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SHORT REPORT
Lack of BCG vaccination and other risk factors for bacteraemia in severely malnourished children with pneumonia

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SUMMARY

We sought to examine the factors associated with bacteraemia and their outcome in children with pneumonia and severe acute malnutrition (SAM). All SAM children of either sex, aged 0–59 months, admitted to the Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh with radiologically confirmed pneumonia from April 2011 to July 2012 were enrolled ($n=405$). Comparison was made between pneumonic SAM children with (cases = 18), and without (controls = 387) bacteraemia. The death rate was significantly higher in cases than controls (28% *vs.* 8%, $P<0{\cdot}01$). In logistic regression analysis, after adjusting for potential confounders, the SAM children with pneumonia and bacteraemia more often had a history of lack of bacillus Calmette-Guérin (BCG) vaccination (odds ratio 7·39, 95% confidence interval 1·67–32·73, $P<0{\cdot}01$). The results indicate the importance of continuation of BCG vaccination which may provide benefit beyond its primary purpose.

Key words: Bacteraemia, BCG vaccination, children, pneumonia, severe acute malnutrition.

Bacteraemia is among the leading causes of global childhood deaths [1]. It is common in children with severe acute malnutrition (SAM) [2], with incidence rates as high as 29% in those with pneumonia with 23% deaths [3]. The comorbidity of SAM and pneumonia is very common, especially in developing countries [3] and clinicians in resource-poor settings mostly rely on clinical features of bacteraemia for the timely management of such children [4]. However, the clinical signs of bacteraemia in SAM children are often subtle [3], probably due to poor inflammatory response [5] and overlapping clinical signs of pneumonia [6]. Such children are often treated with the combination of injectable penicillin/ampicillin and gentamicin [6]. Although, this combination is very effective in

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treating children with severe pneumonia [7], bacteraemia in these cases are due to Gram-negative bacteria [8] which may be multiply drug resistant [4]. SAM children with pneumonia and bacteraemia require aggressive antimicrobial therapy, using a third-generation cephalosporin (ceftriaxone) in addition to other supportive measures to prevent death [9]. Failure to recognize bacteraemia may result in their treatment with standard regimens of penicillin/ampicillin and gentamicin with poor outcomes [10]. Therefore, identification of clinical characteristics and common pathogens causing bacteraemia along with the knowledge of their antimicrobial susceptibility are important for the treatment of SAM children with pneumonia. Further, there are limited data on clinical risks of bacteraemia in SAM children with pneumonia.

The Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B) provides care and treatment to large numbers of SAM children with pneumonia aged <5 years each year, who often have bacteraemia with high case fatality [8]. The aim of our study was to identify clinical predictors of bacteraemia in SAM children with pneumonia and the outcome of such children.

This study was approved by the Institutional Review Board of ICDDR,B (known as the Research Review Committee and Ethical Review Committee). Written informed consent was obtained from attending parents or caregivers of each of the participating children. The study was designed as an unmatched case-control investigation. Severe malnutrition was defined according to WHO anthropometry as described elsewhere [11]. SAM children of both sexes, aged 0–59 months, admitted for intensive or high dependency care unit with radiologically confirmed pneumonia (WHO criteria [6]) during April 2011 to July 2012 were enrolled. Those with bacteraemia, defined as isolation of bacteria from a single specimen of blood culture on admission, constituted the cases and those without bacteraemia were used as controls.

Venous blood (2–5 ml) was taken from all study children before starting antibiotics, and inoculated into standard paediatric blood culture bottles and processed for bacterial culture, species identification and antimicrobial susceptibility as previously described [4].

Antibiotic and supportive therapy was as described elsewhere [12] and all study children received on admittance to ICDDR,B diphtheria-pertussis-tetanus (DPT), oral polio, *Haemophilus influenzae* b vaccine (Hib), hepatitis, measles, and bacillus Calmette-Guérin (BCG) vaccination as recommended by the WHO [13].

Case report forms were developed, pretested, and finalized for data acquisition. Characteristics analysed include demographic and medical history (age, gender, socioeconomic status, lack of previous vaccinations, non-breastfeeding, prior antibiotics before admission), clinical signs such as acute watery diarrhoea (AWD), vomiting, and dehydration according to the 'Dhaka methods' of assessment of dehydration approved by WHO [14]. Other measurements included fever ($\geqslant 38$ °C), hypoxaemia (SPO_2 <90% in air), diastolic hypotension, hypoglycaemia (blood sugar <3 mmol/l), pulmonary tuberculosis, and outcome.

All data were entered into SPSS for Windows version 15.0 (SPSS Inc., USA) and Epi-Info version 6.0 (USD, USA). Proportional differences were compared by χ^2 test. For normally distributed data, differences of means were compared by Student's t test and for non-normal distributions, the Mann–Whitney test was used. $P \leqslant 0{\cdot}05$ was considered statistically significant. Strength of association was determined by odds ratio (OR) and 95% confidence intervals (CIs). For identifying predictors of bacteraemia in children with SAM and pneumonia, variables were initially analysed in a univariate model, and independent predictors were identified using a logistic regression model; significantly associated variables with bacteraemia by univariate model were considered as independent variables and bacteraemia as a dependent variable.

In total, 405 children were enrolled according to the study criteria giving 18 cases and 387 controls. Of the cases, two each yielded two different bacterial species from the same blood culture, and overall 11 species groups were identified. *Streptococcus pneumoniae* was the most common species isolated (four cases) but Gram-negative species accounted for 75% of all isolates recovered and included *Klebsiella* spp. ($n=3$), *Salmonella* spp. ($n=3$, two *S. typhi*). *Pseudomonas* spp. ($n=2$), and *Acinetobacter* spp. ($n=2$), among others. Antimicrobial susceptibility was variable across the range of species.

The death rate was significantly higher in cases (28%) than controls (8%) and of the children that died, two grew *Klebseilla* spp., one each *S. pneumoniae, Pseudomonas* spp., and *Acinetobacter* spp. On the basis of antimicrobial susceptibility test results of these isolates, the patients with *S. pneumoniae* and *Acinetobacter* bacteraemia had received appropriate

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Table 1. *Clinical characteristics of children aged <5 years having pneumonia and severe acute malnutrition with (cases) and without (controls) bacteraemia*

Characteristic	Cases ($n=18$)	Controls ($n=387$)	OR	95% CI	P
Male sex	10 (56)	219 (57)	0·96	0·34 to 2·73	0·87
Age, months, median (IQR)	5·5 (4·0–15·5)	10·0 (5·0–18·0)	—	—	0·57
Poor socioeconomic status (monthly income <US$125)	14 (78)	329 (85)	0·62	0·18 to 2·31	0·49
Lack of intake of BCG vaccination	5 (28)	46 (12)	2·82	0·83 to 9·02	0·04
Lack of intake of DPT/oral polio/Hib/hepatitis vaccination	7 (39)	77 (20)	2·53	0·82 to 7·71	0·06
Lack of intake of measles vaccine	5/9 (56)	86/222 (39)	1·98	0·45 to 9·06	0·32
Not breastfed	2 (11)	61 (16)	0·67	0·10 to 3·14	1·0
Intake of antibiotics before admission	3 (17)	47 (12)	1·49	0·33 to 5·77	0·46
AWD	16 (89)	290 (75)	2·68	0·58 to 17·16	0·26
Children with vomiting	5 (28)	48 (12)	2·72	0·80 to 8·67	0·05
Clinical dehydration (some/severe)	5 (28)	47 (12)	2·78	0·82 to 8·89	0·05
Weight for length Z score (mean ± S.D.)	−4·6 ± 1·5	−3·6 ± 1·4	−1·0*	−1·8 to -0·3	0·01
Fever on admission (⩾38 °C)	13 (72)	218 (56)	2·02	0·65 to 6·61	0·27
Presence of hypoxemia	3 (17)	39 (10)	1·78	0·39 to 6·98	0·41
Diastolic hypotension (⩽50 mmHg) after correction of dehydration or in absence of dehydration	13 (77)	188 (49)	2·72	0·88 to 8·94	0·05
Hypoglycaemia on admission (bedside random blood glucose <3·0 mmol/l)	2 (11)	4 (1)	11·97	1·40 to 85·33	0·02
Pulmonary tuberculosis	0	27 (7)	0	0 to 3·94	0·62
Outcome (died)	5 (28)	30 (8)	4·58	1·32 to 15·08	<0·01

OR, Odds ratio; CI, confidence interval; IQR, interquartile range; BCG, bacillus Calmette-Guérin; AWD, acute watery diarrhoea; S.D., standard deviation.
Figures represent n (%), unless specified otherwise.
* Mean difference.

antibiotics; for the *Klebseilla* spp. cases one had received appropriate and the other inappropriate antibiotics, and similarly the single *Pseudomonas* case had received antibiotics to which the isolate was resistant. Susceptibility reports were received after the death of the patients who had received inappropriate antibiotics.

The distribution of gender, age, socioeconomic condition, breastfeeding, use of antibiotics before admission, AWD, fever, hypoxaemia, and pulmonary tuberculosis was comparable among cases and controls. However, significant differences from controls were identified in the cases for vomiting, clinical dehydration, lower Z score (weight for length), and hypoglycaemia (Table 1). Moreover, in the logistic regression analysis after adjusting for potential confounders listed above, cases more often had a history of lack of BCG vaccination (OR 7·39, 95% CI 1·67–32·73, $P<0·01$).

To our knowledge this is the only study performed outside of Africa that has evaluated the presence of bacteraemia in severely malnourished (SAM) children with pneumonia. The main findings are (i) death rates were significantly higher in those patients with pneumonia and bacteraemia compared to those without bacteraemia, (ii) a wide range of Gram-negative species was evident and these were most associated with mortality, and (iii) there was a strong association of bacteraemia with a lack of BCG vaccination. The predominance of Gram-negative species has been noted previously [2] but the factors underlying the observation are poorly understood. The oropharynx in severely malnourished children is often colonized with enteric bacteria that can potentially spread to the lower respiratory tract with or without additional factors such as viral respiratory tract infections [12]. However, we did not perform nasopharyngeal aspirate culture in cases that may demonstrate the same species as in blood and may help in validating the speculation. Breaches in the integrity of the bowel mucosa as well as translocation of bacteria from the gut might lead to Gram-negative bacteraemia in children with SAM and pneumonia [8] and warrant aggressive management with appropriate broad-spectrum parenteral antibiotics.

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The key observation made here of a strongly significant association between a lack of BCG vaccination and bacteraemia is of profound importance for clinicians and policymakers, especially in developing countries. BCG vaccination against tuberculosis has been associated with non-tubercular beneficial effects [15] and has been reported to reduce ~50% of deaths from infections other than tuberculosis, such as pneumonia-related deaths in high childhood mortality countries in the developing world [16]. However, a lack of BCG vaccination as an independent predictor of bacteraemia in malnourished children aged <5 years has not hitherto been reported. This may be a substantial heterologous effect of BCG in children and suggests its potential for reducing the incidence of bacteraemia in tuberculosis-endemic countries.

A limitation of the study is the lack of data on airways/secretions culture in cases. Demonstration of the same species in such specimens and blood would have been informative.

In conclusion, we have found that SAM children with pneumonia often present with Gram-negative bacteraemia. Infection in these children appears to be strongly associated with a history of lack of BCG vaccination. This finding underscores the importance of the continuation of BCG vaccination in children to attain the non-tubercular substantial benefit of the vaccination.

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DECLARATION OF INTEREST

None.

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