

Epidemiology of post-neonatal bacterial meningitis in Cape Town children

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Bacterial meningitis is a major cause of childhood morbidity and mortality in South Africa. However, comprehensive regional or national epidemiological data, essential for rational public health interventions, are lacking. The purpose of this 1-year prospective study, from 1 August 1991 to 31 July 1992, was to define the magnitude of the problem of childhood bacterial meningitis in Cape Town. The study group consisted of all children, aged > 1 month to < 14 years, who presented with proven bacterial meningitis at all the hospitals in the Cape Town metropolitan area. During the year 201 cases were identified: 101 (50.2%) were due to *Neisseria meningitidis*, 74 (36.8%) were due to *Haemophilus influenzae* and 26 (12.9%) were due to *Streptococcus pneumoniae*. The overall incidence rate (95% confidence interval) for children less than 14 years, 5 years and 1 year was 34 (30 - 40), 76 (65 - 88) and 257 (213 - 309) per 100 000 children, respectively. The rate was highest in black infants, 416 (316 - 545)/100 000. This was 2 times greater than the rate in coloured infants and about 4.5 times greater than the rate in white infants. The median age of all the children was 10 months. The ages of children with haemophilus and pneumococcal meningitis were similar, 9 and 7.5 months respectively ($P = 0.43$), while children with meningococcal meningitis were significantly older (22 months) than the others ($P < 0.01$). The overall case fatality rate was 5%, and 12.9% of survivors had significant neurological sequelae (disability) on discharge.

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The respective mortality and disability rates for meningococcal meningitis were 1% and 8.6%, for haemophilus meningitis 5.3% and 20.7%, and for pneumococcal meningitis 19.2% and 37.5%. The relative risk (95% confidence interval) of an adverse event (either death or disability) in children with pneumococcal meningitis versus haemophilus and meningococcal meningitis was 2.7 (1.6 - 4.6) and 6.5 (3.2 - 13.1) respectively. For haemophilus versus meningococcal meningitis the relative risk was 2.4 (1.1 - 5.2). In conclusion, the high incidence of bacterial meningitis in the Cape Town metropolitan area highlights the need for urgent intervention. It is recommended that *H. influenzae* conjugate vaccines and, at a later stage, pneumococcal and meningococcal vaccines, once effective vaccines become available, be incorporated into the routine immunisation schedule.

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Bacterial meningitis is a major cause of childhood morbidity and mortality worldwide.¹ In Africa it is a well-recognised clinical problem in children. Most published data, however, come from individual hospital-based clinical and microbiological record reviews.²⁻⁹ Comprehensive regional or national epidemiological data, particularly on incidence, morbidity and mortality rates, are lacking, except in the case of Dakar, Senegal.⁵

The majority of cases of bacterial meningitis in the post-neonatal period are caused by *Neisseria meningitidis*, *Haemophilus influenzae* and *Streptococcus pneumoniae*. Haemophilus meningitis is preventable with the use of conjugate vaccines, and in many areas where such vaccines have been introduced, the incidence of disease has declined dramatically.^{10,11} Current vaccines to prevent *S. pneumoniae* and *N. meningitidis* infections are ineffective in preventing disease in early childhood.^{12,13} It is expected that new improved vaccines may be available in the near future.

Accurate data on aetiological agents, incidence and mortality rates, and the population at risk are essential for rational public health interventions. The purpose of this 1-year prospective study, from 1 August 1991 to 31 July 1992, was to define the magnitude of the problem of childhood bacterial meningitis in Cape Town in order to assist decision-making with regard to the possible incorporation of these vaccines into the routine immunisation schedule. The objectives were to define the aetiology, incidence rate in the population, short-term morbidity and mortality rates, the age, sex, race and seasonal distribution, and the haematological and CSF findings of children over the age of 1 month with bacterial meningitis in Cape Town.

Methods

The study group consisted of all children aged < 14 years, seen at all the hospitals in the Cape Town metropolitan area who presented with proven bacterial meningitis.

Children with neonatal meningitis, i.e. aged less than 1 month, tuberculous meningitis and children with pre-existing neurosurgical problems were excluded from the study.

All the hospitals in the greater Cape Town area participated in the study. Patients were enrolled in the study when there was a positive cerebrospinal fluid (CSF) Gram-stain, antigen detection assay or culture. In addition, children who presented with fever, neck stiffness, purpura and who may have had a positive blood culture or skin scraping for *N. meningitidis*, but in whom a CSF examination was not performed, were also included in the study.

For all patients in whom a diagnosis of bacterial meningitis was made, a case report form was completed. Data collected included age, address, sex, race, date of illness, duration of illness prior to admission, weight, aetiological diagnosis, complications, duration of hospitalisation and outcome.

Statistical methods. Data were analysed by computer, using Epi-Info version 5. Categorical data were evaluated by the chi-square test, and continuous data by the non-parametric Kruskal-Wallis test. The 95% confidence intervals for rates and means were also calculated. Incidence rates for children were calculated as follows: the numerator included only those cases where the children were resident in the Cape Town metropolitan area, and the denominator used was derived from the annual birth notifications in the area. For 1991 this amounted to 45 600, of whom 59% were coloured, 29% black and 12% white. The estimated population < 14 years in 1992 was 610 050.

Results

During the 1-year period 251 children over the age of 1 month with bacterial meningitis were hospitalised. Forty-three were referred from outside the study region and were therefore not included in the analysis. In addition 7 other cases were excluded from the analysis: 1 each due to *S. aureus* and *P. mirabilis*, and 2 due to *E. coli* infection in children aged 4 - 6 weeks, 2 cases of meningitis associated with disseminated *S. aureus* infection and 1 case of *K. pneumoniae*. The remaining 201 cases form the basis of the report: 101 (50.2%) cases were due to *N. meningitidis*, 74 (36.8%) were due to *H. influenzae* and 26 (12.9%) were due to *S. pneumoniae*. Of the 101 cases of meningococcal meningitis, 81 had CSF examinations done of which 71 were culture-positive. In the 10 patients with negative CSF cultures, 4 had a positive blood culture. Of the 19 patients who did not have CSF examinations done, 7 had a positive blood culture and 5 had skin scrapings positive for *N. meningitidis*. Therefore 87.1% of children (88/101) could be classified as definite cases, while 12.9% (13/101) could be classified as probable cases.

Age distribution. The median (25th - 75th centile) age of all the children was 10 (6.5 - 23) months. The ages of children with haemophilus and pneumococcal meningitis were similar, 9 (3 - 62) and 7.5 (5 - 28.5) months respectively ($P = 0.43$), while children with meningococcal meningitis were significantly older, 22 (8 - 57) months, than the others ($P < 0.01$). Sixty-nine per cent of cases due to *H. influenzae* and 65% of *S. pneumoniae* cases were younger than 1 year, compared with only 45% of cases due to *N. meningitidis*

(Fig. 1). When stratified by race the only difference noted was with regard to meningococcal meningitis. Black children were significantly younger than coloured children — 11 (6 - 42) versus 26 (9 - 63) months, respectively ($P = 0.04$).

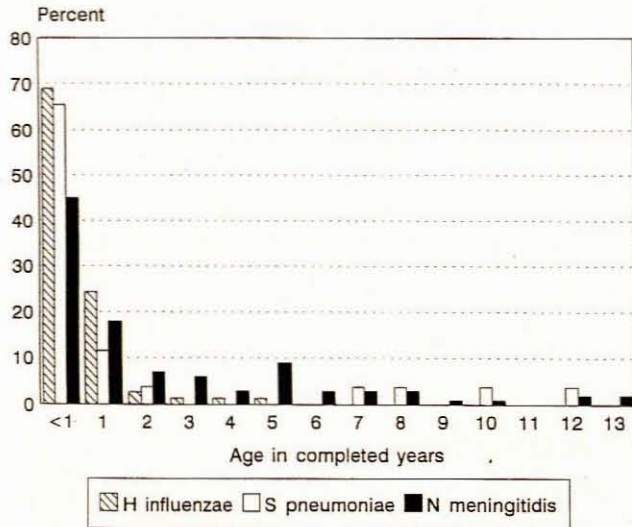


Fig. 1. Age distribution of children with bacterial meningitis.

Incidence. The incidence rate per 100 000 population (with 95% CI) stratified according to age group, specific disease and race is shown in Table I. The overall rates for children less than 14 years, 5 years and 1 year were 34.4, 75.9 and 256.6/100 000, respectively. The rates for children with *S. pneumoniae* at all ages were significantly lower than those for *H. influenzae* and *N. meningitidis*, which were similar (Table I). The rate in black children aged less than 1 year (416/100 000) was double that in coloured children and about 4.5 times greater than that in white children.

Sex ratio. The female/male ratio for *N. meningitidis*, *H. influenzae* and *S. pneumoniae* was 0.78, 0.96 and 0.5, respectively. Despite the male predominance in the *S. pneumoniae* group, this was not significantly different from the other two groups.

Duration of illness prior to admission. The mean (SD) duration of illness prior to admission was similar in all 3 groups (2.29 (1.43) days). No relationship to morbidity or mortality was noted.

Seasonal distribution. The seasonal distribution of cases is shown in Fig. 2. *N. meningitidis* cases peaked during spring and *H. influenzae* cases during winter. No definite trend was apparent with *S. pneumoniae*.

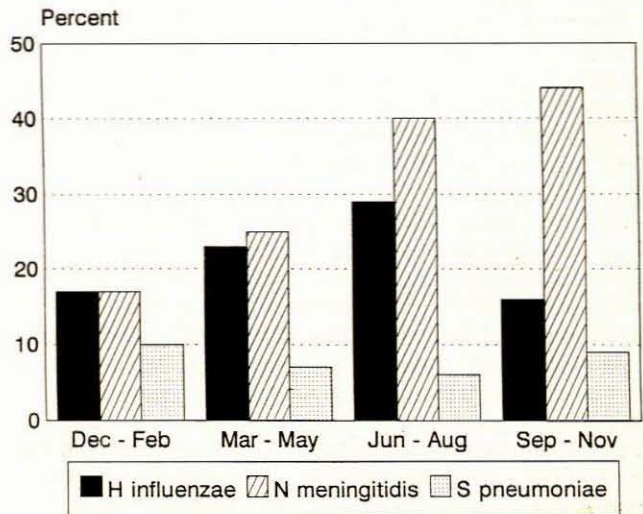


Fig. 2. Distribution of bacterial meningitis by month.

Nutritional status. The mean (SD) percentage weight for age for *H. influenzae*, *N. meningitidis* and *S. pneumoniae* was 94 (17), 93 (15) and 88 (17), respectively. In the 3 groups, 17%, 21% and 32% of children, respectively, were < 80% of expected weight. These differences were not, however, statistically significant.

Duration of hospitalisation. The median (25th - 75th centile) hospital stay for children with meningococcal, pneumococcal and haemophilus meningitis was 8 (7 - 10), 12 (7 - 17) and 14 (12 - 17) days, respectively. A hospital stay of 14 or more days occurred in 9.6%, 33.3% and 42.1% of cases, respectively.

Table I. Incidence rate (95% CI) stratified by diagnosis and age group in Cape Town children with meningitis

Age/race	All causes	<i>N. meningitidis</i>	<i>H. influenzae</i>	<i>S. pneumoniae</i>
< 1 year	257 (213 - 309)	101 (75 - 136)	114 (86 - 151)	42 (26 - 67)
Black	416 (316 - 545)	181 (119 - 275)	210 (132 - 295)	45 (18 - 104)
Coloured	197 (149 - 260)	78 (50 - 122)	114 (54 - 130)	41 (22 - 76)
White	91 (34 - 227)	0	103 (37 - 225)	0
< 5 years	76 (65 - 88)	35 (28 - 43)	32 (25 - 41)	9 (6 - 14)
Black	118 (93 - 148)	53 (38 - 78)	51 (35 - 72)	14 (7 - 27)
Coloured	68 (55 - 84)	33 (24 - 45)	26 (18 - 37)	9 (5 - 17)
White	27 (9 - 62)	4 (0.2 - 27)	25 (10 - 57)	0
< 14 years	34 (30 - 40)	17 (14 - 20)	12 (10 - 15)	4 (3 - 6)
Black	49 (39 - 60)	24 (17 - 32)	19 (13 - 27)	6 (3 - 12)
Coloured	30 (25 - 36)	16 (12 - 21)	10 (7 - 14)	4 (2 - 7)
White	10 (4 - 21)	1 (0.1 - 9)	8 (3 - 19)	0

Haematology. The haemoglobin levels, white blood cell count and platelet counts for the three groups are shown in Table II. The only significant differences between the three groups were a higher median haemoglobin concentration ($P < 0.01$) and a lower median platelet count ($P < 0.01$) in the children with *N. meningitidis* compared with the other two groups. Thrombocytosis ($> 500\ 000 \times 10^9/l$) occurred in 48%, 33% and 19% of haemophilus, pneumococcal and meningococcal cases, respectively.

Thrombocytopenia ($< 100\ 000 \times 10^9/l$), on the other hand, occurred in 1% of haemophilus cases compared with 8% and 9% of pneumococcal and meningococcal cases, respectively. Patients with complicated meningococcal disease had significantly lower platelet counts, 208 (141 - 247) compared with 326 (244 - 469) in uncomplicated cases ($P = 0.009$).

CSF findings. The CSF findings are shown in Table III. The highest values for CSF protein, neutrophil and lymphocyte counts, and the lowest glucose values were recorded in children with meningococcal meningitis. Values for haemophilus and pneumococcal meningitis were similar.

Morbidity and mortality. The complication rate on admission and discharge in the survivors, the case fatality rate and the adverse event rate (the number of deaths added to the number with complications on discharge in the survivors) are shown in Table IV. The highest morbidity and mortality rates occurred in those with pneumococcal meningitis, while the lowest occurred in those with meningococcal meningitis. The relative risk (95% CI) of an adverse event (either death or disability on discharge) in

children with pneumococcal meningitis versus haemophilus and meningococcal meningitis was 2.7 (1.6 - 4.6) and 6.5 (3.2 - 13.1), respectively. For haemophilus versus meningococcal meningitis the relative risk was 2.4 (1.1 - 5.2).

Of the 10 deaths, 7 occurred in children aged less than 1 year. The other 3 children were aged 84, 135 and 150 months; all died of pneumococcal meningitis. The overall annual mortality incidence per 100 000 children aged 1 month - 14 years was 1.5 (0.7 - 2.9). The rate for children aged less than 1 year was significantly greater than in those over 1 year, 13.2 (5.3 - 30.2) versus 0.5 (0.1 - 1.7) respectively.

Mortality was also associated with a higher median (25th - 75th centiles) CSF protein level, 5 (2.7 - 6) versus 2.5 (1.5 - 5) in survivors ($P = 0.04$); a lower median CSF glucose concentration 0.3 (0.05 - 1.5) versus 0.9 (0.4, 2.3) ($P = 0.05$) and a lower median CSF lymphocyte count 190 (31 - 480) versus 400 (165 - 780) ($P = 0.07$).

Discussion

Bacterial meningitis is common in Cape Town, with infants, particularly black infants, having the highest incidence of disease (256.6 and 415.6/100 000, respectively). The reasons for the higher incidence of meningitis in black infants, a phenomenon also reported from the USA,¹⁴ are not clear. Genetic factors may be operative. It is, however, probably related to earlier acquisition of nasopharyngeal colonisation as a consequence of poor living standards. The

Table II. Haematological findings in bacterial meningitis

No.	All 189	<i>N. meningitidis</i> 95	<i>H. influenzae</i> 73	<i>S. pneumoniae</i> 21
Haemoglobin (g/dl)	9.8 (8.9 - 11.1)	10.8 (9.5 - 11.6)	9.5 (8.8 - 10.5)	9.3 (9 - 11)
% of cases < 10	53	38	68	62
Platelet count ($\times 10^9/l$)	376 (249 - 540)	291 (208 - 552)	452 (313 - 626)	429 (208 - 552)
% of cases < 100	4	9	1	8
% of cases > 500	31	19	48	33
WBC count ($\times 10^9/l$)	20 (11.2 - 26)	19.8 (11.9 - 25.2)	19.5 (10.6 - 27.9)	21.7 (13.4 - 26.7)
% of cases < 5	3	4	0	3
% of cases > 15	67	66	64	67
% Neutrophils	70 (54 - 77.5)	73.5 (60 - 83)	69 (55 - 75)	75 (43.5 - 78.5)
% of cases < 40%	11	11	10	27
% of cases > 70%	53	58	34	47
% Lymphocytes	22 (15 - 34)	21 (14 - 30)	26 (16 - 33)	2 (15 - 34)
% of cases < 40%	85	88	88	75
% of cases > 70%	3	3	0	12

Figures represent median (25th - 75th percentiles).

Table III. CSF findings in meningitis

	All cases	<i>N. meningitidis</i>	<i>H. influenzae</i>	<i>S. pneumoniae</i>
Protein	2.3 (1.5 - 5)	3 (1.5 - 6)	2.1 (1.2 - 5)	2.5 (1.6 - 5.2)
Glucose	0.9 (0.3 - 2.2)	0.8 (0.3 - 2.3)	1.2 (0.5 - 2)	1.2 (0.3 - 2.8)
Neutrophils	2 240 (740 - 7 600)	4 900 (1 680 - 6 150)	1 800 (580 - 3 950)	880 (575 - 2 500)
Lymphocytes	396 (142 - 720)	480 (240 - 800)	230 (130 - 720)	205 (55 - 350)

Figures represent median (25th - 75th percentiles).

Table IV. Morbidity and mortality

	All (N = 201) No. (%)	<i>N. meningitidis</i> (N = 101) No. (%)	<i>H. influenzae</i> (N = 74) No. (%)	<i>S. pneumoniae</i> (N = 26) No. (%)	p1	p2	p3
Complications on admission	77 (39.3)	29 (28.7)	33 (44.5)	15 (57.7)	0.03	0.001	0.32
Convulsions	41 (20.4)	12 (11.9)	19 (25.6)	10 (38.5)			
Stupor or coma	28 (13.9)	10 (9.9)	11 (14.9)	7 (26.9)			
Focal neurological signs	19 (9.5)	3 (3)	8 (10.8)	8 (30.8)			
Subdural effusion	12 (6)	0	8 (10.8)	4 (15.3)			
SIADH	7 (3.5)	1 (0.9)	4 (5.5)	2 (7.7)			
Shock	7 (3.5)	6 (5.9)	1 (1.4)	0			
Arthritis	4 (2)	4 (3.9)	0	0			
Complications on disc*	26 (13.6)	8 (8.6)	12 (17.1)	6 (28.6)	0.07	0.01	0.30
Case fatality rate	10 (5)	1 (1)	4 (5.4)	5 (19.2)	0.16	0.005	0.11
Adverse event rate†	36 (17.9)	9 (8.9)	16 (21.6)	11 (42.3)	0.03	< 0.001	< 0.001

* In survivors.

† Adverse event rate refers to the number of deaths and number of survivors with complications on discharge.

p1, p2 and p3 refer to the statistical difference between *H. influenzae* and *N. meningitidis*, *N. meningitidis* and *S. pneumoniae*, and *H. influenzae* and *S. pneumoniae*, respectively.

predominance of males also conforms to what has been reported by others. The incidence rates reported in this study should be regarded as minimum rates since culture-negative cases of bacterial meningitis were not included in the study. Such cases may account for 20 - 40% of cases.^{8,9} Comparative incidence rates from South Africa are not available and data from developing countries are extremely limited. The rate in black infants is similar to that reported from Dakar (400),⁵ while the rate for haemophilus meningitis in black infants (210) was slightly less than that in Gambia (297).⁴ Compared with recent studies from Europe and the Middle East, the overall rate in Cape Town children aged 1 month to 14 years (34.4/100 000) was greater than that in Nottingham children (24) (age 0 - 16 years),¹⁵ children from north-eastern Scotland (17.8) (age 0 - 13 years),¹⁶ children from Sweden (22.4) (age 1 month - 16 years)¹⁷ and children from Kuwait (13) (age < 12 years).¹⁸

Meningococcal meningitis was the most common cause of bacterial meningitis in Cape Town, and has been for the last 3 decades.^{9,19} The incidence of meningococcal meningitis may be a slight overestimate, given that 12.9% of cases were regarded as probable, i.e. diagnosed clinically without laboratory confirmation.

This differs from the experience of other main centres in South Africa where *H. influenzae* is the predominant cause.^{7,8} *S. pneumoniae* infections are the least common of the three in all centres.^{7,9,19} Virtually all cases of *H. influenzae* (97.3%) in this study were type b infections.²⁰ Most of the meningococcal infections were group B infections (G Coetzee — unpublished data), unlike in other areas of Africa where group A infections are more common.^{2,3,5}

The annual mortality incidence rate per 100 000 children overall (1.5) and in those aged 1 - 11 months (13.2) in this study compares favourably with that from developed countries (1.8 and 11.5 in Nottingham respectively,¹⁵ and 1.8 (under 16 years) in Scotland).¹⁶ The case fatality rates (CFRs) in Cape Town have declined substantially over the last 30 years. The current overall CFR rate of 5% and the disease-specific rates (Table IV) are comparable with those in developed countries.²¹ A recent meta-analysis of 19 prospective studies in developed countries reported a

mean rate of 4.8%, while the rates for *H. influenzae*, *N. meningitidis* and *S. pneumoniae* were 3.8, 7.5 and 15.3%.²¹ In developing countries, however, CFRs are often in excess of 20%.²¹ The low rates in this study could be ascribed to the availability and accessibility of both primary and secondary care facilities in Cape Town. Bacterial meningitis is associated with significant short-term morbidity. However, comparison with other studies is difficult because of the differences in study designs and diagnostic criteria. This study has shown that short-term complications are more frequent with *S. pneumoniae* and that *N. meningitidis* was associated with the fewest complications. The reported frequencies should also be regarded as minimums, since evaluation for hearing loss and subdural effusions is not routinely performed. Hearing tests are only done following discharge from hospital and ultrasonography or computed tomography are only done to confirm a diagnosis of subdural effusions in symptomatic children. Studies where such investigations are routinely performed report rates of up to 40%.²²⁻²⁴

The study was not designed to assess risk factors for severity of disease (death or disability on discharge). However, young children, particularly those aged less than 1 year, were at increased risk for severe haemophilus ($P < 0.001$) and meningococcal disease ($P = 0.07$). In pneumococcal meningitis no such association was noted ($P = 0.51$). Other factors identified included a higher CSF protein, and a lower glucose and lymphocyte count. A low platelet count, recognised as a poor prognostic sign in meningococcal septicaemia,²⁵ was associated with more severe meningococcal meningitis. Nutritional status and duration of illness prior to admission did not appear to influence disease severity, as has been documented previously.^{8,26}

Thrombocytosis was present in 30% of patients on admission, which was a higher proportion than that reported previously.^{27,28} In the other studies the proportion of children with thrombocytosis increased in frequency from 13% to 45%²⁷ and from 4% to 49%²⁸ after the first week of the illness. In one study, thrombocytosis was associated with age less than 1 year, longer duration of illness prior to

admission and subdural effusions.²⁸ No such associations were noted in this study. The reason for the thrombocytosis is unknown, but is probably a manifestation of the acute phase response. Thrombocytopenia in meningococcal disease was associated with more severe disease, as has been demonstrated previously.²⁵ Other haematological parameters were similar for all causes of meningitis.

Seasonal variations in disease occurrence are difficult to explain. Haemophilus meningitis showed a definite increased prevalence during the winter months. Meningococcal infections tended to peak during winter and spring, while no trend was noted in respect of pneumococcal disease. The increased occurrence during winter may be attributed to enhanced person-to-person transmission as a consequence of household crowding.

The difference in the duration of hospitalisation reflects the severity of the respective infections and current treatment policies. The current treatment policy in most of the hospitals in the area is that meningococcal meningitis is treated for at least 7 days, while the other types are treated for 10 - 14 days.

If this study cohort had been appropriately vaccinated with the currently available *H. influenzae* conjugated vaccine, 70/74 cases of haemophilus meningitis (94.6%) would have been averted. This statement is based on the assumption that at least two doses of the vaccine (given at 3 and 4.5 months in terms of current recommendation) are required to prevent disease in young infants.²⁹ The 4 (5.4%) cases that would not have been prevented would have occurred in children aged less than 5 months.

There are currently no conjugated *S. pneumoniae* vaccines licensed for use. However, were such vaccines available, they should ideally give protection against disease after one dose. In this cohort it would have prevented 25/26 (96.2%) of our cases. If 2 doses were required for protection, 21/26 (81.8%) of cases would have been prevented.

In conclusion, bacterial meningitis is a major cause of childhood morbidity and mortality in Cape Town. The high incidence of bacterial meningitis in this area highlights the need for urgent intervention. The incorporation of *H. influenzae* conjugated vaccines, and at a later stage pneumococcal and meningococcal vaccines, into the routine immunisation schedule is recommended.

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