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Risk and causes of paediatric hospital-acquired bacteraemia in Kilifi District Hospital, Kenya: a prospective cohort study



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Summary

Background In sub-Saharan Africa, community-acquired bacteraemia is an important cause of illness and death in children. Our aim was to establish the magnitude and causes of hospital-acquired (nosocomial) bacteraemia in African children.

Methods We reviewed prospectively collected surveillance data of 33 188 admissions to Kilifi District Hospital, Kenya, between April 16, 2002, and Sept 30, 2009. We defined bacteraemia as nosocomial if it occurred 48 h or more after admission. We estimated the per-admission risk, daily rate, effect on mortality, and microbial cause of nosocomial bacteraemia and analysed risk factors by multivariable Cox regression. The effect on morbidity was measured as the increase in hospital stay by comparison with time-matched patients without bacteraemia.

Findings The overall risk of nosocomial bacteraemia during this period was 5.9/1000 admissions (95% CI 5.2–6.9) but we recorded an underlying rise in risk of 27% per year. The incidence was 1.0/1000 days in hospital (0.87–1.14), which is about 40 times higher than that of community-acquired bacteraemia in the same region. Mortality in patients with nosocomial bacteraemia was 53%, compared with 24% in community-acquired bacteraemia and 6% in patients without bacteraemia. In survivors, nosocomial bacteraemia lengthened hospital stay by 10.1 days (3.0–17.2). *Klebsiella pneumoniae*, *Escherichia coli*, *Staphylococcus aureus*, *Acinetobacter* spp, group D streptococci, and *Pseudomonas aeruginosa* accounted for three-quarters of nosocomial infections. Nosocomial bacteraemia was significantly associated with severe malnutrition (hazard ratio 2.52, 95% CI 1.79–3.57) and blood transfusion in children without severe anaemia (4.99; 3.39–7.37).

Interpretation Our findings show that although nosocomial bacteraemia is rare, it has serious effects on morbidity and mortality, and the microbiological causes are distinct from those of community-acquired bacteraemia. Nosocomial infections are largely unrecognised or undocumented as a health risk in low-income countries, but they are likely to become public health priorities as awareness of their occurrence increases and as other prominent childhood diseases are progressively controlled.

Funding Wellcome Trust.

Introduction

“Health-care-associated infection in developing countries is a serious issue that is scarcely addressed in the scientific literature”.¹ In sub-Saharan Africa, community-acquired paediatric bacteraemia imposes a major health burden.^{2–6} However, almost no regional information is available about hospital-acquired (nosocomial) bacteraemia. The WHO Patient Safety programme⁷ did a systematic review of health-care-associated infection in developing countries between 1995 and 2008 and found no reports about nosocomial bacteraemia in adults or children in Africa, and only five studies of paediatric nosocomial bacteraemia from developing countries worldwide. A review focusing on infections in hospital-born neonates suggested a high risk of disease in this age group across the region.⁸ Untreated maternal HIV infection is an important risk factor for neonatal nosocomial sepsis.⁹ Outbreak reports^{10–12} show that this disease occurs in the region but do not provide the denominator data necessary for estimation of risk or incidence.

We aimed to assess the risk, rate, effect on mortality and morbidity, microbiological causes, and risk factors for paediatric nosocomial bacteraemia by analysing surveillance data obtained prospectively for a continuous period at one Kenyan hospital.

Methods

Study design and patients

Kilifi District Hospital is in a rural area in Coast Province of Kenya. The Kenya Medical Research Institute-Wellcome Trust Research Programme has undertaken surveillance for invasive bacterial disease in children admitted to this hospital for more than a decade. Further information about Kilifi District Hospital is available in the webappendix. Throughout the analysis period between April 16, 2002, and Sept 30, 2009, we obtained specimens from all paediatric inpatients (except those with minor trauma or undergoing elective surgery) to investigate clinical illness both on admission and during the hospital stay. All children (except those described above) admitted to the paediatric ward were investigated

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with blood cultures on admission. We systematically obtained detailed clinical and laboratory information from all patients at admission. We used WHO standard techniques to take anthropometric measurements and we calculated weight-for-age Z scores using American National Centre for Health Statistics reference data.

We investigated patients with persistent or new fever, or clinical deterioration after admission, with a septic screen consisting of blood cultures, urine testing, and other samples as clinically indicated. Blood samples were taken by the admitting clinician, or by a ward aide (ie, a clinical support worker with phlebotomy training) after cleansing of the child's skin with 70% alcohol. Blood was inoculated into a culture bottle (BACTEC Peds Plus, Becton Dickinson, Franklin Lakes, NJ, USA) after the top of the bottle had been disinfected. We used an automated culturing system (BACTEC 9050, Becton Dickinson) to process blood cultures. We subcultured positive samples onto standard media and used standard microbiological techniques to identify the microorganisms. Laboratory procedures were internally controlled, and quality was monitored externally by the UK National External Quality Assessment Service. The monthly performance score for culturing of simulated specimens and identification of test organisms was higher than 95%.

Our study included an analysis of bacterial surveillance data that were drawn from two studies of invasive bacterial diseases at Kilifi District Hospital. Parents or guardians of all patients gave written informed consent for participation in these studies, which included cultures of blood taken at admission and routine investigations of clinical care. Both studies were approved by the Kenya Medical Research Institute National Ethics Review Committee.

Case definition

We defined an episode of nosocomial bacteraemia as isolation of a pathogenic organism (bacterial or fungal) from the blood of a child when the sample was taken more than 48 h after admission. We classified bacteraemia on readmission (within 28 days of discharge or hospital birth) as health-care-associated and all other positive blood cultures as community acquired. We regarded repeated isolation of the same pathogen in blood cultures within 14 days as one disease episode, whereas we regarded isolation of a different pathogen as a distinct disease episode. Coagulase-negative staphylococci, *Bacillus* spp, *Micrococcus* spp, viridans group streptococci, and coryneform bacteria were regarded as contaminants.

Statistical analysis

We did analyses in STATA version 11.0. We calculated the risk of at least one episode of nosocomial bacteraemia per admission and the incidence per 1000 days of inpatient hospital stay. We used log-linear binomial regression to characterise trends in the yearly risk of nosocomial bacteraemia and the probability of identifying

a pathogen if a blood sample for culture had been taken. We analysed change in duration of hospital stay by year using Cox regression.

We used multivariable Cox regression to investigate the association of risk factors with the development of nosocomial bacteraemia. This approach is independent of length of hospital stay and is suitable for analysis of nosocomial infections in inpatient cohort data¹³ even if the outcome is rare.¹⁴ We used adjustment of variance for clustering within individuals with several admissions, and log-log plots for each variable to graphically confirm the validity of the proportional hazards assumption. We converted risk factor data, originally recorded in continuous variables, to binary or categorical variables before examining the effects of risk factors. Variables were included in a multivariable model if they showed a univariate association of $p < 0.1$. We tested for interactions between biologically associated variables in the final model.

To produce unbiased estimates of the additional length of hospital stay attributable to nosocomial bacteraemia, we used a confounder and time matching approach.¹⁵ When possible, we randomly selected four patients who survived to discharge without nosocomial bacteraemia and matched by age and nutritional status to a patient with nosocomial bacteraemia, with the further constraint that they had been in hospital at least as long as the index patient at the point he or she developed bacteraemia. With an assumed mean hospital stay of 20 days (SD 25 days) in unexposed patients, matching of four patients to each case provides more than 90% power to detect an increased duration of 10 days in the exposed group.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

35 143 admissions were made to Kilifi District Hospital in the study period, of which 1316 (4%) were excluded because no blood was taken for culture, and 639 (2%) were excluded because of missing data or errors in the dates of admission or discharge. We analysed 33 188 admissions (94%) in 26 721 patients.

The median length of hospital stay was 3.7 days (IQR 2.0–6.8 days) and the median age at admission was 1.3 years (range 0 days to 15 years, IQR 157 days to 3.0 years). About 14% of the children admitted were neonates (age ≤ 28 days, table 1), though the proportion increased from 11% (904 of 8547) in 2002–03 to 18% (1219 of 6889) in 2008–09.

We identified 212 episodes of nosocomial bacteraemia. 13 children had two episodes and one child had three episodes during the same admission, so the total number

of admissions with at least one episode of nosocomial bacteraemia was 197. Most episodes of nosocomial bacteraemia were preceded by one or more negative blood cultures (88%, 186 of 212) or by an admission blood culture isolating a different pathogen (5%, 11 of 212), supporting the inference of hospital-acquired disease. The risk of development of nosocomial bacteraemia at least once during a hospital stay was 5.9 per 1000 admissions (95% CI 5.2–6.9).

We included 212 933 inpatient days of observation in the study period, giving an overall rate of nosocomial bacteraemia of 1.00 episode per 1000 person-days (0.87–1.14) or 36 340 episodes per 100 000 person-years (31 777–41 639). In children younger than 2 years at admission, the rate was 42 398 episodes per 100 000 person-years (36 222–49 626). The estimated incidence of community-acquired bacteraemia in children younger than 2 years living in the same community is 1080 per 100 000 person years,³ which suggests that the incidence rate ratio for acquisition of bacteraemia in hospital compared with in the community is about 40. The rate of nosocomial bacteraemia was higher than at baseline (day 2–7) in the second week (relative risk [RR] 1.61, 95% CI 1.16–2.23) and third week (1.77, 1.18–2.66) of hospital stays but not thereafter. The rate of nosocomial bacteraemia increased progressively throughout the study from 0.59 per 1000 person-days (95% CI 0.44–0.78) in 2002–04, to 1.66 per 1000 person-days (1.34–2.04) in 2008–09. The number of blood samples for culture taken more than 48 h after admission increased progressively from 163 in 2003, to 408 in 2008, with an annual increase of 19% (17–22%). Duration of hospital stay also increased throughout the study period. The average annual increase in duration of admissions was 3.8% (3.3–4.4%); the median duration was 3.15 days (IQR 1.90–5.92) in 2002 and 3.98 days (2.06–7.96) in 2009. We recorded no difference in this trend when the analysis was restricted to children who survived to discharge. The probability of detection of nosocomial bacteraemia when blood samples were taken more than 48 h after admission increased slightly during the study (RR per year=1.07, 95% CI 1.00–1.14).

Table 1 shows the distribution of children with nosocomial bacteraemia by each risk factor, together with univariable hazard ratios (HRs). Notably, nosocomial bacteraemia was not associated with age group ($p=0.18$). A multivariable proportional hazards model showed significant effects for nutritional status defined in terms of weight-for-age Z score, prescription of a blood transfusion, and study period. We recorded a significant interaction between transfusion and severe anaemia. To elucidate the factors behind this interaction, we re-examined the multivariable model in two exclusive age strata, patients aged 28 days or younger (neonates), and patients older than 28 days (infants and children). The pattern of risk factors differed sufficiently between these strata to justify separate presentation of the results (table 2). Severe anaemia and blood transfusion were not risk factors for

nosocomial bacteraemia in neonates. In infants and children, blood transfusion (as prescribed at admission) was a highly significant risk factor for nosocomial bacteraemia, but only in children who did not have severe anaemia (table 2). Poor nutritional status was a risk factor at all ages but it showed a more pronounced association in neonates than in infants and children (table 2).

In 197 patients who developed one or more episodes of nosocomial bacteraemia, the case-fatality rate was 53% (105 of 197; 95% CI 46–60), compared with 24% (372 of 1528; 22–26) in patients with community-acquired

	Number of admissions (% of all admissions)	Outcome events	Univariable hazard ratio (95% CI)
Age group			
0–28 days	4668 (14%)	53	1.38 (0.97–1.94)
29–59 days	1056 (3%)	6	1.18 (0.46–3.00)
60–365 days	8275 (25%)	49	1.40 (0.97–2.01)
Older than 366 days	19 189 (58%)	104	1.0
Sex			
Female	14 552 (44%)	97	1.0
Male	18 636 (54%)	115	0.98 (0.74–1.31)
Nutritional status (WAZ)			
>3	26 050 (79%)	78	1.0
–3 to –4	4179 (13%)	52	2.06 (1.42–2.99)
<–4	2692 (8%)	77	2.52 (1.79–3.57)
Missing	267 (1%)	5	3.52 (1.20–10.29)
HIV status			
Known negative	8150 (25%)	71	1.0
Known positive	696 (2%)	20	1.60 (0.97–2.66)
Unknown	24 342 (73%)	121	0.67 (0.49–0.92)
Transfusion prescribed			
No	30 563 (92%)	153	1.0
Yes	2573 (8%)	58	2.73 (1.98–3.76)
Unknown	52 (<1%)	1	3.90 (0.53–28.7)
Severe malaria*			
No	30 205 (91%)	208	1.0
Yes	2789 (9%)	4	0.45 (0.13–1.51)
Severe anaemia†			
No	30 132 (91%)	189	1.0
Yes	2167 (7%)	11	0.75 (0.40–1.43)
Unknown or not tested	889 (3%)	12	2.00 (0.97–4.14)
Burns on admission			
No	32 724 (99%)	202	1.0
Yes	464 (1%)	10	0.81 (0.41–1.60)
Time admitted			
2002–04	13 300 (40%)	48	1.0
2005–07	12 998 (39%)	78	1.58 (1.07–2.32)
2008–09	6890 (21%)	86	2.53 (1.74–3.68)
Total			
All admissions	33 188 (100%)	212	..

WAZ=weight-for-age Z score. *Defined as per WHO criteria⁶ for clinically severe malaria. †Defined as haemoglobin <50 g/L (for patients older than 28 days) or haemoglobin <90 g/L (for neonates).

Table 1: Risk factors in study patients and univariable hazard ratios

	Age younger than 28 days* (HR [95% CI])	Age older than 28 days (HR [95% CI])
Nutritional status (WAZ)		
>-3	1.00	1.00
-3 to -4	1.73 (0.71-4.23)	1.99 (1.31-3.04)
<-4	3.40 (1.60-7.26)	1.95 (1.29-2.97)
Missing	5.22 (0.93-29.4)	1.78 (0.42-7.48)
Severe anaemia and transfusion		
No severe anaemia, not transfused	..	1.00
Severe anaemia, not transfused	..	1.04 (0.33-3.26)
No severe anaemia, transfused	..	4.99 (3.39-7.37)
Severe anaemia, transfused	..	0.62 (0.23-1.66)†
Time admitted		
2002-04	1.00	1.00
2005-07	1.87 (0.73-4.82)	1.43 (0.93-2.20)
2008-09	2.34 (0.89-6.14)	2.01 (1.29-3.12)

Severe anaemia and receipt of a blood transfusion had no significant effect in neonates and were not included in this model for this age group. WAZ=weight-for-age Z score. HR=hazard ratio. *Patients with missing data for blood transfusion or anaemia status on admission were excluded from this analysis. †Likelihood ratio test for inclusion of interaction term has p=0.015.

Table 2: Risk factors for nosocomial bacteraemia analysed with multivariable Cox regression models

	Nosocomial (total [%])	Health-care-associated* (total [%])	Community-acquired (total [%])
Gram-negative organisms			
<i>Escherichia coli</i>	44 (21%)	16 (11%)	144 (9%)
<i>Proteus mirabilis</i>	3 (1%)	1 (1%)	6 (<1%)
<i>Klebsiella pneumoniae</i>	43 (20%)	2 (1%)	37 (2%)
<i>Klebsiella</i> spp (other)	9 (4%)	1 (1%)	5 (<1%)
<i>Pseudomonas aeruginosa</i>	16 (8%)	8 (6%)	31 (2%)
<i>Pseudomonas</i> spp (other)	3 (1%)	1 (1%)	24 (2%)
<i>Acinetobacter</i> spp	19 (9%)	12 (9%)	159 (10%)
Non-typhi <i>Salmonella</i> spp	3 (1%)	10 (7%)	136 (9%)
<i>Salmonella</i> typhi	2 (1%)	0 (0%)	12 (1%)
Other enterobacteriaceae	8 (4%)	4 (3%)	26 (2%)
<i>Haemophilus influenzae</i>	2 (1%)	4 (3%)	99 (6%)
Other Gram-negative organisms	4 (2%)	0 (0%)	59 (4%)
Gram-positive organisms			
<i>Staphylococcus aureus</i>	20 (9%)	22 (16%)	198 (13%)
<i>Streptococcus pneumoniae</i>	3 (1%)	23 (16%)	459 (29%)
Group A streptococci	1 (1%)	5 (4%)	71 (5%)
Group B streptococci	2 (1%)	18 (13%)	26 (2%)
Group D streptococci	18 (9%)	12 (9%)	53 (3%)
Other gram-positive organisms	1 (1%)	2 (1%)	37 (2%)
Fungi			
Yeasts	11 (5%)	1 (1%)	8 (1%)
Total pathogens†	212 (100%)	141 (100%)	1590 (100%)

Data are number of episodes. *Health-care-associated infection was defined as bacteraemia within the first 48 h of admission to hospital when within 28 days of discharge from hospital or hospital birth. †Contaminants were grown from 19.5% of samples collected in the first 48 h after admission and 18.1% of samples obtained 48 h or more after admission. These proportions did not differ significantly (p=0.11).

Table 3: Pathogens causing paediatric bacteraemia in Kilifi District Hospital, 2002-09

bacteraemia and 6.2% (1930 of 31347; 5.9-6.4) in patients with no detected episodes of bacteraemia in this period. The median interval from sample collection to death for patients with nosocomial bacteraemia was 44 h (IQR 17-120 h). During the study, 4.3% (105 of 2423) of all hospital inpatient deaths occurred in patients in whom nosocomial bacteraemia was identified.

89 patients developed nosocomial bacteraemia and survived to discharge; the median length of hospital stay for these patients was 28.9 days (IQR 13.0-41.6). In 353 matched patients without nosocomial bacteraemia, whose hospital stay lasted at least as long as the time when bacteraemia developed in the index child, the median duration was significantly shorter (18.8 days; 8.1-30.9; difference between medians 10.1 days, p=0.006). Three patients with nosocomial bacteraemia were transferred to other facilities, and their eventual outcome is unknown.

Gram-negative organisms caused 74% of episodes of nosocomial bacteraemia (table 3); *Escherichia coli* and *Klebsiella pneumoniae* accounted for 21% and 20% of all episodes, respectively. Gram-positive organisms, of which *Staphylococcus aureus* was the most common, accounted for 21% of cases. Yeasts accounted for 5% of episodes of nosocomial bloodstream infection. Health-care-associated (readmission after recent discharge) pathogens were much the same as those causing community-acquired bacteraemia.

In patients with nosocomial bacteraemia the case-fatality rate varied significantly by organism class (χ^2 test p=0.023), being 61% in Gram-negative infections, 38% in Gram-positive infections, and 45% in fungal infections. Case-fatality rates were highest in patients infected with *Acinetobacter* spp (74%), *Pseudomonas aeruginosa* (75%), and *E coli* (77%). We detected no evidence of increased mortality in patients with isolates considered to be contaminants compared with all other patients (χ^2 test p=0.49).

Discussion

Our large study provides a comprehensive description of the epidemiology and microbiological causes of nosocomial bacteraemia in a representative paediatric service in sub-Saharan Africa. With a conventional case definition,¹⁷ the risk of nosocomial bacteraemia was 5.9 per 1000 admissions. This finding is consistent with a risk of 5.0 per 1000 admissions recorded in a study in South Africa in 1989,¹⁸ although the cutoff used to define infections as nosocomial in that study was 72 h after admission rather than 48 h as we used. The risk of nosocomial bacteraemia increased significantly throughout the study, which could be attributable, in part, to increased length of hospital stay in the later years of the study. This increase in turn is probably attributable to declining numbers of short admissions for malaria¹⁹ and an increasing proportion of neonatal admissions. These factors suggest that the 2008-09 nosocomial

bacteraemia rate (1.66 per 1000 days in hospital) is a better estimate of the present rate in Kilifi District Hospital than the study mean (1.00 per 1000 days in hospital). The effect of admission is clear from the fact that the incidence of nosocomial bacteraemia was about 40 times greater than the previously estimated incidence of community-acquired bacteraemia.³

Nosocomial bacteraemia is associated with high mortality; more than half of all patients (53%) died in hospital. Particular pathogens (such as *P aeruginosa* and *E coli*) were associated with very high case-fatality rates. Although other factors might have contributed to the risk of both bacteraemia and death, such as nutritional status, the case-fatality rate for nosocomial bacteraemia was more than double that for community-acquired bacteraemia (24%). The interval between detection of nosocomial bacteraemia and death (median 44 h) means that in many cases bacteraemia could have been the cause of death. The crude mortality of paediatric nosocomial bacteraemia at 49 hospitals in the USA between 1995 and 2001 was 14%.²⁰ At Kilifi District Hospital, survivors of nosocomial bacteraemia had a substantial morbidity burden, leading to an additional 10.1 days in hospital per case.

The factor most strongly associated with nosocomial bacteraemia in our study was prescription of blood transfusion, though this association was confined to children who did not have severe anaemia. We assume that most children prescribed transfusions at admission subsequently received the same, although data were not collected on the actual administration of transfusions. Overall, 2% (52 of 2573) of transfusion recipients subsequently developed nosocomial bacteraemia, which is similar to a rate of 3–5% of post-transfusion bacteraemia recorded in Malawi.²¹ In African hospitals, clinicians often use blood transfusions to resuscitate shocked patients and for treatment of severe anaemia. In this study, 55% of patients prescribed a transfusion were severely anaemic (1408 of 2573), 27% (689 of 2573) were clinically shocked (as per WHO criteria), and 33% were neither severely anaemic nor shocked (847 of 2573). One possible explanation for the association of bacteraemia with transfusion is that these nosocomial infections were, in fact, delayed detection of community-acquired septicaemic shock. A second possible explanation for the reported association is contamination of blood for transfusion. In a study in Mombasa, Kenya, 8% of blood packs in the transfusion service had bacterial contamination.²² The absence of transfusion-associated risk in severely anaemic patients argues against this interpretation. However, the combination of a strong association in patients without severe anaemia and local evidence of blood contamination supports a critical assessment of the role of blood transfusion in nosocomial bacteraemia in Africa.²³

Malnutrition was a risk factor for nosocomial bacteraemia at all ages. This finding is consistent with studies

Panel: Research in context

Systematic review

A systematic review by WHO in 2010 identified no reports about paediatric or adult nosocomial bacteraemia in African countries between 1995 and 2008.⁷ We searched PubMed using the MeSH terms (“nosocomial” OR “hospital-acquired”) AND (“bacteraemia” OR “septicaemia”) AND (Africa) in July, 2011, and found no subsequent studies of relevance.

Interpretation

As far as we are aware, our study is the only recent description of hospital-acquired paediatric bacteraemia in sub-Saharan Africa, other than outbreak reports. Although this form of disease is rare, it has serious effects on morbidity and mortality, and the microbiological causes are distinct from those of community-acquired bacteraemia. Malnutrition is a risk factor for hospital acquired bacteraemia.

of both community-acquired bacteraemia²⁴ and late hospital mortality in the region.²⁵ Other factors previously identified as risks for bacteraemia in general are (neonatal) age,⁸ HIV infection, and anaemia.²⁶ That HIV infection was not significant in the multivariable model is indicative of underascertainment of HIV status in our study population—more than 70% of patients were of unknown HIV status because universal HIV testing was not implemented in Kilifi District Hospital until 2008. Furthermore, some of the risk of HIV infection might be indicated through nutritional status. Unexpectedly, patients with unknown HIV status seemed to be at decreased risk of disease in the univariable analysis—this finding is largely attributable to the confounding effect of the time period. Anaemia was not a risk factor after the effects of blood transfusion had been incorporated in the model, though, notably, children admitted to Kilifi District Hospital are much more anaemic than the general population.²⁷ No data were available for peripheral intravenous catheter use, which is likely to be an important risk factor in paediatric nosocomial bacteraemia.²⁰

Our study might have underestimated the true risk of nosocomial bacteraemia for two reasons. First, the sensitivity of paediatric blood cultures is inherently poor, especially when antibiotic use is common and only one small-volume culture is collected.³ Second, not all children who deteriorate in Kilifi District Hospital are investigated with blood cultures. For example, blood for culture was obtained during the 48 h before death from less than 50% of children dying in hospital. Even if only 10% of these children had had hospital-acquired bacteraemia, the calculated risk of nosocomial bacteraemia would have doubled.

We used a standard 48 h cutoff to separate hospital and community acquisition, which might have misclassified some community-acquired infections as hospital-acquired. The low sensitivity of blood cultures³

could have contributed to this misclassification—some community-acquired pathogens might have been missed on admission cultures. However, we believe that this 48 h threshold is validated, post hoc, by the distribution of pathogens isolated. Organisms that are usually acquired in the community (such as *S pneumoniae*) were very rarely classified as hospital-acquired in our analysis. Organisms such as *K pneumoniae*, which are typically associated with hospital acquisition,¹¹ were mainly classified as nosocomial cases.

Concerns about generalisability naturally arise with any single centre study. The risk of paediatric nosocomial bacteraemia at Kilifi District Hospital is substantial but it is probably even higher in other regional district hospitals. Clinical care at Kilifi District Hospital is supported by sustained research funding from the Kenya Medical Research Institute-Wellcome Trust Research Programme. Although the hospital has difficulties of overcrowding and high patient to staff ratios, the clinical services (including infection prevention and control) are probably of a higher standard in this institution than in other regional facilities.

To what extent are cases of nosocomial bacteraemia preventable in a setting such as Kilifi District Hospital? The WHO Patient Safety programme²⁸ argues that nosocomial disease should never be regarded as an unavoidable part of care, even in settings in which funds are limited. Indeed, measures to prevent nosocomial disease could be some of the most cost-effective interventions in low-income hospital settings.²⁹ In our study, many nosocomial bacteraemia cases occurred in easily identifiable high-risk groups of patients, so the efficiency of interventions could be increased through targeting. Promotion of hand hygiene, safe blood transfusions, and appropriate care of intravascular catheters could all greatly reduce the spread of invasive bacterial infections. In Kenya, national guidelines for infection prevention and control were published by the Ministry of Medical Services in December, 2010;³⁰ enforcement of these basic infection control principles could achieve substantial reductions in the burden of nosocomial disease.

As far as we are aware, our study is the largest analysis of nosocomial bacteraemia in sub-Saharan Africa (panel) and it provides the information base both for future research and for immediate efforts to tackle this disease. In Kilifi District Hospital, nosocomial bacteraemia occurs in six of every 1000 paediatric inpatients and accounts for almost 5% of deaths in hospital and extended hospital stay in survivors. The inherent insensitivity of paediatric blood cultures means that these findings are probably substantial underestimates. As the major paediatric infectious diseases of developing countries are brought under control by insecticide-treated bednets, effective antimalarial drugs, and vaccines against *Haemophilus influenzae* type b, pneumococcus, and rotavirus, the importance of hospital-acquired infections will become

increasingly apparent and an effective response from doctors, nurses, hospital managers, and policy makers will be essential.

Contributors

JAGS, JAB, IMW, IK, and the Kilifi Bacteraemia Surveillance Group designed and did the surveillance for paediatric bacteraemia at Kilifi District Hospital. NM, PN, and SM led paediatric clinical services at Kilifi Hospital. SM, BCL, BSK, and SCM were responsible for microbiological parts of surveillance. AA, AJH, and JAGS planned the analysis. AA wrote the report and all authors reviewed and approved it before submission.

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Conflicts of interest

We declare that we have no conflicts of interest.

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References

- Rosenthal VD. Health-care-associated infections in developing countries. *Lancet* 2011; **377**: 186–88.
- Walsh AL, Phiri AJ, Graham SM, Molyneux EM, Molyneux ME. Bacteremia in febrile Malawian children: clinical and microbiologic features. *Pediatr Infect Dis J* 2000; **19**: 312–18.
- Berkley JA, Lowe BS, Mwangi I, et al. Bacteremia among children admitted to a rural hospital in Kenya. *N Engl J Med* 2005; **352**: 39–47.
- Hill PC, Onyema CO, Ikumapayi UN, et al. Bacteraemia in patients admitted to an urban hospital in West Africa. *BMC Infect Dis* 2007; **7**: 2.
- Bahwere P, Levy J, Hennart P, et al. Community-acquired bacteremia among hospitalized children in rural central Africa. *Int J Infect Dis* 2001; **5**: 180–88.
- Blomberg B, Jureen R, Manji KP, et al. High rate of fatal cases of pediatric septicemia caused by gram-negative bacteria with extended-spectrum beta-lactamases in Dar es Salaam, Tanzania. *J Clin Microbiol* 2005; **43**: 745–49.
- Allegranzi B, Bagheri Nejad S, Combescure C, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. *Lancet* 2011; **377**: 228–41.
- Zaidi AK, Huskins WC, Thaver D, Bhutta ZA, Abbas Z, Goldmann DA. Hospital-acquired neonatal infections in developing countries. *Lancet* 2005; **365**: 1175–88.
- Aiken CG. HIV-1 infection and perinatal mortality in Zimbabwe. *Arch Dis Child* 1992; **67**: 595–99.
- Iregbu KC, Anwaal U. Extended spectrum Beta-Lactamase-producing *Klebsiella pneumoniae* septicaemia outbreak in the Neonatal Intensive Care Unit of a tertiary hospital in Nigeria. *Afr J Med Med Sci* 2007; **36**: 225–28.
- Murphy SA, Lowe B, Maghenda JK, Apollo JG. An outbreak of intravenous cannulae associated nosocomial septicaemia due to multidrug-resistant *Klebsiella pneumoniae*. *East Afr Med J* 1994; **71**: 271–72.
- Vaagland H, Blomberg B, Kruger C, Naman N, Jureen R, Langeland N. Nosocomial outbreak of neonatal *Salmonella enterica* serotype *Enteritidis meningitis* in a rural hospital in northern Tanzania. *BMC Infect Dis* 2004; **4**: 35.

- 13 de Irala-Estevez J, Martinez-Concha D, Diaz-Molina C, Masa-Calles J, Serrano del Castillo A, Fernandez-Crehuet Navajas R. Comparison of different methodological approaches to identify risk factors of nosocomial infection in intensive care units. *Intensive Care Med* 2001; **27**: 1254–62.
- 14 Callas PW, Pastides H, Hosmer DW. Empirical comparisons of proportional hazards, poisson, and logistic regression modeling of occupational cohort data. *Am J Ind Med* 1998; **33**: 33–47.
- 15 Schulgen G, Kropec A, Kappstein I, Daschner F, Schumacher M. Estimation of extra hospital stay attributable to nosocomial infections: heterogeneity and timing of events. *J Clin Epidemiol* 2000; **53**: 409–17.
- 16 Severe falciparum malaria. World Health Organization, Communicable Diseases Cluster. *Trans R Soc Trop Med Hyg* 2000; **94** (suppl 1): S1–90.
- 17 Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008; **36**: 309–32.
- 18 Cotton MF, Burger PJ, Bodenstern WJ. Bacteraemia in children in the south-western Cape. A hospital-based survey. *S Afr Med J* 1992; **81**: 87–90.
- 19 O'Meara WP, Bejon P, Mwangi TW, et al. Effect of a fall in malaria transmission on morbidity and mortality in Kilifi, Kenya. *Lancet* 2008; **372**: 1555–62.
- 20 Wisplinghoff H, Seifert H, Tallent SM, Bischoff T, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in pediatric patients in United States hospitals: epidemiology, clinical features and susceptibilities. *Pediatr Infect Dis J* 2003; **22**: 686–91.
- 21 Walsh AL, Molyneux EM, Kabudula M, Phiri AJ, Molyneux ME, Graham SM. Bacteraemia following blood transfusion in Malawian children: predominance of Salmonella. *Trans R Soc Trop Med Hyg* 2002; **96**: 276–77.
- 22 Hassall O, Maitland K, Pole L, et al. Bacterial contamination of pediatric whole blood transfusions in a Kenyan hospital. *Transfusion* 2009; **49**: 2594–98.
- 23 Tagny CT, Mbanya D, Tapko JB, Lefrere JJ. Blood safety in Sub-Saharan Africa: a multi-factorial problem. *Transfusion* 2008; **48**: 1256–61.
- 24 Bejon P. Fraction of all hospital admissions and deaths attributable to malnutrition among children in rural Kenya. *Am J Clin Nutr* 2008; **88**: 1626–31.
- 25 Berkley JA, Ross A, Mwangi I, et al. Prognostic indicators of early and late death in children admitted to district hospital in Kenya: cohort study. *BMJ* 2003; **326**: 361.
- 26 Calis JC, Phiri KS, Faragher EB, et al. Severe anemia in Malawian children. *N Engl J Med* 2008; **358**: 888–99.
- 27 Pedro R, Akech S, Fegan G, Maitland K. Changing trends in blood transfusion in children and neonates admitted in Kilifi District Hospital, Kenya. *Malar J* 2010; **9**: 307.
- 28 Pittet D, Allegranzi B, Storr J, et al. Infection control as a major World Health Organization priority for developing countries. *J Hosp Infect* 2008; **68**: 285–92.
- 29 Allegranzi B, Pittet D. Healthcare-associated infection in developing countries: simple solutions to meet complex challenges. *Infect Control Hosp Epidemiol* 2007; **28**: 1323–27.
- 30 Ministry of Medical Services, Kenya. National infection prevention and control guidelines for health care services in Kenya; 2010. http://nascop.or.ke/library/PEP/infection_control_policy.pdf (accessed Nov 5, 2011).