Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Burden, spectrum, and impact of healthcare-associated infection at a South African children’s hospital

A. Dramowski a,*, A. Whitelaw b, M.F. Cotton a

a Department of Pediatrics and Child Health, Division of Pediatric Infectious Diseases, Stellenbosch University, Cape Town, South Africa
b Department of Medical Microbiology, Stellenbosch University and the National Health Laboratory Service (NHLS), Cape Town, South Africa

ARTICLE INFO

Article history:
Received 27 June 2016
Accepted 25 August 2016
Available online 1 September 2016

Keywords:
Paediatrics
Healthcare-associated infection
Infection prevention
Sub-Saharan Africa
Nosocomial infection
Antimicrobial resistance

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.

"© 2016 The Healthcare Infection Society. Published by Elsevier Ltd. All rights reserved.

* Corresponding author. Address: Department of Pediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, PO Box 241, Cape Town, 8000, South Africa. Tel.: +27 21 938 9506; fax: +27 21 938 9138.
E-mail address: dramowski@sun.ac.za (A. Dramowski).
Introduction

Healthcare-associated infection (HCAI) is the most frequent complication of hospitalization affecting 4–8% of paediatric admissions in high-income settings.\(^9,10\) 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 \textit{Staphylococcus aureus} and \textit{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.\(^13,14\) 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 \(\sim 17,000\) 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 \(\geq 48\) 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 \textit{Pseudomonas aeruginosa} is considered unlikely and meningitis is excluded. Vancomycin is added if meticillin-resistant \textit{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 \(\geq 48\) h or transferred in from another facility between May 1\textsuperscript{st}, 2014 to October 31\textsuperscript{st}, 2014 (A) and May 1\textsuperscript{st}, 2015 to October 31\textsuperscript{st}, 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 \(\geq 48\) h. Ethical approval and waiver of individual informed consent was obtained from the Human Health Research Ethics committee of Stellenbosch University (S13/09/171).
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

### 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     |                                                                             |                                                                   | <0.001  | 2.2                   | 1.6                     | 1.1–2.1 |
| McCabe scorea                 |                                                                             |                                                                   |         |                       |                         |       |
| 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 deviceb | 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
HCAIs were infections present on admission in a child with a history of hospitalization in the preceding 30 days. Pathogens from specimens obtained within 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. 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. 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. Surgical procedures were categorized using the CDC/NHSN criteria as: wound class (clean/clean contaminated vs contaminated/dirty); ASA score (1 to 5); emergency vs elective procedure and operation duration <60 min vs >60 min.

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.

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 123 (9%) were HIV-infected. Most were to the medical disciplines (981; 73%) with fewer transfers in: 28 (5%) from other wards at our institution; 121 (18%) from primary care facilities; 453 (36%) from secondary/district hospitals, and 25 (4%) from tertiary or private hospitals. Most transfers in: 28 (5%) from other wards at our institution; 121 (18%) 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%) orSSI 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%).
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 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 (the mean excess laboratory tests for admissions with HCAI × total admission episodes with HCAI).

### Table II

| Event type                        | No. | %   | 95% CI |
|-----------------------------------|-----|-----|--------|
| Hospital-acquired pneumonia       | 185 | 44  | 40–49  |
| ‘Presumed’ HA sepsis              | 63  | 15  | 12–19  |
| (Catheter-associated) UTI         | 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.

### Table III

| 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                           | No. | Total eligible | %   |
|--------------------------------------|-----|----------------|-----|
| New antimicrobial prescription       | 397 | 417            | 95  |
| ICU admission                        | 80  | 264            | 30  |
| Respiratory support (only patients from wards) | 56  | 417            | 13  |
| Inotropes                            | 28  | 417            | 7   |
| Surgical procedure(s)                | 16  | 417            | 4   |
| Device removal                       | 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 V

| 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   |
| Othersa                             | 326         | 14  |

a Ciprofloxacin, erythromycin, azithromycin, clarithromycin, clindamycin, metronidazole, gentamicin, ampicillin, cephalosporins.
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 (362/60,483), ‘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 resulted in death vs 12/1022 (1.2%) HCAI-unaffected episodes.

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 isolates, 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); \( E. \) cloacae (one); \( P. \) aeruginosa (one); \( A. \) baumannii (one); \( C. \) albicans (two), \( C. \) parapsilosis (one) and \( E. \) faecalis (one). By contrast, only one out of 12 children who died during HCAI-unaffected hospitalizations had a pathogen isolated (\( S. \) 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; 95% CI: 2.9–18.5), death being HAP-associated, and hospital stays exceeding 14 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%). Although similar to other LMICs, our HCAI prevalence was three- to six-fold greater than rates in high income settings. 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. 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 exceed 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).  

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 VI

| 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 | |

### Table VII

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

### Table VIII

| 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 \( \times \) number of HCAI events of that type, e.g., HAP - median 2 days excess stay \( \times \) 185 HAP events = 370 additional bed-days.
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

| Pathogen                          | LCBSI (N = 41) | CLABSIa (N = 7) | UTI (N = 45) | SSI (N = 21) | HAPb (N = 185) |
|----------------------------------|---------------|----------------|-------------|-------------|----------------|
| **Gram-negatives (N = 72)**      |               |                |             |             |                |
| Klebsiella pneumoniae (ESBL)     | 5 (5)         | 2 (2)          | 24 (22)     | 2 (0)       | 2 (2)          |
| Enterobacter cloacae             | 4             |                |             |             |                |
| Escherichia coli (ESBL)          | 5 (2)         |                |             |             |                |
| Acinetobacter spp. (MDR)         | 3 (1)         |                |             |             |                |
| Pseudomonas aeruginosa (MDR)     | 2 (0)         |                |             |             |                |
| Serratia marcescens              | 1             |                |             |             |                |
| Salmonella non-typhi             | 1             |                |             |             |                |
| Morganella morganii              |               |                |             |             |                |
| Bordetella pertussis             |               |                |             |             |                |
| Stenotrophomonas maltophilia     |               |                |             |             |                |
| **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               |               |                |             |             |                |
| **Viruses (N = 93)**             |               |                |             |             |                |
| Respiratory syncytial virus      |               |                |             |             |                |
| Adenovirus                       |               |                |             |             |                |
| Parainfluenza virus              |               |                |             |             |                |
| Influenza                        |               |                |             |             |                |
| Corona virus OC43                |               |                |             |             |                |
| Human metapneumovirus            |               |                |             |             |                |
| Rhinovirus                       |               |                |             |             |                |
| Bocavirus                        |               |                |             |             |                |
| No pathogen isolated             |               |                |             |             |                |
| No specimen sent                  |               |                |             |             |                |

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
phenotypes. 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, SSI 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. 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.

Acknowledgements

We thank T. Esterhuizen from the SU Biostatistics department, Unine Odendaal for assistance with two weeks of data collection, Dr A. Aiken (London School of Hygiene and Tropical Medicine), Professor S. Coffin (UPENN School of Medicine) and Professor E. Sinanovic (Health Economics Unit, UCT) for helpful advice in the study design/analysis and the staff, patients and parents of TCH.

Conflict of interest statement

None declared.

Funding sources

A.D. is supported by the South African Medical Research Council’s Clinician Researcher Programme and the Discovery Foundation’s Academic Fellowship Award.

References

1. Magill SS, Edwards JR, Bamberg W, et al. Emerging Infections Program Healthcare-Associated Infections and Antimicrobial Use Prevalence Survey Team. Multistate point-prevalence survey of health care-associated infections. N Engl J Med 2014;370:1198–1208.

2. European Centre for Disease Prevention and Control (ECDC). Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals. Stockholm: ECDC; 2013. Available at: https://epidemiol.wiv-isp.be/.../EU%20Point%20Prevalence%20Survey.pdf [last accessed May 2016].

3. Ciolfi Degli Atti ML, Cuttini M, Ravà L, et al. Trend of healthcare-associated infections in children: annual prevalence surveys in a research hospital in Italy, 2007–2010. J Hosp Infect 2012;80:6–12.

4. Deptała A, Trejnowska E, Ozorowski T, et al. Risk factors for healthcare-associated infection in light of two years of experience with the ECDC point prevalence survey of healthcare-associated infection and antimicrobial use in Poland. J Hosp Infect 2015;90:310–315.

5. Rutledge-Taylor K, Mathow A, Gravel D, et al. Canadian Nosocomial Infection Surveillance Program. A point prevalence survey of health care-associated infections in Canadian pediatric inpatients. Am J Infect Control 2012;40:491–496.

6. Bagheri Nejad S, Allegranzzi B, Syed SB, et al. Health-care-associated infection in Africa: a systematic review. Bull WHO 2011;89:757–765.

7. Rothe C, Schlaich C, Thompson S. Healthcare-associated infections in Sub-Saharan Africa. J Hosp Infect 2013;85:257–267.
8. Duse AG. Infection control in developing countries with particular emphasis on South Africa. *Southern Afr J Epidemiol Infect* 2005;20:37–41.

9. Cotton MF, Berkowitz FE, Berkowitz Z, et al. Nosocomial infections in black South African children. *Pediatr Infect Dis J* 1989;8:676–683.

10. Bowen-Jones J, Wesley A, van den Ende J. Nosocomial colonisation and infection in a pediatric respiratory intensive care unit. *S Afr Med J* 1992;82:309–313.

11. Duse AG. Surveillance of healthcare-associated infections (HAIs) South Africa. Available at: http://www.cdcdep.org/sites/default/files/prof_adriano_duse-2_0.pdf [last accessed May 2016].

12. Durlach R, McIlvenny G, Newcombe RG, et al. Prevalence survey of healthcare-associated infections in Argentina; comparison with England, Wales, Northern Ireland and South Africa. *J Hosp Infect* 2012;80:217–223.

13. Murni IK, Duke T, Kinney S, et al. Reducing hospital-acquired infections and improving the rational use of antibiotics in a developing country: an effectiveness study. *Arq Bras Pediatr* 2015;100:454–459.

14. Cavalcante SS, Mota E, Silva LR, et al. Risk factors for developing nosocomial infections among pediatric patients. *Pediatr Infect Dis J* 2006;25:438–445.

15. Zamudio-Lugo I, Espinosa-Vital GJ, Rodriguez-Sing R, et al. Nosocomial infections. Trends over a 12 year-period in a pediatric hospital. *Rev Med Inst Mex Seguro Soc* 2014;52(Suppl 2):S38–S42.

16. Greco D, Magombe I. Hospital acquired infections in a large north Ugandan hospital. *J Prev Med Hyg* 2011;52:55–58.

17. Aiken AM, Mturi N, Njuguna P, et al. Kilifi Bacteraemia Surveillance Group. Risk and causes of pediatric hospital-acquired bacteraemia in Kilifi District Hospital, Kenya: a prospective cohort study. *Lancet* 2011;378:2021–2027.

18. Rosenthal KD, Jarvis WR, Jamulitrat S, et al. International Nosocomial Infection Control Members. Socioeconomic impact on device-associated infections in pediatric intensive care units of 16 limited-resource countries. *Pediatr Crit Care Med* 2012;13:399–406.

19. Patrick SW, Kawai AT, Kleinman K, et al. Health care–associated infections among critically ill children in the US, 2007–2012. *Pediatrics* 2014;134:705–712.

20. Dramowski A, Cotton MF, Rabie H, et al. Trends in pediatric bloodstream infections at a South African referral hospital. *BMC Pediatr* 2015;15:33.

21. National Department of Health, South Africa (Pretoria). 2012: *National Antenatal Sentinel HIV & Syphilis Prevalence Survey*. Available at: http://www.health.gov.za/docs/reports/2013/report2014.pdf CDC/NHSN [last accessed May 2016].

22. National Healthcare Safety Network. Surveillance definition of healthcare-associated infection and criteria for specific types of infections in the acute care setting. January 2013 (v.17-1). Available at: https://www.cdcph.ca.gov/programs/hai/Documents/Slide-Set-20-Infection-Definitions-NHSN-2013.pdf [last accessed May 2016].

23. de Onis M, Habicht JP. Anthropometric reference data for international use: recommendations from a World Health Organization Expert Committee. *Am J Clin Nutr* 1996;64:650–658.

24. Centers for Disease Control and Prevention/National Healthcare Safety Network. *CDC/NHSN Bloodstream Infection Event (central line-associated bloodstream infection and non-central line-associated bloodstream infection)* 2015. Available at: www.cdc.gov/nhsn/PDFs/pscManual/4PSC_CLABScurrent.pdf and http://www.cdc.gov/nhsn/XLS/Common-Skin-Contaminant-List-June-2011.xlsx [last accessed May 2016].

25. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012;18:268–281.

26. Reilly JS, Coignard B, Price L, et al. The reliability of the McCabe score as a marker of co-morbidity in healthcare-associated infection point prevalence studies. *J Infect Prevent 2016;17:127–129.*

27. Simmons BP. Guideline for prevention of surgical wound infections. *Infect Control* 1982;3:185–196.

28. Schulgen G, Krepec A, Kappstein I, et al. Estimation of extra hospital stay attributable to nosocomial infections: heterogeneity and timing of events. *J Clin Epidemiol* 2000;53:409–417.

29. Ogwang M, Paramatti D, Molteni T, et al. Prevalence of hospital-associated infections can be decreased effectively in developing countries. *J Hosp Infect* 2013;84:138–142.

30. Dramowski A, Cotton MF, Whitelaw A. Utilization of paediatric isolation facilities in a TB-endemic setting. *Antimicrob Resist Infect Control* 2015;4:36.

31. Zimlichman E, Henderson D, Tamir O, et al. Health care–associated infections: a meta-analysis of costs and financial impact on the US health care system. *JAMA Intern Med* 2013;173:2039–2046.