneumonia	n.a.	Central	BC	Recovered	n.a.
27	A	59	F	Fijian	n.a.	n.a.	Central	BC	Recovered	n.a.
28	A	60	F	Fijian	Soft tissue	Diabetes	Eastern	BC	Recovered	22·1
29	A	60	M	Other	Chest abscess	Diabetes/Pyoderma*	Central	BC	Deceased	86.2
30	A	65	M	Fijian	Wound infection	Diabetes/Pyoderma*	Central	BC	Recovered	74
31	A	66	F	Fijian	Leg abscess	Pyoderma*	Central	BC	Deceased	4·5
32	A	67	F	Indo-Fijian	Cellulitis	n.a.	Central	BC	Deceased	n.a.
33	A	68	F	Fijian	Cellulitis	n.a.	Northern	BC	n.a.	n.a.
34	A	71	F	Fijian	Sepsis	Diabetes/Pyoderma*	Central	BC	Recovered	n.a.
35	A	73	F	Fijian	Septic arthritis	No risk factor identified	Central	BC	Recovered	STN5554.1
36	A	79	M	Fijian	Pneumonia	Diabetes	Central	BC	Deceased	71
37	A	83	M	Fijian	Pneumonia	n.a.	Central	BC	Recovered	n.a.
38	A	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	BC	n.a.	STN5554.1
39	A	n.a.	F	Fijian	n.a.	n.a.	Northern	BC	n.a.	n.a.
40	G	3 yr 6 mo.	F	Fijian	Pneumonia	No risk factor identified	Central	BC	Recovered	STC74A

Table 2 (*cont.*)

Patient no.	BHS group	Age	Gender	Ethnicity	Clinical infection	Risk factors	Residence by division	Culture site	Outcome	*emm*-subtype
41	G	37	M	Fijian	Sepsis	No risk factor identified	Central	BC	Recovered	STC36
42	G	56	M	Indo-Fijian	Septic arthritis	n.a.	n.a.	BC	n.a.	n.a.
43	G	57	M	Fijian	Pneumonia	No risk factor identified	Central	BC	Recovered	STG480
44	G	68	M	Fijian	Pneumonia	No risk factor identified	Central	BC	Deceased	STC74A
45	G	82	F	Fijian	Septic arthritis	n.a.	Central	BC & joint aspirate	Deceased	12.8
46	C	31	F	Fijian	Abscess	n.a.	Central	BC	Recovered	n.a.
47	C	57	F	Fijian	Sepsis	Diabetes	Central	BC	Recovered	STC74A
48	C	75	M	Fijian	Pneumonia	n.a.	Northern	BC	Recovered	n.a.
49	C	77	M	Fijian	Septic arthritis	No risk factor identified	Central	BC	Recovered	STC5345

n.a., Information not available; BC, blood culture.
* Pyoderma reported in preceding 28 days.

The findings in this study of a high number of invasive skin infections and the apparent association of pyoderma with invasive disease suggests a potential role for skin sore and scabies control programmes in reducing invasive disease incidence. The findings also support the need to consider prevention of pyoderma as well as pharyngitis in the development of GAS vaccines.

Although the number of isolates that were *emm*-typed in this study was small, there was relatively high genetic diversity, with 17 different *emm*-types among the 23 isolates from invasive BHS infections and 12 different *emm*-types among the 16 isolates from invasive GAS infections. In recent surveillance studies of invasive GAS isolates in the United States, only 41 *emm*-types were found among 1064 isolates [14]. In addition to this comparatively higher genetic diversity of *emm*-types, the *emm*-types recovered from the isolates in this study were different to those found in the United States. This mirrors the findings for both invasive and non-invasive GAS isolates in other tropical areas, including in Hawaii and in Aboriginal populations in northern Australia, and in other developing countries [11, 25, 26]. These findings have implications for the development of a GAS vaccine. There are a number of GAS vaccine candidates currently under development but only one vaccine has reached clinical trials – this vaccine is a multivalent vaccine containing N-terminal protein fragments from 26 common serotypes of GAS from the United States [27]. In our study only two of the 17 different *emm*-types found are included in this vaccine (*emm*-type 18 and *emm*-type 22). A vaccine based upon the conserved region of the M protein may circumvent this problem of serotype specificity. An epitope, J8, has been identified in the conserved C-repeat portion of the M protein and is the subject of vaccine research [22]; in our study all GAS, GCS and GGS isolates tested contained a conserved region epitope that is recognized by antisera to the J8 vaccine candidate.

The epidemiology of invasive GAS infections and other invasive BHS infections is poorly understood in most developing nations. The data from this study represent the beginning of more detailed epidemiological research in Fiji and indicate that invasive GAS disease is more common in Fiji than in industrialized nations and that the case-fatality rate is high. This study also indicates that *emm*-type profile is different from industrialized nations, but appears similar to the Aboriginal population in northern

Table 3. *Incidence of invasive beta-haemolytic streptococcal* (*BHS*) *disease and group A streptococcal* (*GAS*) *disease in the Central Division of Fiji, June 2004 to February 2005*

Age group (years)	Population	Cases of invasive BHS infection*	Annual incidence of invasive BHS infection per 10 000 (95% CI)	Cases of invasive GAS infection†	Annual incidence of invasive GAS infection per 100 000 (95% CI)
Whole population					
0–4	35 759	12	44·7 (23·1–78·2)	11	41 (20·5–73·4)
5–14	65 890	0	—	0	—
15–34	109 966	4	4·9 (1·3–12·4)	3	3·6 (0·8–10·6)
35–64	76 880	13	22·6 (12–38·6)	10	17·3 (8·3–31·9)
>65	9112	10	146·3 (70·2–269)	7	102·4 (41·2–210·9)
Total	297 607	39	17·5 (12·4–23·9)	31	13·9 (9·4–19·7)
Indigenous Fijian population					
0–4	23 308	10	57·2 (27·4–105·2)	9	51·5 (23·5–97·7)
5–14	40 955	0	—	0	—
15–34	63 398	4	8·4 (2·3–21·6)	3	6·3 (1·3–18·5)
35–64	42 520	11	34·5 (17·2–61·7)	8	25·1 (10·8–49·4)
>65	5697	9	210·6 (96·4–399·5)	6	140·4 (51·6–305·4)
Total	175 878	34	25·9 (17·9–36·2)	26	19·8 (12·9–29)

Incidence rate ratio (Indigenous Fijians compared to other races): * BHS disease 4·7 (95% CI 1·8–15·4; † GAS disease 3·6 (95% CI 1·4–12).

Australia and possibly in other developing nations in tropical and subtropical regions.

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DECLARATION OF INTEREST

None.

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