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Burden, spectrum, and impact of healthcare-associated infection at a South African children's hospital

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SUMMARY

Background: In most African countries the prevalence and effects of paediatric healthcare-associated infection (HCAI) and human immunodeficiency virus (HIV) infection are unknown.

Aim: To investigate the burden, spectrum, risk factors, and impact of paediatric HCAI by prospective clinical surveillance at a South African referral hospital.

Methods: Continuous prospective clinical and laboratory HCAI surveillance using Centers for Disease Control and Prevention (CDC)/National Healthcare Safety Network (NHSN) definitions was conducted at Tygerberg Children's Hospital, South Africa, from May 1st to October 31st in 2014 and 2015. Risk factors for HCAI and associated mortality were analysed with multivariate logistic regression; excess length of stay was estimated using a confounder and time-matching approach.

Findings: HCAI incidence density was 31.1 per 1000 patient-days (95% CI: 28.2–34.2); hospital-acquired pneumonia (185/417; 44%), urinary tract infection (UTI) (45/417; 11%), bloodstream infection (BSI) (41/417; 10%), and surgical site infection (21/417; 5%) predominated. Device-associated HCAI incidence in the paediatric intensive care unit (PICU) was high: 15.9, 12.9 and 16 per 1000 device-days for ventilator-associated pneumonia, central line-associated BSI and catheter-associated UTI, respectively. HCAI was significantly associated with PICU stay (odds ratio: 2.0), malnutrition (1.6), HIV infection (1.7), HIV exposure (1.6), McCabe score 'fatal' (2.0), comorbidities (1.6), indwelling devices (1.9), blood transfusion (2.5), and transfer in (1.4). Two-thirds of paediatric deaths were HCAI-associated, occurring at a median of four days from HCAI onset with significantly higher crude mortality for HCAI-affected vs HCAI-unaffected hospitalizations [24/325 (7.4%) vs 12/1022 (1.2%); $P < 0.001$]. HCAI resulted in US$371,887 direct costs with an additional 2275 hospitalization days, 2365 antimicrobial days, and 3575 laboratory investigations.

Conclusion: HCAI was frequent with significant morbidity, mortality, and healthcare costs. Establishment of HCAI surveillance and prevention programmes for African children is a public health priority.

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Introduction

Healthcare-associated infection (HCAI) is the most frequent complication of hospitalization affecting 4–8% of paediatric admissions in high-income settings.[1–5] In most African countries, paediatric HCAI burden, spectrum, and impact is unknown and the influence of human immunodeficiency virus (HIV) infection is unquantified.[6,7] South Africa similarly lacks data on HCAI prevalence and impact, despite a comparatively better-resourced health sector with access to microbiology laboratories and infection prevention personnel at many hospitals.[8]

South African data on 'whole house' surveillance for paediatric HCAI was last published almost three decades ago. A single-centre study (at the country's largest hospital) reported HCAI rates of 14.3% and 22.4 HCAI events per 100 admissions with gastrointestinal and respiratory tract infections predominating.[9] A small study in a paediatric intensive care unit (PICU) determined HCAI prevalence rates of 43%; both studies identified *Staphylococcus aureus* and *Klebsiella pneumoniae* as the predominant nosocomial pathogens.[9,10] In 2005, a one-day HCAI point prevalence study at six hospitals established a prevalence of 9.7% for four HCAI types: bloodstream (BSI), urinary tract (UTI), respiratory tract (RTI) and surgical site (SSI) infections ($N = 2652$ adult and paediatric patients). Highest HCAI prevalence was recorded for patients admitted to ICU and paediatric wards (28.6% and 16.5%, respectively). The spectrum of HCAI types varied markedly by discipline and age, with paediatric patients experiencing higher rates of BSI and RTI.[11,12]

Studies of paediatric inpatients in other low/middle-income countries (LMIC) since 2000 also document substantial HCAI prevalence and incidence densities: 22.6% and 29 per 1000 patient-days in Indonesia, 15.4% and 9.2 per 1000 patient-days in Brazil, 15 per 1000 patient-days in Mexico and 21% in Uganda.[13–16] Risk factors for paediatric HCAI identified in these settings include malnutrition, prolonged hospital stay, use of indwelling devices, PICU admission, non-surgical disease, RTI on admission, blood transfusion, and young age.[9,10,13–17] HCAI infection density is even higher in the paediatric ICU setting, with greater contribution of device-associated HCAI including ventilator-associated pneumonia (VAP), central line-associated BSI (CLABSI), and catheter-associated UTI (CAUTI). In 2012, the International Nosocomial Infection Control Consortium (INICC) reported VAP, CLABSI, and CAUTI rates from 16 LMIC PICUs of 6, 8.1, and 4.1 infections per 1000 device-days, respectively, vs rates reported from US PICUs of 0.7, 1.0, and 3.5, respectively.[18,19] Although the INICC device-associated HCAI rates far exceed rates in high-income settings, the true burden is probably even higher as 75% of INICC PICUs were located in private hospitals.

Few studies of paediatric HCAI in resource-limited settings have included estimations of HCAI impact beyond additional hospital stay and mortality. Excess mortality attributable to nosocomial vs community-acquired BSI has been reported in two African paediatric cohorts from Kenya (53% vs 24%) and South Africa (25% vs 16%).[17,20] The extreme paucity of data from paediatric inpatients in Sub-Saharan Africa limits estimation of HCAI impact on childhood mortality and healthcare costs. This article investigates burden, spectrum, risk factors, and impact of paediatric HCAI measured by prospective clinical surveillance at a South African referral hospital.

Methods

Setting

The Tygerberg Children's Hospital (TCH) in Cape Town, South Africa has 300 paediatric beds in a 1384-bedded academic hospital complex. Sick neonates, infants and children (0–14 years) are admitted to 13 neonatal and paediatric wards (including surgical, medical generalist, specialty, and intensive care facilities); critically ill children requiring ventilation or inotropic support are managed in the 10-bed medical/surgical PICU (neonates are managed in a separate 12-bed neonatal ICU). There are ~17,000 neonatal and paediatric admissions to TCH annually; bed occupancy rates were 93% (PICU), 92% (general wards), and 87% (subspecialist wards) in 2014/15. The burden of community-acquired infectious diseases is high, with HIV, tuberculosis, RTI, and gastroenteritis predominating. In 2013, the antenatal HIV prevalence in the Western Cape Province was 19% (vs 30% nationally) and HIV prevalence among children (2–14 years) was 0.7% (vs 2.4% nationally).[21]

Investigation and management of HCAI at Tygerberg Children's Hospital

Current standard practice for investigation of patients with suspected HCAI (new-onset fever or clinical deterioration ≥48 h after admission) is submission of blood culture and other clinically indicated samples at the attending clinician's discretion. Empiric treatment of HCAI at TCH includes meropenem, or ertapenem if *Pseudomonas aeruginosa* is considered unlikely and meningitis is excluded. Vancomycin is added if meticillin-resistant *Staphylococcus aureus* (MRSA) is likely, e.g. with suspected central line or soft tissue infection. There were no significant changes in clinical practice, laboratory investigations, empiric antibiotic treatment, infection prevention practice, isolation facility availability or major outbreaks of community- or hospital-acquired infection during the study periods.

Study design

Prospective clinical surveillance for HCAI events meeting 2013 CDC/NHSN surveillance definition criteria was conducted in three paediatric wards: subspecialist infectious diseases/gastroenterology/cardiology (A), general paediatrics (B), paediatric surgery (C), and the PICU (neonatal wards were not included).[22] Demographics, admissions history, laboratory investigations, antimicrobial prescription data and information on any HCAI event(s) were collected on weekdays for all patients admitted ≥48 h or transferred in from another facility between May 1st, 2014 to October 31st, 2014 (A) and May 1st, 2015 to October 31st, 2015 (B, C, PICU). At the end of each six-month study period, children still hospitalized were followed-up for an additional four weeks, or until discharged. We calculated weight-for-age *Z*-scores (WAZ) using WHO anthropometric reference data, and defined severe acute malnutrition as WAZ score of less than −3 standard deviations (SD).[23] We included all surgical procedures for patients hospitalized ≥48 h. Ethical approval and waiver of individual informed consent was obtained from the Human Health Research Ethics committee of Stellenbosch University (S13/09/171).

Table I
Factors associated with healthcare-associated infection (HCAI)

	No. (%) of hospitalization episodes with one or more HCAI events ($N = 325$)	No. (%) of hospitalization episodes with no HCAI events ($N = 1022$)	*P*-value	Univariate odds ratio	Multivariate odds ratio	95% CI
Gender (male)	182 (56)	582 (57)	0.78	0.97	–	–
Age category (days)						
0–59	70 (21.5)	194 (19)		1.4	1.1	0.7–1.6
60–365	119 (36.6)	300 (29.4)	0.02	0.97	0.8	0.5–1.2
366–1825	79 (24.3)	310 (30.3)		1.5	1.0	0.7–1.5
>1825 (ref.)	57 (17.6)	218 (21.3)				
HIV status						
HIV-infected	46 (14.2)	79 (7.7)		2.1	1.7	1.1–2.7
HIV-exposed, uninfected	51 (15.7)	113 (11.1)	<0.001	1.6	1.6	1.1–2.4
HIV unknown	23 (7.1)	97 (9.5)		0.9	1.1	0.7–1.9
HIV negative (ref.)	205 (63)	733 (71.7)				
Ward type at HCAI diagnosis						
Paediatric ICU	105 (32)	147 (14)	<0.001	2.8	2.0	1.4–2.7
General/specialty ward (ref.)	220 (68)	875 (86)				
Discipline						
Medical	255 (78)	726 (71)	0.009	1.5	1.1	0.7–1.5
Surgical (ref.)	70 (22)	296 (29)				
Bed type on admission						
Isolation	49 (15)	118 (12)	0.09	1.4	1.3	0.8–2.0
Cohort (ref.)	276 (85)	904 (88)				
Transferred in	189 (58.2)	438 (42.9)	<0.001	1.9	1.4	1.03–1.8
Recent hospitalization	223 (68.6)	213 (20.8)	<0.001	8.2	–	–
Severe acute malnutrition (WAZ <−3 SD)	133 (41)	239 (23)	<0.001	2.3	2.9	1.2–2.1
Underlying comorbidity/ies	163 (50.2)	321 (31.4)	<0.001	2.2	1.6	1.1–2.1
McCabe score[a]						
Rapidly or ultimately fatal	28 (8.6)	19 (2)	<0.001	5.0	2.0	1.4–2.8
Non-fatal (ref.)	297 (91.4)	1003 (98)				
Blood transfusion(s)	66 (20.3)	58 (5.7)	<0.001	4.2	2.5	1.6–3.8
Total parenteral nutrition	12 (100)	0	<0.001	–	–	–
Recent surgery last 30 days	88 (27.1)	241 (23.6)	0.2	1.2	–	–
Presence of any indwelling device[b]	297 (91.4)	830 (81.2)	<0.001	2.5	1.9	1.2–3

CI, confidence interval; ref., reference category; HIV, human immunodeficiency virus; ICU, intensive care unit; WAZ, weight-for-age *z*-score; SD, standard deviation.

[a] McCabe score for underlying condition: non-fatal (expected survival at least five years); ultimately fatal: expected survival between one and five years; rapidly fatal: expected death within one year.

[b] Indwelling device included nasogastric tube, urinary catheter, intravenous catheter, and/or endotracheal tube. Only factors with $P < 0.1$ and all cell counts >0 were entered into the multivariate model with adjustment for robust estimation of variance (standard error adjusted for 1201 clusters); recent hospitalization was removed from the model owing to collinearity.

Study definitions

A hospitalization episode was any patient admitted for ≥48 h to one or more of the selected wards. Patients could have one or more hospitalization episode and one or more HCAI events during each hospitalization. Readmission was repeat hospitalization to any ward in our institution within 30 days of discharge. Several measures of HCAI occurrence were calculated: (1) HCAI patient prevalence (patient hospitalizations with at least one HCAI event/total hospitalization episodes); (2) HCAI event prevalence (total HCAI events/total hospitalization episodes); (3) HCAI incidence density (HCAI events/1000 patient-days); (4) device-associated HCAI (VAP, CLABSI, CAUTI) rates (total of each event type/total number of specific device-days ×1000); (5) device use ratios (total device-days/total patient-days); (6) average device-days per

patient. HCAIs were infections present on admission in a child with a history of hospitalization in the preceding 30 days. Pathogens from specimens obtained <48 h after admission (without recent hospitalization) were classified as community-acquired; those isolated on hospital transfer (>48 h at the referral hospital) or >48 h post-admission were considered healthcare-associated or hospital-acquired pathogens. Laboratory isolates (bacterial, fungal, and/or viral) were considered causative pathogens if identified at the time of HCAI investigation and compatible with the clinical diagnosis, e.g. MRSA from wound swab in a patient with SSI. Bacterial isolates were categorized using the CDC list of pathogens and contaminants; repeated isolation of the same pathogen from the same site within 14 days was considered a single HCAI event.[24] Fluconazole-resistant *Candida* species, MRSA, multidrug-resistant (MDR) *Acinetobacter baumannii* (resistant to at least three classes of antimicrobials), and extended spectrum β-lactamase (ESBL)-producing Enterobacteriaceae were classified as antimicrobial-resistant pathogens using proposed standard definitions.[25] A 'presumed' sepsis event was a clinically diagnosed HCAI episode occurring >48 h after hospitalization, treated empirically with broad-spectrum antimicrobials for at least five calendar days, and lacking an identified focus of infection/laboratory confirmation of a pathogen. The McCabe score was used to stratify risk of death from underlying comorbid conditions: 'non-fatal' being expected survival of at least five years, 'ultimately fatal' being expected survival of between one and five years; and 'rapidly fatal' being expected death within one year.[26] Surgical procedures were categorized using the CDC/NHSN criteria as: wound class (clean/clean contaminated vs contaminated/dirty); ASA score (1–2 vs 3–5); emergency vs elective procedure and operation duration <60 vs >60 min.[22,27]

Cost analysis

Cost analysis of HCAI impact was performed from the healthcare provider perspective using 2015 costs entered into the following formula (for each of the five major HCAI subtypes): number of HCAI events × median excess length of stay for that HCAI type × unit cost per patient day (including all laboratory investigation, radiology, and pharmacy costs).

Statistical analysis

All analyses were performed using Stata Statistical Software version 13.0 IC (StataCorp LP; College Station, TX, USA). HCAI prevalence and incidence densities were calculated with 95% confidence interval (CI). Risk factor data were converted from continuous to binary or categorical variables, where needed. Forward stepwise logistic regression analysis was used to test variables for association with HCAI events and death from HCAI (all risk factor variables with univariate association of $P < 0.1$ were included in the model). To account for patients with multiple admission episodes, adjustment of variance for clustering within individuals was used. $P < 0.05$ was considered statistically significant. To estimate excess hospitalization for different HCAI types, affected patients were compared with three randomly selected age- and ward-matched 'controls' per HCAI event (who had been hospitalized for at least as long as the index patient). A confounder and time-matching approach was used, after excluding patient admission episodes with outcome of death or transfer, for HCAI events with a minimum of 20 events.[28]

Results

A total of 1347 paediatric hospitalizations occurred during the two study periods, including 315 to Ward A and 451, 329, and 252 to Wards B, C, and PICU, respectively. One or more HCAI events complicated 325/1347 hospitalizations (24.1% HCAI patient prevalence; 95% CI: 21.9–26.5); 417 HCAI events occurred in 296 patients during 325 hospitalizations (HCAI event prevalence of 31 per 100 hospitalizations; 95% CI: 28.6–33.5). Overall HCAI incidence density was 31.1 per 1000 patient-days (95% CI: 28.2–34.2): 94.4 (95% CI: 80.6–109.8) in PICUs vs 22.5 (95% CI: 19.9–25.3) per 1000 patient-days in wards.

Of the study cohort, 763 (57%) were male, median age was 12.1 months (IQR: 3–47), 372 (28%) were severely malnourished, and 125 (9%) were HIV-infected [86/125 (69%)] on antiretroviral therapy (ART). The median (IQR) length of hospitalizations complicated by HCAI was 13 days (7–24) vs 6 days (4–9) for HCAI-unaffected hospitalizations ($P < 0.001$). Patients experiencing HCAI events were younger (median 8.4 vs 13.7 months; $P < 0.007$) and more likely to be HIV-infected, malnourished, have pre-existing comorbidities, and a McCabe score of ultimately/rapidly fatal (all $P < 0.001$) (Table I). For HIV-infected children, ART status did not influence HCAI occurrence [35/86 (41%) vs 11/39 (28%); $P = 0.23$] although patients on ART had higher median (IQR) $CD4^+$ T-cell counts and percentages [497 (230–1011), 23% (11–33) vs 373 (79–915), 18% (9–21); $P = 0.04$ and $P = 0.02$, respectively]. Among 484 patients with comorbidities, the predominant underlying conditions were: chronic organ or multi-system diseases (264, 57%) and premature birth (<37 weeks of gestation) (185, 38%).

Nearly half of all hospitalizations (47%; 627/1347) were transfers in: 28 (5%) from other wards at our institution; 121 (19%) from primary care facilities; 453 (72%) from secondary/district hospitals, and 25 (4%) from tertiary or private hospitals. Most were to the medical disciplines (981; 73%) with fewer surgical (paediatric surgery, orthopaedics and urology) admissions (366; 27%). Among medical hospitalizations ($N = 981$), community-acquired infections predominated: RTI (379, 39%); other infectious diseases including tuberculosis (252; 25%) and acute gastroenteritis (96; 10%). HCAI events occurred more frequently in the medical disciplines ($P < 0.009$), with history of recent hospitalization ($P < 0.001$) and with use of any indwelling device, e.g. intravascular and urinary catheters ($P < 0.001$). Repeat hospitalization (re-admission within 30 days of discharge) was more likely following an initial stay complicated by HCAI [21% (63/301) vs 8% (81/1010); $P < 0.001$].

Of 417 HCAI events, 294 (71%) were hospital-acquired and 123 (29%) were healthcare-associated. Most transfers in with HCAI (following deterioration at referring hospital) had hospital-acquired pneumonia (HAP) (63/123; 51%), 'presumed' hospital-acquired (HA) sepsis (22/123; 18%) or SSI events (11/123; 9%). Forty percent of HCAI-affected admission episodes had more than one HCAI event (119 had two events, 28 had three events, and 21 had four events). The most frequent HCAI event types overall (355/417; 85%) were: HAP (185; 44%),

Table II
Healthcare-associated infection event type ($N = 417$)

Event type	No.	%	95% CI
Hospital-acquired pneumonia	185	44	40–49
'Presumed' HA sepsis	63	15	12–19
(Catheter-associated) UTI[a]	45	11	8–14
Laboratory-confirmed BSI	41	10	7–13
Surgical site infection	21	5	3.3–7.6
Skin and soft tissue infection	19	5	3–7
Ventilator-associated pneumonia	13	3	1.8–5.3
Gastroenteritis	12	3	1.6–5
Central line-associated BSI	7	1.5	0.7–3.5
Ear, nose, throat, and eye infection	7	1.5	0.7–3.5
Bone and joint infection	4	1	0.3–2.5

CI, confidence interval; HA, hospital-acquired; UTI, urinary tract infection; BSI, bloodstream infection.
[a] Ten catheter-associated UTI and 35 UTI episodes.

'presumed' HA sepsis (63; 15%), UTI (45; 11%), LCBSI (41; 10%), and SSI (21; 5%) (Table II). Excluding patients transferred in with HCAI ($N = 123$) or with HCAI onset <48 h after transfer in ($N = 20$), median (IQR) interval between admission and HCAI onset was: for HAP 8 (4–16), LCBSI 10 (7–16), 'presumed' HA sepsis 5 (3.5–11), UTI 6.5 (3–18), SSI 13 (5–23), CLABSI 10 (8–12), and VAP 5 (4–9) days.

Although there were relatively few device-associated infections in the PICU, infection density rates were high: VAP (15.9 per 1000 ventilator-days), CLABSI (12.9 per 1000 central line-days), and CAUTI (16 per 1000 catheter-days) (Table III). Mean device use ratios and total device days in the PICU were: 0.14 (233 days) for central lines, 0.5 (819 days) for endotracheal tubes, and 0.39 (625 days) for urinary catheters. The average device-days per PICU patient were 0.9, 3.3, and 2.5 and mean dwell times were 10.1, 10, and 11.3 days per patient for central lines, endotracheal tubes and urinary catheters respectively. All 12 children receiving total parenteral nutrition developed HCAI events including: three CLABSI, four LCBSI, three 'presumed' HA sepsis and two SSI events.

SSI was the fifth most prevalent HCAI type, although nearly half were transfers in. The demographic profile of patients ($N = 329$) who underwent recent or current surgery differed markedly from non-surgical admissions. Patients were older (mean age 25 vs 11 months; $P < 0.001$), less likely to be HIV-infected [8/329 (3%) vs 117/1018 (12%); $P < 0.001$] and less likely to have underlying comorbidities (97/329 (29%) vs 387/1018 (38%); $P = 0.005$). Of the 327 current surgeries, 67 (20%) were emergency procedures, 25 (8%) had American Society of Anesthesiologists (ASA) score >2, 54 (17%) were classified as contaminated/dirty, and 107 (33%) procedures lasted >60 min. No potential risk factors for SSI were significant on univariate analysis: wound class ($P = 0.71$); ASA score ($P = 0.19$); emergency vs elective procedure ($P = 0.78$), and operation duration ($P = 0.35$). Notably patients in surgical disciplines had fewer HCAI events overall [70/366 (19%) vs 255/981 (26%); $P = 0.009$] and no fatal outcomes.

Table III
Device-associated healthcare-associated infection in paediatric intensive care units

Infection	No. of events	Device-days	Rate per 1000 device-days
Ventilator-associated pneumonia	13	819	15.9
Catheter-associated urinary tract infection	10	625	16
Central line-associated bloodstream infection	3	233	12.9

Table IV
Management of healthcare-associated infection (HCAI) events

Management	No.	Total eligible	%
New antimicrobial prescription	397	417	95
ICU admission (only patients from wards)	80	264	30
Respiratory support (ventilation or CPAP)	56	417	13
Inotropes	28	417	7
Surgical procedure(s)[a]	16	417	4
Device removal[b]	9	73	12

ICU, intensive care unit; CPAP, continuous positive airways pressure.
[a] Excess surgical procedures: re-look laparotomy, incision and drainage, etc.
[b] Removal of central line or urinary catheter; excess laboratory investigations (the mean excess laboratory tests for admissions with HCAI × total admission episodes with HCAI).

Table IV describes the management and impact of the 417 HCAI events. Some patients experienced severe morbidity requiring ICU admission with/without respiratory support, inotropes, and additional surgical procedures as a direct consequence of the HCAI event. Ninety-five percent of HCAI events prompted a new antimicrobial prescription (2365 additional days of therapy) (Table V) at a cost of US$14,370. HCAI-affected hospitalization episodes produced significantly more laboratory investigation requests (mean of 16 vs 5 tests per admission; $P < 0.001$), totalling an additional 3575 laboratory investigations (Table VI). After excluding outcomes of death or transfer (Table VII), 1058 hospitalizations remained (five HCAI types with ≥20 events). When compared to age- and ward-matched 'controls' (three per HCAI event), HAP, LCBSI, and 'presumed' HA sepsis events significantly prolonged median (IQR) hospital stay: HAP [11 (7–24) vs 9 (6–20) days; $P = 0.03$]; LCBSI [20 (11–32) vs 11 (7–23) days; $P = 0.02$] and 'presumed'

Table V
Antimicrobial therapy for healthcare-associated infection (excess days) ($N = 2365$)

Antimicrobial therapy	Excess days	%
Meropenem	780	33
Ertapenem	650	28
Vancomycin	228	10
Amoxicillin + clavulanic acid	130	5
Cloxacillin	120	5
Fluconazole	96	4
Colistin	35	1
Others[a]	326	14

[a] Ciprofloxacin, erythromycin, azithromycin, clarithromycin, clindamycin, metronidazole, gentamicin, ampicillin, cephalosporins.

Table VI
Laboratory investigations

Laboratory investigations	Mean	Total admissions	Excess tests
Mean investigations per hospitalization without HCAI	5	1022	
Mean investigations per hospitalization with HCAI	16	325	
Difference of means	11		3575

HCAI, healthcare-associated infection.

HA sepsis [14 (7–24) vs 8 (5–14) days; $P = 0.001$]. SSI and UTI events prolonged median (IQR) length of stay, but did not achieve statistical significance [11 (5–25) vs 7 (5–14) days; $P = 0.1$] and [16 (7–19) vs 10 (5–23) days; $P = 0.21$], respectively (Table VIII). Direct hospital costs incurred for the five major HCAI event types were (US$ per patient/total US$ per event type): HAP (326/60,483), 'presumed' HA sepsis (981/61,790), LCBSI (1471/60,319), UTI (981/44,136), and SSI (654/13,731). Overall direct cost of the excess 2275 inpatient days was US$371,887.

Table IX summarizes the pathogens associated with five HCAI types. *K. pneumoniae* (35/72; 49%) and *S. aureus* (13/25; 52%) were the leading Gram-negative and -positive bacterial isolates for LCBSI, CLABSI, UTI, and SSI events. Of the 61 Enterobacteriaceae isolated, 35 (57%) were ESBL producers, and 3/13 (23%) *S. aureus* isolates were MRSA. Viral pathogens (particularly respiratory syncytial virus and adenovirus) predominated in HAP events, with 82/151 (54%) patients investigated yielding one or more RTI pathogens.

Of hospitalizations complicated by HCAI, 24/325 (7.4%) resulted in death vs 12/1022 (1.2%) HCAI-unaffected episodes ($P < 0.001$). Deaths associated with HCAI occurred at a median of 4 days (IQR: 2–6.8) from onset of infection. Crude mortality by HCAI event type was highest for LCBSI (9/41; 22%), followed by VAP (2/13; 15%), HAP (10/185; 5%), and 'presumed' HA sepsis (3/63; 5%). Proportionally, HAP contributed the most HCAI-associated deaths (42%) followed by LCBSI (38%), 'presumed' HA sepsis (13%), and VAP (7%). Of 10 children whose death was HAP-associated, five isolated one or more respiratory pathogens including: adenovirus (five); respiratory syncytial virus (three), influenza (one), bocavirus (one), and five had no pathogen identified. Gram-negatives and fungal pathogens predominated from fatal LCBSI events including: *K. pneumoniae* (three); *Enterobacter cloacae* (one); *Pseudomonas aeruginosa* (one); *A. baumannii* (one), *C. albicans* (two), *C. parapsilosis* (one) and *Enterococcus faecalis* (one). By contrast, only one out of 12 children who died during HCAI-unaffected hospitalizations had a pathogen isolated (*Streptococcus pneumoniae*). Risk factors for HCAI-associated death with $P < 0.1$ on univariate analysis were entered into a multivariate model including: age category, ward type, discipline, blood transfusion, isolation room stay, and McCabe score. Discipline and McCabe score were subsequently removed from the model owing to collinearity; factors independently associated with death from HCAI were PICU admission (OR: 7.6; IQR: 3.3–17.6; $P < 0.001$), blood transfusion (8.1; 3.9–16.6; $P < 0.001$) and stay in an isolation room (7.6; 2.9–19.6; $P < 0.001$).

Table VII
Final outcome of hospitalizations with healthcare-associated infection events ($N = 325$)

Outcome	No.	%
Discharged	217	67
Transferred out	84	26
Died	24	7

Table VIII
Additional bed-days occupied for healthcare-associated infection (HCAI)[a]

Infection type	Median excess days	No. of HCAI events	No. of days
Hospital-acquired pneumonia (HAP)	2	185	370
'Presumed' hospital-acquired sepsis	6	63	378
Laboratory-confirmed bloodstream infection	9	41	369
Surgical site infection	4	21	84
Urinary tract infection	6	45	270
All HCAI-affected admission episodes	7	325	2275

[a] Calculated as median excess days from HCAI event × number of HCAI events of that type, e.g. HAP = median 2 days excess stay × 185 HAP events = 370 additional bed-days.

Discussion

These data represent the first comprehensive description of HCAI burden at any paediatric facility in South Africa since 1987. We documented overall HCAI prevalence (24.1%) higher than previously reported in hospitalized South African children on general wards (14.3%), PICUs (43%), and a point prevalence study that included paediatric wards (16.5%).[9–11] Although similar to other LMICs, our HCAI prevalence was three- to six-fold greater than rates in high income settings.[1–5,13–16] However, three out of four publications from these LMICs subsequently reported major reductions in HCAI prevalence (to 8.6%, 7.4%, and 5%) after implementing infection prevention programmes.[13,15,29]

HCAI rates and incidence density on the PICUs were four-fold higher than in wards, reflecting the increased likelihood of infection in critically ill patients with greater use of indwelling devices and higher antimicrobial usage. Although device-associated HCAI contributed only 7% of all HCAI events, PICU patients with indwelling central lines, catheters, and endotracheal tubes were at very high risk of infection. VAP, CAUTI and CLABSI rates at our institution far exceeded those from 16 LMIC PICU, despite having lower (for central lines) or comparable (for ventilation and urinary catheters) device use ratios. However, mean device-days per patient and device dwell times in our setting exceeded those of the INICC PICUs (except for average central-line-days which were 0.9 in our PICUs vs 2.4 in INICC PICUs).[18]

Our population's HCAI spectrum approximated that published from other paediatric settings with predominance of HAP, BSI, and UTI. By contrast, our cohort experienced relatively few SSI

Table IX
Pathogens associated with selected healthcare-associated infection types

Pathogen	LCBSI ($N = 41$)	CLABSI[a] ($N = 7$)	UTI ($N = 45$)	SSI ($N = 21$)	HAP[b] ($N = 185$)
Gram-negatives ($N = 72$)					
Klebsiella pneumoniae (ESBL)	5 (5)	2 (2)	24 (22)	2 (0)	2 (2)
Enterobacter cloacae	4	–	–	1	–
Escherichia coli (ESBL)	5 (2)	–	7 (2)	4 (0)	–
Acinetobacter spp. (MDR)	3 (1)	–	–	–	–
Pseudomonas aeruginosa (MDR)	2 (0)	–	1 (1)	3 (1)	–
Serratia marcescens	1	–	–	–	1
Salmonella non-typhi	1	–	–	–	–
Morganella morganii	–	–	–	2	–
Bordetella pertussis	–	–	–	–	1
Stenotrophomonas maltophilia	–	–	–	–	1
Gram-positives ($N = 25$)					
Staphylococcus aureus (MRSA)	6 (1)	1 (1)	2 (0)	4 (1)	–
Enterococcus faecium	3	–	1	–	–
Enterococcus faecalis	1	–	1	–	–
CoNS	4	–	–	–	–
Leuconostoc spp.	–	1	–	–	–
Streptococcus agalactiae	1	–	–	–	–
Fungi ($N = 18$)					
Candida albicans	3	1	6	–	–
Candida glabrata (azole-resistant)	–	2 (2)	1	–	–
Candida parapsilosis	2	1	–	–	–
Candida lusitaniae	–	–	2	–	–
Viruses ($N = 93$)					
Respiratory syncytial virus					38
Adenovirus					25
Parainfluenza virus					14
Influenza					5
Corona virus OC43					4
Human metapneumovirus					4
Rhinovirus					2
Bocavirus					1
No pathogen isolated	–	–	–	3 (14%)	69 (37%)
No specimen sent	–	–	–	2 (10%)	34 (18%)

LCBSI, laboratory-confirmed bloodstream infection; CLABSI, central line-associated bloodstream infection; UTI, urinary tract infection; SSI, surgical site infection; HAP, hospital-acquired pneumonia; ESBL, extended-spectrum β-lactamase producer; IBL, inducible β-lactamase producer; MDR, multidrug-resistant; MRSA, meticillin-resistant *S. aureus*; CoNS, coagulase-negative staphylococci.

[a] One patient had polymicrobial infection, hence eight pathogen isolates for seven CLABSI episodes.

[b] Specimens included nasopharyngeal, tracheal and bronchoalveolar lavage specimens submitted for microscopy, culture and sensitivity testing and respiratory viral pathogen polymerase chain reaction testing (19 HAP events had more than one pathogen isolated). Bacterial pathogens' resistance profiles were classified using proposed standard definitions.[25]

events despite a high rate of surgical interventions; this finding may partly be explained by demographic and risk factor differences in our surgical vs medical admissions. We also documented very few HA gastroenteritis events, possibly owing to the study period (May to October are low prevalence months for rotaviral disease in South Africa). Conversely, HAP events may have been over-represented in this cohort as the study months included our region's winter season with peak hospitalizations for community-acquired respiratory tract infections.[30]

Risk factors for HCAI in our cohort included some factors reported from other LMIC, including malnutrition, presence of indwelling devices, underlying comorbidities, McCabe score (fatal disease), and PICU admission. HIV infection and HIV exposure are novel risk factors for paediatric HCAI in this cohort (although we have previously documented HIV as an independent predictor of antimicrobial-resistant HABSI and death from HABSI in hospitalized children).[20] Although malnutrition, underlying comorbidities, PICU admission, and HIV disease/exposure are not modifiable risk factors, they are useful to identify children at highest risk of HCAI. Similarly, the significant univariate association of HCAI with total parenteral nutrition and independent association with blood transfusion and indwelling devices provide motivation to retrain staff on intravascular device insertion/maintenance and to encourage timely removal of such devices.

In keeping with previous South African studies, *K. pneumoniae* and *S. aureus* were our most frequently isolated HCAI pathogens with high prevalence of antimicrobial-resistant

phenotypes.[9,10] Viral pathogens were identified in more than half of all patients with HAP who underwent laboratory testing, highlighting the importance of laboratory identification of pathogens in children with RTI (who serve as reservoirs of nosocomial virus transmission). In 20% of HAP events, no respiratory pathogen testing was performed, representing missed opportunities for identification and isolation of patients with transmissible pathogens.

The impact of HCAI events was significant, with excess crude mortality, requirement for ICU admission, additional procedures, extended hospitalization, excess antimicrobial and laboratory test usage. In keeping with US HCAI cost analysis data, BSI events (and in this cohort HAP events) were the major drivers of direct costs, with SSI and UTI important but smaller contributors to overall costs.[31] The finding of blood transfusion, PICU stay, and patient isolation as independent predictors of mortality probably reflects the consequences of the HCAI event rather than true risk factors for death.

Other consequences of extended hospital stay in our setting include overcrowding, inability to admit new patients (especially to our PICU) and a greater potential reservoir of patients with transmissible pathogens. This latter point is particularly problematic in resource-limited settings where isolation facilities are limited/non-existent and infection prevention precautions inconsistently applied. Crude mortality associated with HCAI events in our cohort was 7.4% (as compared to 3.3% from the 1987 study which preceded the South African HIV epidemic, 2.4% in Brazil, and 8% in Indonesia). Although our mortality rate is high, paediatric HCAI mortality is likely even higher in facilities lacking ICU access, laboratory investigations and antimicrobials for MDR pathogens.

Concerns around generalizability of study findings may arise given the single centre, academic setting; however, our patient population is similar to those of other hospitals in our region (in terms of HIV prevalence, malnutrition, and admission diagnosis profile). Of note, our institution has arguably better infection prevention services/resources than most paediatric wards in the region and thus should have lower HCAI prevalence: an infection prevention nurse practitioner is dedicated to the obstetric/paediatric/neonatal platform (one nurse per 300 beds); we have the only paediatric airborne-isolation unit and many more single rooms than other paediatric inpatient facilities; and the infection prevention service is provided by one of only three academic units for infection prevention and control in the country. The true HCAI frequency may have been underestimated owing to a lack of prospective follow-up for HCAI events post discharge (only readmissions were included), lack of laboratory investigation of all HCAI events (specimens were sent at the attending clinician's discretion) and the low sensitivity of some laboratory investigations to detect HCAI, e.g. blood cultures, especially when antibiotic administration precedes specimen collection. The standard 48 h cut-off for separating community-acquired infections from HCAI may have resulted in some misclassification of pathogens. The calculation of excess healthcare costs arising from HCAI was not comprehensive and did not include costs related to patient isolation, additional staffing, consumables for transmission-based precautions, additional surgical/medical procedures and opportunity costs to children/parents from extended hospital stay. We were also unable to differentiate subcomponents of the direct costs (i.e. fixed vs variable costs) as only the total patient day cost was available.

Nevertheless, this is the first study (since 1987) to comprehensively document the substantial burden, risk factors for, impact and cost of HCAI in hospitalized South African children. It is also the first study to quantify the influence of HIV exposure and infection on risk of HCAI in children from an HIV-endemic setting. This study confirms that HCAI events are the leading contributors to inpatient mortality at our institution. Programmes to monitor and prevent HCAI should be prioritized as part of a comprehensive patient safety agenda for hospitalized children in LMIC.

In conclusion, hospitalization complicated by HCAI occurred frequently with significant morbidity, mortality, and healthcare costs (including additional bed-days, antimicrobial use, and laboratory investigations). The burden of paediatric HCAI in low-resource settings is underappreciated; HCAI surveillance and prevention programmes for African children are vital means to secure greater resources to tackle this problem as a public health priority.

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None declared.

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