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Meningitis in children in Fiji: etiology, epidemiology, and neurological sequelae

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SUMMARY

Objectives: To describe the etiology, epidemiology, neurological sequelae, and quality of life of children aged 1 month to less than 5 years admitted with meningitis to the Colonial War Memorial Hospital (CWMH), Suva, Fiji.

Methods: Over a 3-year period, all eligible children with suspected meningitis admitted to CWMH had blood drawn for culture. Of these children, those for whom it was possible were tested for a four-fold rise in antibody titers to *Haemophilus influenzae* type b (Hib) and pneumococcal surface adhesin A (PsaA). Cerebrospinal fluid (CSF) was taken for bacteriological culture and antigen testing. CSF was also tested by PCR for *Streptococcus* species, *Neisseria meningitidis*, Hib, *Mycobacterium tuberculosis*, and enterovirus. Pneumococcal isolates were serotyped using multiplex-PCR reverse-line blot hybridization. Following discharge, cases underwent a neurological assessment, audiometry, and quality of life assessment (Pediatric Quality of Life Inventory (PedsQL) tool).

Results: There were 70 meningitis cases. Meningitis was more common in indigenous Fijian than Indo-Fijian children. Enterovirus was the most common etiological agent and appeared to be outbreak-associated. *Streptococcus pneumoniae* was the most common bacterial cause of meningitis with an annual incidence of 9.9 per 100 000 under 5 years old (95% confidence interval 4.9–17.7) and a case fatality rate of 36%. With the exception of deafness, neurological sequelae were more frequent in cases of bacterial meningitis than in viral meningitis (18.5% vs. 0%, $p = 0.04$). Quality of life at follow-up was significantly lower in patients with bacterial meningitis than in those with viral meningitis ($p = 0.003$) or meningitis of unknown etiology ($p = 0.004$).

Conclusions: During the study period an outbreak of enterovirus occurred making it the most common etiological agent identified. However in the absence of this outbreak, *S. pneumoniae* was the most common cause of childhood meningitis in Fiji. Bacterial meningitis is associated with serious sequelae and a reduced quality of life.

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1. Introduction

Bacterial meningitis (BM) is a serious cause of morbidity and mortality in children worldwide.¹ BM is more common in resource-poor countries than in industrialized countries.² Excluding cases arising from epidemics, approximately one million cases of BM occur every year, with approximately 170 000 of these being fatal.³ As a number of new vaccines to prevent meningitis are either available or

in development, it is important to determine the etiology and burden of meningitis to allow governments to make evidence-based decisions about the introduction of these new vaccines. For a variety of reasons, including disparities in drawing appropriate specimens and suboptimal laboratory techniques, many low-resource countries have low yields of bacterial isolates making it difficult to quantify the disease burden due to specific organisms.

Childhood meningitis is caused by a number of viruses, bacteria, and other microorganisms. The predominant causes of BM in children older than 2 months of age are *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type b (Hib).⁴ Since the introduction of Hib vaccine, the incidence of Hib meningitis has declined.⁴ *S. pneumoniae* is now the predominant

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cause of non-epidemic BM; it was estimated to cause 103 000 cases globally in the year 2000.⁵ The case fatality rate (CFR) for children with BM varies by age of onset and etiology, but typically ranges from 3% to 19% in industrialized settings.⁶ Higher CFR (37–60%) have been reported in resource-poor countries, which may partly be due to delayed access to health care.⁶ Neurological sequelae following BM are common and occur more frequently in resource-poor countries (up to 65%)^{7,8} compared with industrialized countries (up to 25%). Rates of sequelae differ by etiology.⁷

For viral meningitis (otherwise known as aseptic meningitis), enteroviruses are the most common cause.⁹ Certain enteroviruses (coxsackie B5, echovirus 6, 9 and 30) are more likely to cause meningitis outbreaks, while others (coxsackie A9, B3 and B4) are mostly endemic.¹⁰

In Fiji, the Ministry of Health is currently contemplating the introduction of a pneumococcal conjugate vaccine (PCV). In order to make an evidence-based decision on the need for this vaccine, the burden of disease needs to be established. The aim of this prospective study was to describe the etiology, incidence, CFR, neurological sequelae, and quality of life of children aged 1 month to less than 5 years admitted with meningitis to the Colonial War Memorial Hospital (CWMH) in Suva, Fiji.

2. Methods

2.1. Background to the study site

Fiji is located in the South Pacific and consists of over 300 islands. The two main islands are Viti Levu and Vanua Levu, the former being the largest. The total population of Fiji is 837 271 (2007 census). The total population aged under 5 years in the catchment area is 33 979, with approximately 71% of these being indigenous Fijian and 22% Indo-Fijian (Indian ethnicity) (2007 census). Health care is provided free of charge. Access to health care is good as transport is generally affordable, most roads are well developed, and health centers and nursing stations are widely distributed in the rural areas. The infant mortality rate is 15.2/1000 live births,¹¹ and it is uncommon for children to die at home before receiving health care. The bacille Calmette–Guérin (BCG) vaccine is given to all infants at birth, and a national three-dose infant Hib vaccination schedule was introduced in Fiji in 1995, achieving high coverage in recent years. PCV is not in routine use.

The health services in Fiji are divided into four medical divisions. The population of children aged under 5 years in the Central Medical Division is 33 979 (2007 census). All suspected meningitis cases within the catchment population of the Central Medical Division are referred and admitted to CWMH. CWMH is the only hospital in the Central Medical Division that provides pediatric intensive care services and is also the only hospital with microbiology laboratory facilities. There are no private inpatient services available in the catchment area.

2.2. Study design

This was a prospective study including children aged 1 month to less than 5 years with suspected meningitis residing within the Central Medical Division during the period October 1, 2004 to September 30, 2007. All children admitted to CWMH with suspected meningitis had a blood culture drawn and lumbar puncture taken (unless contraindicated), and were commenced on dexamethasone and intravenous ceftriaxone. In addition, infants aged 1–2 months were commenced on intravenous ampicillin. Antimicrobials were continued for 10 days and dexamethasone for 4 days. Infants less than 2 months of age were treated with antimicrobials for 21 days. Antimicrobials were rationalized according to the antimicrobial sensitivity pattern.

Cerebrospinal fluid (CSF) was transported immediately to the CWMH microbiology laboratory for microscopy, cell count, biochemical analysis, and culture for bacteria. CSF was also tested for pneumococcal antigen by immunochromatography (Binax-NOW[®] *S. pneumoniae*, Inverness Medical, Cranfield, UK) and latex antigen for *S. pneumoniae*, Hib, and *N. meningitidis* (Wellcogen[®] bacterial antigen kit rapid latex agglutination test). Any remaining CSF was stored at -70°C . Blood was cultured using the BacT/ALERT[®] system (bioMérieux, Durham, NC, USA). Blood was redrawn 7–10 days later, with serum separated by centrifugation and stored at -70°C until tested. Serum and CSF were transported on dry ice to overseas laboratories for further testing. All pneumococcal isolates were sent to the Pneumococcal Reference Laboratory, Centre for Infectious Diseases and Microbiology, Institute for Clinical Pathology and Medical Research, Westmead, New South Wales, Australia, where they were serotyped using a multiplex-PCR reverse-line hybridization assay.^{12,13}

A meningitis case was defined as having a CSF white blood cell count (WBC) of $>10 \times 10^6/\text{l}$ or clinical features of meningitis as determined by a pediatrician. A BM case included those with: bacteria isolated from CSF; a positive CSF for bacterial antigen; a purulent but sterile CSF with a positive blood culture; autopsy confirmation; a subdural effusion on computed tomography (CT) scan; CSF WBC $\geq 100 \times 10^6/\text{l}$; CSF WBC $10\text{--}99 \times 10^6/\text{l}$ with glucose <4 mmol/l and protein >100 mg/dl; causative organisms identified through CSF PCR for *Streptococcus spp.*, *N. meningitidis*, Hib, or *Mycobacterium tuberculosis*; a four-fold rise in anti Hib-ELISA or pneumococcal surface adhesin A (PsaA) titer¹⁴ on paired sera (performed at the Royal Children's Hospital, Melbourne, and the Vaccine Trials group of the Telethon Institute, Princess Margaret Hospital, University of Western Australia, respectively).

Cases of viral meningitis included those with negative laboratory results as previously listed, and a positive CSF PCR for enterovirus.¹⁵ A case of meningitis of unknown etiology included those negative for all criteria listed previously, or with clinical meningitis as confirmed by a pediatrician, in whom a lumbar puncture was contraindicated.

Children with nosocomial infections and those admitted for bacterial meningitis who lived outside the defined catchment area were excluded from the study.

Clinical management, outcomes, and complications were documented during the hospital admission. Short- and long-term morbidities were assessed at approximately 6–8 weeks and 6 months following discharge. The children were reviewed to assess neurological sequelae by a neurological examination undertaken by a trained doctor (VB). Tests for vision included the assessment of pupillary light reflex, presence of nystagmus, extraocular movements, and visual field testing where possible. At review, all parents were asked to complete a validated¹⁶ standardized quality of life questionnaire (Pediatric Quality of Life Inventory tool (PedsQL); Mapi Research Institute, Lyon, France) to rate their child's functioning. The questionnaire assessed functioning in four broad areas: physical, emotional, social, and, where old enough, school performance.^{17,18} An experienced pediatric audiologist performed audiometry including pure tone audiometry, behavioral observation audiometry, auditory brainstem response testing, visual reinforcement audiometry, or impedance audiometry on all available children. Mild, moderate, severe, and profound hearing loss were defined as on average the most quiet sounds heard with the better ear at 26–35 dB, 36–60 dB, 61–90 dB, and ≥ 90 dB, respectively.

2.3. RNA extraction from CSF

All procedures were carried out in a class II biohazard cabinet to minimize the risk of contamination. Bacterial RNA was extracted

from CSF using the FastRNA[®] Pro Blue Kit (Qbiogene), and viral RNA was extracted using the High Pure Viral Nucleic Acid Kit (Roche), in accordance with the manufacturers' instructions. Briefly, CSF was centrifuged for 20 min at 4 °C and 16 100 × g. The volume of each sample was recorded and the CSF was transferred to a new 1.5-ml Eppendorf tube for RNA extraction, whilst the pellet was processed using the bacterial RNA kit. Finally, the RNA was resuspended in either 50 µl of diethylpyrocarbonate (DEPC)-water (bacteria) or 50 µl of elution buffer (virus). RNA was also extracted from a pool of CSF taken from control patients and proved to be bacteria- and virus-negative by reverse transcriptase (RT)-PCR.

2.4. Detection of bacterial and enteroviral RNA

Bacterial and enteroviral RNA was detected using the Superscript III One Step RT-PCR System with Platinum Taq DNA Polymerase (Invitrogen). Each 50-µl reaction contained 10 µM of each primer (Table 1^{3,19–21}) and 5 µl of RNA template. Cycle conditions were as per the manufacturer's instructions with slight modifications. For bacterial detection, cDNA was amplified at 55 °C for 15 min, followed by heat denaturation at 94 °C for 2 min, 30 cycles with heat denaturation at 94 °C for 15 s, 55 °C annealing for 30 s, and extension at 68 °C for 40 s. Enterovirus RNA was detected by amplifying cDNA at 55 °C for 30 min, followed by heat denaturation at 94 °C for 2 min, 40 cycles of heat denaturation at 94 °C for 15 s, 55 °C annealing for 30 s, and extension at 68 °C for 15 s. First round enteroviral products were diluted 1:500 in PCR-grade water; 2 µl of this sample served as template in the second round PCR, which was performed in a 26-µl reaction mixture containing 2 mM of MgCl₂, each of the deoxyribonucleotides at 0.2 µM, each primer at 0.4 µM, and 0.025 U of Taq DNA polymerase. The following cycles were applied: initial heat denaturation at 94 °C for 2 min, 35 cycles with heat denaturation at 94 °C for 20 s, 55 °C annealing for 20 s, and extension at 72 °C for 30 s. PCR products were visualized by 2.0% agarose gel electrophoresis with 1X Tris–acetate–EDTA (TAE) buffer containing 1X SYBR[™] Safe (Invitrogen).

2.5. Specificity and sensitivity of the RT-PCR assays

RNA extracted from the four control bacteria were used as positive controls to test the specificity of the multiplex RT-PCR. Negative controls consisted of *Escherichia coli* RNA and RNA extracted from a pool of normal CSF samples. Only the bacteria of interest produced an amplicon of the relevant size.^{20,22} RNA extracted from enterovirus 71 (EV71) was used as positive enterovirus control. RNA extracted from a pool of patient CSF was used as a negative control.

To determine the lower limit of detection, 10-fold serial dilutions of *S. pneumoniae* ranging from 7.5 × 10⁴ to 10⁻³ CFU/ml were prepared. For *M. tuberculosis*, 100 µl of spiked sputum was used neat and serially diluted. The dilutions of bacteria were used to spike 500 µl of the control CSF. Similarly, 100 µl of EV71 was serially diluted 10-fold (10⁶ to 10⁻¹ TCID₅₀ (median tissue culture infective dose)) and used to spike 100 µl of control CSF. All spiked controls were frozen at -70 °C for approximately 4 weeks to mimic the Fijian CSF storage conditions. The sensitivity of detection of *S. pneumoniae* from frozen CSF was 750 genomes per CSF sample, and 50 µl of the *M. tuberculosis* suspension, whilst the limit of RNA detection was 1.3 pg. The sensitivity for viral detection was 10 TCID₅₀ of EV71 extracted from frozen CSF.

2.6. Sequencing and bioinformatics

PCR products were excised from agarose and purified using the QIAquick Gel Extraction Kit (Qiagen) in accordance with the manufacturer's instructions. The sequencing reactions were performed with the Big Dye Terminator Cycle Sequencing Kit v1.3 (Applied Biosystems) and cycle reactions were then purified using the DyeEx 2.0 Spin Kit (Qiagen) in accordance with the manufacturers' instructions. The resulting sequences were compared to sequences stored in GenBank using the local alignment search tool (BLAST; <http://www.ncbi.nlm.nih.gov/BLAST/>).

2.7. Statistical analysis

Data were exported to Stata version 9.0 (Stata Corp., College Station, TX, USA) for analysis. Chi-square or Fisher's exact tests were used to test for statistically significant differences between categorical variables at the *p* < 0.05 level. For the PedsQL questionnaire, a total score was calculated for each case using an internationally validated standard PedsQL scoring system.^{17,18} As a reference point, a total score of 90 was the mean score found in healthy children in developed countries.^{17,18} A mean total score was calculated for each of the three categories of meningitis. In addition, mean scores were calculated for each PedsQL subgroup: the mean psychosocial health summary (the mean of the sum of the items in this category divided by the number of items answered in the emotional, social, and school functioning scales) and the mean physical health summary (the physical functioning scale score). The mean scores were compared using an unpaired *t*-test for each meningitis category. Incidence rates were calculated based on the number of cases for each organism with the catchment population taken from the 2007 census.

Table 1
Details of oligonucleotide primers used in this study

Primer name	Sequence (5'–3')	Target organism and gene	Position in gene sequence	Amplicon size (bp)	Reference
TB1	CGAACGGAAAGGTCTCTTCGGAGA	<i>Mycobacterium tuberculosis</i> 16S rRNA	65–88	138	19
TB2	ACCACAAGACATGCATCCCGTGGT	<i>M. tuberculosis</i> 16S rRNA	202–179		
STREP	GTACAACGAGTCGCAAGC	<i>Streptococcus spp</i> 16S rRNA		265 ^a	20
HI	CCTAAGAAGAGCTCAGAG	<i>Haemophilus influenzae</i> 16S rRNA	909–926	513 ^a	20
NM	TGTTGGGCAACCTGATTG	<i>Neisseria meningitidis</i> 16S rRNA	823–840	679 ^a	20
1492R	GGTTACCTTGTACGACTT	16S rRNA universal for domain Bacteria	1510–1492 ^b		3
EV1-R ^c	GCCGCATTACGGGGCCG	Enterovirus (family <i>Picornaviridae</i>) gene polyprotein, VP4 and VP2 region	468–451 ^d	303	Winnie Sim ^e
UG52	CAAGCACTTCTGTTTCCCGG		165–185 ^d	-	21
UC53 ^c	TTGTACCATAASCAGCCA		600–581 ^d	435	21

^a When paired with universal primer 1492R.

^b Location in the *Escherichia coli* 16S rRNA gene.

^c When paired with sense primer UG52.

^d Location in enterovirus 71 strain TW/2086/98.

^e Enteric Virus Group, Murdoch Children's Research Institute.

2.8. Ethics approval

Ethics approval for this study was granted by the Human Research Ethics Review Committee, the University of Melbourne, Australia, and the Fiji National Research Ethics Review Committee.

3. Results

During the 3-year study period, 112 cases of suspected meningitis were identified, with 76 fitting the inclusion criteria. Six refused consent resulting in 70 cases of meningitis that were available for analysis. Table 2 shows the demographic characteristics of the cases. Most patients with meningitis were indigenous Fijians (89%), and were infants (70%). Although enterovirus was the single most common cause of meningitis, BM was diagnosed in 46 (66%) of the patients overall.

Table 3 shows the clinical features of children with meningitis. Data on clinical features on admission were collected for 35 of the 46 children with BM, as 11 children died on arrival at hospital. These 11 children had meningitis confirmed by autopsy. Children with BM commonly presented with high fever, neck stiffness, and signs of raised intracranial pressure. Children with viral meningitis commonly presented with high fever and vomiting and less frequently presented with features of raised intracranial pressure compared with those with BM. High fever and neck stiffness were common in cases of meningitis of unknown etiology.

During admission, seizures were significantly more common in BM cases compared with viral meningitis and cases of unknown etiology (Table 3). There were no significant differences in sensorineural deafness between any of the three meningitis groups. The frequency of other neurological sequelae was significantly higher in the BM group compared with the viral meningitis group (18.5% vs. 0%, $p = 0.04$). The CFR for BM was 34%.

Of the survivors, the overall quality of life score (mean PedsQL score) was significantly lower in the cases with BM compared with both those with viral meningitis ($p = 0.003$) and those with meningitis of unknown etiology ($p = 0.004$) (Table 3). Also, significantly lower scores were found in BM cases compared with viral meningitis cases and with cases of unknown etiology for the two PedsQL subcategories: the mean psychosocial health score and the mean physical health score.

Of the 59 survivors, 40 had CSF samples available for PCR testing, and of these 14 (35%) were positive for a causative organism that was otherwise undetected by routine laboratory methods. Twelve CSF samples were positive for enterovirus only (30%), representing 17.1% of all meningitis cases. Five (12.5%) CSF samples were positive for *S. pneumoniae* and two (5%) were positive for *H. influenzae*. No samples were positive for *N. meningitidis* or *M. tuberculosis*.

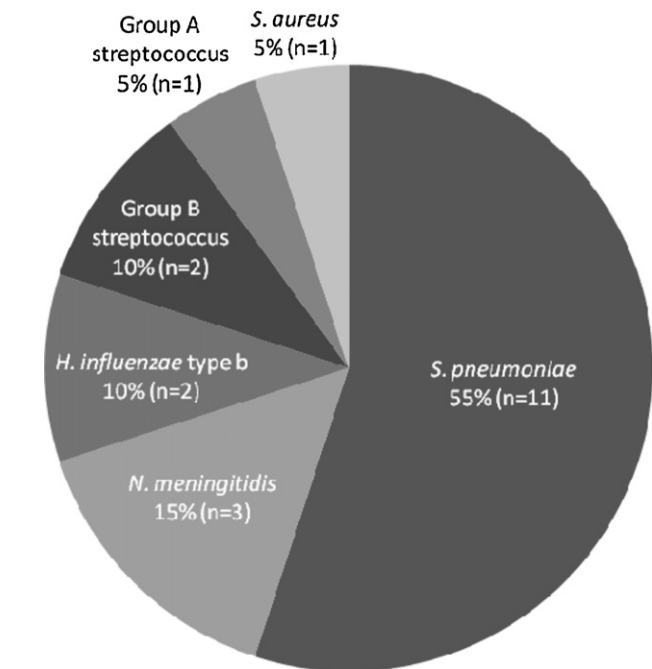


Figure 1. Etiology of bacterial meningitis (n = 20).

Forty of the 59 CSF samples were tested using BinaxNOW *S. pneumoniae* with 10 positive results. One additional pneumococcal case was identified by PCR and no additional cases were identified by BinaxNOW *S. pneumoniae* alone.

Figure 1 shows the etiology of BM cases. Of the 46 BM cases, 43% had a specific etiologic agent identified. *S. pneumoniae* was the most common bacterial cause of meningitis ($n = 11$), followed by *N. meningitidis* ($n = 3$). The *N. meningitidis* cases were all identified by routine laboratory tests as there was insufficient CSF available to perform PCR. There were two cases each of Hib and group B Streptococcus. The two cases of Hib meningitis were blood culture-confirmed as well as CSF latex antigen-positive and had previously received three doses of Hib vaccine at 6, 10, and 14 weeks respectively, as per the immunization schedule of Fiji.

There were 14 paired sera available for testing. No additional pneumococcal or Hib cases were identified by serology. Only one case had a two-fold rise in PsaA titer.

The annual incidence of pneumococcal meningitis in those aged under 5 years was 9.9 per 100 000 (95% confidence interval (CI) 4.9–17.7). All of the children with pneumococcal meningitis were

Table 2
Demographic features of children with meningitis (n = 70)

	Bacterial meningitis (n = 46), n (%)	Viral meningitis (n = 12), n (%)	Meningitis of unknown etiology (n = 12), n (%)
Ethnicity			
Indigenous Fijians	40 (87.0)	10 (83.3)	12 (100)
Indo-Fijian	3 (6.5)	2 (16.7)	0
Others	3 (6.5)	0	0
Gender			
Male	23 (50)	8 (66.7)	7 (58.3)
Female	20 (43.5)	4 (33.3)	5 (41.7)
Unknown	3 (6.5)	0	0
Age			
1 month	4 (8.7)	1 (8.3)	0
2–5 months	17 (37.0)	2 (16.7)	3 (25)
6–11 months	14 (30.4)	3 (25)	5 (41.7)
1 year	4 (8.7)	2 (16.7)	1 (8.3)
2–4 years	5 (10.9)	4 (33.3)	3 (25)
Unknown	2 (4.3)	0	0

Table 3

Clinical presentation, complications, neurological sequelae, and quality of life scores of children with meningitis

	Bacterial meningitis (n=35 ^a), n (%)	Viral meningitis (n=12), n (%)	Meningitis of unknown etiology (n=12), n (%)
Clinical features			
Temperature ≥ 38.0 °C	19 (54.3)	8 (66.7)	9 (75)
Glasgow coma score <15	17 (48.6)	0	2 (16.7)
Neck stiffness	21 (60)	3 (25) ^b	4 (33.3) ^c
Photophobia	1 (2.9)	1 (8.3)	0
Vomiting	13 (37.1)	10 (83.3)	3 (25) ^{c,d}
High pitched crying	2 (5.7)	0	0
Bulging fontanelle	17 (48.6)	1 (8.3) ^b	3 (25) ^c
Papilledema	0	0	0
Shock	4 (11.4)	0	0
Focal neurological signs	0	0	0
Seizures	19 (54.3)	2 (16.7) ^b	4 (33.3) ^c
SIADH	2 (5.7)	0	0
Pneumonia	3 (8.6)	0	0
Circulatory shock	3 (8.6)	0	0
Subdural effusion	7 (20)	0 ^b	0 ^c
Spasticity	4 (11.4)	0	1 (8.3)
Paresis	2 (5.7)	0	1 (8.3)
Sequelae at discharge	3/30 ^e (10)	0	3 (25)
Sequelae at follow-up			
Sensorineural deafness ^f	1/16 (6.3)	2/8 (25)	2/9 (22.2)
Other neurological sequelae	5/27 ^g (18.5)	0 ^b	1 (8.3)
Mean PedsQL score ^h at follow-up	64.8 (95% CI 43.9–85.8)	93.4 ^b (95% CI 82.2–104.5)	97.4 ^c (95% CI 88.2–106.4)
Mean psychosocial health score	77.5 (95% CI 59.8–95.2)	93.2 ^b (95% CI 83.7–102.7)	96.8 ^c (95% CI 93.6–100.1)
Mean physical health score	73.2 (95% CI 52.2–94.2)	93 ^b (95% CI 77.5–108.4)	98.3 ^c (95% CI 96.4–100.3)
Case fatality rate	34%	0	0

BM, bacterial meningitis; SIADH, syndrome of inappropriate anti diuretic hormone; 95% CI, 95% confidence interval.

^a Clinical data were available for 35/46 children with BM; the 11 children without clinical presentation data available died prior to hospitalization.^b $p < 0.05$, comparing BM with viral meningitis.^c $p < 0.05$, comparing BM with meningitis of unknown etiology.^d $p < 0.05$, comparing viral meningitis with meningitis of unknown etiology.^e Data for sequelae at discharge were available for 30/35 children as five died whilst in hospital.^f 33/54 survivors were available for audiology, with 21 being lost to follow-up.^g 27/35 BM children had a follow-up neurological assessment; three were lost to follow-up and five died during hospital admission.^h 46/54 of the surviving children were evaluated by using the PedsQL; of the eight who were not evaluated, five could not be contacted and three were out of the age range for testing.

indigenous Fijian. The annual incidence for pneumococcal meningitis in indigenous Fijians was 15.3 per 100 000 (95% CI 5.1–16.4) in those under 5 years old. The CFR for pneumococcal meningitis was 36% ($n = 4$). Eight of the pneumococcal isolates were serotyped and included both PCV serotypes (1, 3, 6B (2 cases), and 14 (2 cases)) and non-PCV serotypes (8 and 10F). Two of the eight serotyped cases died. Both were PCV serotypes. Three of the children with pneumococcal meningitis had neurological sequelae. The child with serotype 1 was hemiplegic; the child with serotype 3 had hypotonia of the lower limbs; and the child with serotype 8 had ongoing seizures.

4. Discussion

In this study, enterovirus was the most common cause of childhood meningitis. Interestingly, all enterovirus-associated cases occurred within a 5-month period, with most of the cases (75%) occurring within 2 months of study commencement, indicating an epidemic. Enteroviral meningitis epidemics have been described in many other settings²³ and are commonly due to coxsackie B5 and echoviruses 6, 9, and 30.¹⁰ Importantly, these enteroviral meningitis cases fitted the purulent meningitis case definition, which is used in many BM surveillance studies, and therefore this may overly attribute the meningitis disease burden to a bacterial rather than a viral etiology. However, the duration of the enterovirus outbreak was very short (5 months out of 36 months of surveillance). Had this outbreak not occurred, *S. pneumoniae* would have been the most common cause of childhood meningitis. This is consistent with other countries where Hib vaccine is routinely used resulting in very low rates of

Hib meningitis.²⁴ Comparing disease burden rates between geographical sites is difficult due to many factors including under-reporting, differences in reporting methods, antimicrobial prescribing practices, and disparities in blood culture practice and laboratory techniques. To address this, the World Health Organization and the Pneumococcal vaccines Accelerated Development and Introduction Plan (PneumoADIP) have standardized case definitions and have supported a coordinated multisite surveillance project of pneumococcal disease in Asia and Africa.²⁵ The incidence of pneumococcal meningitis in our study is slightly higher than that found in the UK²⁶ and non-indigenous Australia prior to PCV introduction,²⁷ but lower than reported rates in the Gambia²⁸ and in the indigenous Australian population.²⁹ In our study the CFR for pneumococcal meningitis was higher (34%) than that in Bangladesh⁸ and in the multisite surveillance studies in Asia and Africa,²⁵ but lower than that in Malawi.³⁰ Of the seven pneumococcal meningitis survivors, neurological sequelae were evident in 14%, which is a lower rate than that in Bangladesh⁸ and considerably lower than in a cohort study in Senegal.⁷ These differences may be due to under-reporting from loss to follow-up and differences in the neurological and developmental assessments undertaken.

Pneumococcal meningitis occurred only in indigenous Fijian children. Higher rates of pneumococcal nasopharyngeal carriage,³¹ hospitalization with X-ray confirmed pneumonia,³² and invasive pneumococcal disease (IPD) have been documented previously amongst the indigenous pediatric population in Fiji.³³ This may be due to environmental factors or a genetic susceptibility. Ethnic disparities in pneumococcal disease burden have been described elsewhere.^{29,34}

In this study, there were few pneumococcal isolates available for serotyping. However the potential PCV coverage of IPD for those under 5 years of age in Fiji has been reported previously.³⁴ Potential coverage by PCV for IPD improved as the valency increased (7-valent 53.3%, 10-valent 66.7%, 13-valent 83.3%).³³

Hib meningitis was uncommon in our study, as Hib vaccine has been part of the national immunization schedule in Fiji for over 10 years. The annual incidence was 1.8 per 100 000 children aged under 5 years, which is similar to that in other countries that routinely use Hib vaccine²⁴ and is the rate expected due to vaccine failures.²⁵ Fiji has achieved this low rate despite a 6, 10, 14 week primary series schedule without a booster. In contrast, the UK introduced a Hib vaccine booster in 2006 following a rise in the incidence of invasive Hib disease with a three-dose primary series without a booster.²⁴ Ongoing surveillance in Fiji will be required to ensure that this low rate is sustained.

Meningococcal meningitis was uncommon in our study. This is in contrast to the high rates documented in the Pacific Islander community living in New Zealand and necessitating the implementation of a novel vaccine.³⁵ It is unclear why the rates of meningococcal meningitis differ in different geographic areas among ethnically similar populations, but this is likely to be due to environmental factors such as overcrowding. In addition, there were no cases of TB meningitis in this study.

Low rates of sensorineural deafness were observed at follow-up, with no significant difference found by type of meningitis. This may be due to the small sample size and the fact that follow-up was not complete for all study participants, as these rates are lower than those reported from Mexico,³⁶ Bangladesh,⁸ and the Netherlands.³⁷

Our study also showed that 10% of BM cases had documented sequelae at the time of hospital discharge, and that 18.5% had neurological sequelae 6 months later. In addition, the quality of life in survivors was significantly lower than that in children with viral meningitis. A previous cohort study from Fiji showed that the quality of life in children with BM was significantly lower than that in otherwise healthy controls.¹⁶ A meta-analysis in the UK found a 10-fold increase in the risk of severe or moderate disability at 5 years of age among children who had BM compared with controls (relative risk = 10.3, 95% CI 6.7–16.0, $p < 0.001$), with sequelae noted in 15.6% of the cases.²⁶ A prospective cohort study in Senegal found multiple impairments and reduced quality of life in survivors of BM, which varied by etiology.⁷ A review of African studies showed pneumococcal and Hib meningitis to cause clinically evident sequelae in a quarter of survivors prior to hospital discharge.³⁸ These findings indicate that significant lifelong disabilities are common following BM. Moreover, it is important that services are developed to improve the detection and clinical care of children at risk of sequelae that may not be evident at the time of hospital discharge or too subtle to detect at an early age.⁸

In the current study, more than one third of children with BM died during the episode, which is similar to findings from Africa^{5,38} and much higher than rates documented in the Apache Indians of Alaska.³⁹ The global CFR for *S. pneumoniae* meningitis is estimated to be 59%, ranging from 29% in the Western Pacific to 73% in Africa.⁵ The high CFR in this study may be due to delayed health seeking behavior or delays in treatment and referral from the referral center, or may reflect an under-reporting in other centers, as it is unlikely that any deaths were missed during the study period. In other studies, Malawian and Bangladeshi children with BM who presented late for health care had poorer outcomes.³⁰

Our reason for using 16S rRNA as the target for our PCR was that the volume of CSF available for testing was extremely small and also that we wanted to examine each sample for *M. tuberculosis*, Hib, meningococcus, Streptococcus, and enterovirus. Specifically,

the rationale for our decision was that: (1) multiplex PCR allowed us to test for a range of agents in a sample of limited volume, and (2) targeting 16S rRNA took advantage of a very high copy number target compared with genomic DNA (1 copy of a diagnostic marker per cell) or rDNA (7–8 copies per cell). Because RNA degrades when bacterial cells die, we conducted a preliminary study to compare fresh and frozen (stored for a month) spiked specimens of sterile CSF, and found that our sensitivity of detection fell by less than 1 log, demonstrating that the rRNA was still largely intact. This is partly because rRNA persists far longer after cell death than mRNA.⁴⁰ Another advantage of our method is that it combined the generation of cDNA and its subsequent amplification in a single tube, thus reducing the possibility of contamination from excessive handling.

Our decision to target 16S rRNA was vindicated by the results of the study, which showed the PCR to be 67% sensitive and 91% specific (with positive and negative predictive values of 80% and 83%, respectively) compared with traditional diagnosis (positive blood or CSF culture, antigen detection, or Gram stain). However, only one additional bacterial cause of meningitis was identified using PCR that was not otherwise detected by routine laboratory tests. In 12 of the 70 cases the etiology could not be established. These 12 cases had purulent CSF and the meningitis may have been caused by other organisms that were not tested for. Another contributing factor is that the tests used were not 100% sensitive or specific.

BinaxNOW *S. pneumoniae* did not identify any additional cases of pneumococcal meningitis that were not identified by routine laboratory tests. Other studies have found BinaxNOW *S. pneumoniae* to be a useful additional test in identifying additional pneumococcal cases in Asian, but not African, sites.⁴¹ Despite these additional diagnostic tests adding little value in our setting, these tests may well add value in other settings where the burden of these diseases may be higher and there are more samples for testing. On the other hand, analysis of CSF by PCR did enable the identification of enterovirus as an etiological agent that was otherwise not detected by routine laboratory examination.

In summary, enteroviral meningitis was the most common childhood meningitis in Fiji, but appears to be outbreak-associated. In the absence of the outbreak, *S. pneumoniae* was the most common cause of endemic meningitis. Overall, BM was associated with serious sequelae and a lower quality of life in Fijian children.

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