

Determinants of healthcare-associated infection among hospitalized children

by

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Declaration

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own original work, that I am the authorship owner thereof (unless to the extent explicitly otherwise stated) and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

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Summary

Healthcare-associated infection (HAI) is the most frequent complication of hospitalization resulting in suffering, excess mortality and increased healthcare costs. Although paediatric HAI burden and impact is well-described in high-income countries, it is largely unquantified in Africa. Our research aimed to: (i) comprehensively describe the epidemiology and impact of HAI and HA-bloodstream infections in an African cohort of hospitalized children; (ii) establish appropriate HAI surveillance methods for our setting; (iii) investigate selected local determinants of paediatric HAI (including healthcare worker HAI-related knowledge, attitudes and practices, isolation facility utilization and terminal cleaning practices).

In a retrospective analysis of paediatric bloodstream infection trends at Tygerberg Hospital, we reported the highest estimate of HA-bloodstream infections rates among African children to date. HIV-infection, HA-bloodstream infection, fungal and Gram-negative pathogens were important predictors of bloodstream infection-associated mortality.

We conducted prospective clinical surveillance in paediatric wards and the intensive care unit at Tygerberg Children's Hospital. HAI incidence (31/1000 patient days) exceeded published rates in high and low-middle income countries, with highest infection density in the paediatric intensive care unit (94/1000 patient days). Children experiencing HAI events were young (median 8.4 months), more likely to be malnourished, HIV-exposed uninfected or HIV-infected and to have pre-existing co-morbidities. Hospital-acquired pneumonia, bloodstream and urinary tract infections predominated. The increased odds for HAI in HIV-exposed uninfected and HIV-infected children is a novel association. Two-thirds of in-patient mortality was associated with HAI and patients with any HAI event had a 6-fold increase in crude mortality. Patients experiencing HAI had 3-fold higher rates of re-hospitalization within 30 days. Direct costs of HAI were substantial; mean duration of hospitalization, bed availability, antimicrobial consumption and laboratory investigation usage were significantly impacted by HAI.

Although prospective clinical HAI surveillance is considered the reference standard, its use in Africa is limited by lack of resources and expertise. We compared the performance of three alternate HAI surveillance methods (point prevalence surveys [PPS], laboratory surveillance

and tracking of antimicrobial prescriptions) using the prospectively collected paediatric HAI dataset as the reference standard. Although repeated PPS, laboratory and antimicrobial prescription tracking were demonstrated to be feasible HAI surveillance methods, a combination of laboratory-antimicrobial surveillance achieved best sensitivity (85%) and positive predictive value (97%), and required fewer resources to perform. South African paediatric healthcare facilities should individualise HAI surveillance, selecting a method suited to available resources and practice context.

We identified a shortage of isolation facilities and sub-optimal identification of patients requiring isolation as potential contributors to infection transmission. The need for negative-pressure ventilation and airborne isolation facilities on children's wards in TB-endemic settings was also highlighted. For terminal cleaning of paediatric isolation rooms we investigated three evaluation methods; fluorescent markers emerged as most cost-effective and feasible for our resource-limited setting. Finally, we surveyed two-thirds of our paediatric department's staff regarding their knowledge, attitudes and practices related to HAI, identifying several knowledge gaps and opportunities for improved infection prevention practice.

Owing to the extreme paucity of data, paediatric HAI in Africa remains an underappreciated and underfunded public health problem. We believe that this doctoral research dissertation provides unequivocal justification for greater resource allocation to HAI surveillance and prevention programmes for hospitalized African children.

Opsomming

Gesondheidsorgverwante infeksie (GVI) is die mees algemene komplikasie van hospitalisasie en kan lyding, sterftes en verhoogde gesondheidsorgkoste tot gevolg hê. Alhoewel die omvang en impak van pediatriese GVI omvattend in hoë-inkomste lande beskryf is, is die voorkoms van GVI in Afrika grootliks onbekend. Ons navorsingsdoelwitte het die volgende ingesluit: (i) om volledig die epidemiologie en impak van GVI en gesondheidsorgverwante (GV)-bloedstroominfeksies in 'n groep gehospitaliseerde Afrika-kindere te beskryf; (ii) om toepaslike GVI-waarnemingstoetsmetodes vir ons omgewing te identifiseer; en (iii) om plaaslike oorsake van pediatriese GVI te ondersoek (insluitend gesondheidswerkers se GVI-verwante kennis, houdings en praktyke, en benutting van isolasiefasiliteite en terminale skoonmaakpraktyke).

In 'n retrospektiewe ontleding van tendense in pediatriese bloedstroominfeksies by Tygerberg Kinderhospitaal het ons die hoogste beraming tot op hede van GV-bloedstroominfeksiëkoerse onder Afrika-kindere gedokumenteer. Die teenwoordigheid van MIV-infeksie, GV-bloedstroominfeksies, swamme en Gram-negatiewe organismes het 'n belangrike voorspellingswaarde gehad tot sterftes verwant aan bloedstroominfeksies.

Ons het prospektiewe kliniese waarneming vir GVI in die pediatriese sale en intensiewesorgeenheid van Tygerberg Kinderhospitaal gedoen. Die GVI-koers (31/1000 pasiëntdae) was hoër as dié van gepubliseerde GVI-koerse in hoë en lae-middel-inkomstelende, met die hoogste infeksiedigtheid in die intensiewesorgeenheid (94/1000 pasiëntdae). Kindere met GVI-episodes was jonk (mediaan van 8.4 maande), meer geneig tot wanvoeding, MIV-blootgestel (geïnfekteerd en nie-geïnfekteerd) en het meer onderliggende siektetoestande gehad. Hospitaalverworwe longontsteking, bloedstroom- en urienweginfeksies was die mees algemene GVI's wat voorgekom het. Die verwantskap tussen 'n verhoogde kans op GVI en MIV-blootgestelde, ongeïnfekteerde en MIV-geïnfekteerde kindere is 'n nuwe bevinding. Tweederdes van binne-pasiëntsterftes het verband gehou met GVI en daar was 'n sesvoudige toename in die onverwerkte sterftesyfer van pasiënte met 'n GVI-episode. Pasiënte met GVI het 'n drievoudige hoër risiko vir hertoelating binne 30 dae tot die hospitaal gehad. Die direkte koste verbonde aan 'n GVI was aansienlik; GVI het die gemiddelde duur van hospitalisasie, beskikbaarheid van beddens, verbruik van antimikrobiese middels en laboratoriumondersoeke aansienlik beïnvloed.

Hoewel prospektiewe kliniese GVI-waarneming as die standaardmetode van waarneming beskou word, word die gebruik daarvan in Afrika beperk deur 'n tekort aan hulpbronne en kundigheid. Ons het die resultate van drie verskillende GVI-waarnemingsmetodes (tydstipvoorkomsstudies, laboratorium-gebaseerde GVI-waarneming en die monitering van uitgereikte antibiotika-voorskrifte) teen data opgeweeg wat deur middel van die standaardmetode van prospektief-ingesamelde pediatriese GVI-waarneming ingesamel is. Alhoewel herhaalde tydstipvoorkomsstudies, laboratorium-gebaseerde waarneming en die monitering van uitgereikte antibiotika-voorskrifte almal haalbare GVI-waarnemingsmetodes was, het 'n kombinasie van laboratorium-gebaseerde waarneming en monitering van uitgereikte antibiotika-voorskrifte die hoogste sensitiwiteit (85%) en positiewe voorspellingswaarde (97%) gehad. Minder hulpbronne was ook nodig met die kombinasie van hierdie twee GVI-waarnemingsmetodes. Suid-Afrikaanse pediatriese gesondheidsorg-fasiliteite moet GVI-waarneming individualiseer en aanpas na gelang van beskikbare hulpbronne en die konteks waarbinne gesondheidsorg verleen word.

Ons het 'n tekort aan isolasiefasiliteite, asook die gebrek aan identifisering van pasiënte wat isolasie benodig, geïdentifiseer as moontlike faktore wat kon bydra tot die verspreiding van infeksies. Daar is ook klem gelê op die behoefte aan negatiewe druk ventilasie vir die voorkoming van lugoordraagbare infeksies in kindersale waar tuberkulose endemies is. Ons het drie tegnieke ondersoek vir die evaluering van terminale skoonmaak van pediatriese isolasiekamers; fluoressentmerkers was die koste-effektiefste en ook die mees haalbare metode vir ons omgewing met beperkte hulpbronne. Ten slotte het ons twee derdes van ons pediatriese departement se personeellede oor hulle kennis, houdings en praktyke met betrekking tot GVI uitgevra. In die proses het ons verskeie areas geïdentifiseer waar kennis tekort skiet, asook areas waar infeksievoorkomingspraktyke verbeter kan word.

As gevolg van 'n groot leemte in pediatriese GVI data in Afrika, bly dit 'n openbare gesondheidsprobleem wat onvoldoende aandag en beperkte befondsing ontvang. Ons glo dat hierdie doktorale navorsing onomwonde bewys hoekom meer fondse bewillig moet word vir GVI-waarneming en voorkomingsprogramme vir gehospitaliseerde kinders in Afrikalande.

Dedication

I dedicate this work to my sons, Matthew Roy and Jake Josef Weeks.

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Chapter 1

Introduction

Healthcare-associated infection at Tygerberg Children's Hospital: a clinical vignette

A previously well and thriving, HIV-negative 16-month old female child presented to a district hospital with a short history of breathlessness and fever. She was diagnosed with community-acquired pneumonia and given supplemental oxygen and intravenous ampicillin for seven days. Following clinical deterioration with respiratory failure at the district hospital, she was intubated and transferred to Tygerberg Children's Hospital (TCH) paediatric intensive care unit (PICU) for ventilation.

*On arrival she had cardiac failure, attributed to a dilated cardiomyopathy (diagnosed by echocardiogram) with bronchopneumonic changes on chest radiograph. Her PICU management included diuresis, inotropic support (via a subclavian central venous catheter [CVC]), blood transfusion, intermittent positive pressure ventilation and intravenous cefotaxime. Despite improvement in her cardiopulmonary status, she developed low-grade fever, increased white cell count and raised C-reactive protein levels on Day five in PICU. Meropenem and vancomycin were empirically commenced for suspected nosocomial sepsis. Paired blood cultures from the CVC and a peripheral blood draw cultured *Candida albicans* and *Klebsiella pneumoniae* (an extended spectrum β -lactamase producing strain). The CVC was removed and targeted antimicrobial therapy was initiated with intravenous fluconazole for 14 days and meropenem for seven days. A nasopharyngeal aspirate had tested positive for respiratory syncytial virus B (on admission tracheal aspirate specimens for respiratory viruses were negative by polymerase chain reaction [PCR]). Her condition improved steadily and she was weaned from mechanical ventilation to nasal continuous positive airways pressure (nCPAP) for a further six days in the high care unit.*

On Day 16 of admission she again deteriorated, exhibiting high-grade fever, dyspnoea and increasing oxygen requirement. She was restarted on nCPAP, recultured and commenced empirically on ertapenem for suspected hospital-acquired pneumonia. Chest radiograph confirmed new pulmonary infiltrates bilaterally and three nasopharyngeal swab specimens

*revealed adenovirus on PCR testing. Despite initial improvement, she became increasingly unstable, requiring inotropic support and ventilation. A peripheral blood culture submitted shortly before her demise (on Day 27 of admission) isolated *Serratia marcescens*.*

Healthcare-associated infection in children

Healthcare-associated infections (HAI) cause suffering, excess mortality and increased healthcare costs.¹⁻³ HAI may occur during hospitalization (>48 hours after admission) or develop after hospital discharge. The spectrum of HAI is broad including bloodstream, surgical site, respiratory tract and device-associated infections, among others.⁴ Although paediatric HAI burden and impact is well-described in high-income countries⁵⁻⁸, HAI among hospitalized African children remain largely unquantified.

Prospective clinical surveillance for HAI is seldom undertaken in Africa owing to an absence of national surveillance programmes, lack of healthcare epidemiology expertise and competing health priorities.^{9,10} In a meta-analysis of HAI burden in developing countries, the World Health Organisation (WHO) could only identify three studies of paediatric HAI published from Africa between 1995 and 2008 (none were from South Africa).⁹ Many studies were of low-quality, reporting retrospective, laboratory-based or point prevalence data only.⁹ In addition, HAI studies from low-middle income countries (LMIC) often focus mostly on intensive care (ICU)¹¹⁻¹⁵ and neonatal¹⁶⁻¹⁹ settings with limited descriptions of paediatric HAI.²⁰⁻²³ Furthermore, important risk factors for paediatric HAI transmission in Africa such as the impact of endemic HIV/TB and limited isolation facilities, are unexplored.¹⁰ Even in the comparatively well-resourced South African context, paediatric HAI surveillance data was last published two decades ago.²⁴ Epidemiological data on antimicrobial resistance patterns in South Africa is somewhat better described^{25,26} but local HAI data to inform antimicrobial regimens is limited. A further limitation of these laboratory datasets is that they represent pooled community- and hospital-acquired isolates and combined neonatal, paediatric and adult data.

Research outline

The central theme of this dissertation is the “*Determinants of HAI in hospitalized South African children.*” We aimed to: (i) comprehensively describe the burden, spectrum and impact of paediatric HAI and HA-bloodstream infection at Tygerberg Children’s Hospital; (ii) determine suitable HAI surveillance methods for South African paediatric wards and (iii) investigate selected local determinants of paediatric HAI (including healthcare worker HAI-related knowledge, attitudes and practices, isolation facility utilization and terminal cleaning practices). Six hypotheses and their related publications comprise this dissertation.

Burden, spectrum, risk factors for and impact of paediatric HAI (Chapter 2)

The most recent South African study to report prospective, “whole-house” surveillance of paediatric HAI was published from the country’s largest hospital, Chris Hani Baragwanath hospital in Soweto in 1987 (prior to the onset of the HIV epidemic). Cotton et al documented HAI prevalence of 14.3% with a predominance of HA-respiratory tract infections and gastroenteritis.²⁴ A paediatric intensive care unit (PICU) at King Edward Hospital in Durban determined HAI prevalence rates of 43%¹²; both studies identified *S. aureus* and *K. pneumoniae* as the predominant nosocomial pathogens. In 2005, a one-day HAI point prevalence study (PPS) of 2652 adult and paediatric patients at 6 hospitals established a prevalence of 9.7% for four HAI types: bloodstream (BSI), urinary tract (UTI), respiratory tract (RTI) and surgical site (SSI) infection. HAI prevalence among children was 16.5%, with paediatric patients experiencing higher rates of BSI and RTI.^{27,28}

In comparison, data from the WHO meta-analysis of HAI in LMIC showed pooled paediatric HAI incidence of 5.7% (95% CI 2.3 - 13.1) in South America.⁹ Recent point prevalence studies of paediatric HAI have produced burden estimates of 3-4% from high income settings.^{5,6} The profile of HAI in hospitalized children differs from that of adult populations, with a relative predominance of bloodstream infections (BSI) and hospital-acquired pneumonia (HAP). Although a wealth of published data exists for community-acquired bloodstream infections, data on nosocomial BSI in African children is scarce.⁹ Recent data on hospital-acquired bacteraemia rates in Kenya report a rate of 1.0 BSI per

1000 patient days²⁹; 7.0 BSI per 1000 patient days have been reported from a Tunisian paediatric intensive care unit.³⁰

Studies reporting risk factors for paediatric HAI in LMIC are also limited.^{21,23,29} Although some risk factors for HAI are common to children globally e.g. prematurity, prolonged hospitalization, presence of indwelling devices and malnutrition, others of regional relevance are unexplored e.g. HIV status. From the limited, and dated pool of South African paediatric HAI literature, severe malnutrition, prolonged hospitalization and black ethnicity were significant risk factors for all HAI types and thrombophlebitis was a risk factor for nosocomial bacteraemia.^{12,24}

Although most LMIC paediatric HAI studies report prolonged hospitalization and increased mortality, estimations of HAI-associated cost to the health system are rare. Detailed information on the burden, impact and economic consequences of HAI are needed to raise awareness and motivate for funding of HAI surveillance and prevention programmes in LMIC. Therefore, we proposed two hypotheses for HAI characterization at Tygerberg Children's Hospital (TCH):

Hypothesis 1. The burden of HAI among hospitalized children at TCH exceeds that of high-income countries;

Hypothesis 2. HA-BSI rates at TCH exceed those of high-income countries.

Surveillance methods for paediatric HAI (Chapter 3)

HAI surveillance is a key component of effective infection prevention and control (IPC) programmes, facilitating evaluation of prevention efforts and allowing for comparison of HAI rates (benchmarking) at different healthcare facilities. Benchmarking is an increasingly used tool for evaluation of internal performance (comparing current and historic HAI rates at the same institution) and external performance (comparing local data to national or international rates). Benchmarking has several limitations though, mostly related to variance in surveillance definitions/methodologies used and heterogeneity in facility size, services and patient populations. One approach that adjusts for risk of confounding is use of a Standardized Infection Ratios (SIR) that compare the

total number of locally-reported HAI with a national benchmark based on previously reported data.

Despite ongoing advancement of HAI surveillance methods and reporting globally, few LMIC healthcare facilities have the resources to perform comprehensive HAI surveillance.³¹⁻³³ The paucity of data on incidence, spectrum and local determinants of HAI also impedes development of appropriate IP interventions. Given these constraints, many LMIC institutions perform continuous retrospective laboratory-based HAI surveillance, repeated HAI point prevalence studies (PPS) or limited prospective surveillance for device-associated HAI in ICU settings only.^{27,34,35}

The Tygerberg Hospital's Unit for Infection Prevention and Control (UIPC) conducts limited institution-wide HAI surveillance (including paediatric/neonatal wards) reporting quarterly rates of laboratory-confirmed BSI for six bacterial pathogens only: methicillin-resistant *S. aureus*; *P. aeruginosa*; *A. baumannii*; *S. marcescens*; *E. cloacae* and *Klebsiella* spp. Although data is reported by ward and department, there is no distinction between community-acquired, healthcare-associated and hospital-acquired pathogens in the aggregated dataset and infection rate. There is no clinical or prospective HAI surveillance programme and no implementation of care bundles to prevent device-associated infections in the PICU (although implementation of a ventilator-associated pneumonia [VAP] bundle is in progress). The true burden and spectrum of paediatric HAI (particularly that from viral pathogens) is thus likely to be grossly underestimated. In addition, antimicrobial usage for HAI and pooled data on resistance phenotypes of nosocomial pathogens are not routinely measured or reported. Therefore we developed 2 hypotheses and devised a study to determine which HAI surveillance method would be suitable for future implementation on the paediatric wards and PICU at TCH:

Hypothesis 3a. Clinical HAI surveillance at TCH will result in a doubling of paediatric HAI prevalence compared with current laboratory surveillance;

Hypothesis 3b. Repeated point prevalence studies (PPS) and/or monitoring of antimicrobial prescriptions and/or expanded laboratory surveillance for HAI are viable alternatives to prospective, continuous clinical HAI surveillance.

Paediatric isolation facilities: utilization and terminal cleaning (Chapter 4)

Patient isolation or cohorting is a commonly used strategy for limiting transmission of (usually antimicrobial resistant) infections in hospital.³⁶ Paediatric wards in many high-income settings have multiple single-bedded rooms to reduce potential for cross-contamination through shared equipment and staff contact. In addition, most United States children's hospitals provide for airborne isolation, with a median of four negative pressure ventilation rooms in each paediatric emergency department.³⁷ Most LMIC paediatric wards have multi-bedded, cohort nursing areas but lack isolation rooms.^{10,31} Although TCH has some provision for paediatric isolation (including a 6-bed airborne isolation unit built in 2013), the current number of single beds is insufficient for the large burden of community-acquired and HA-infections encountered. We postulate that transmission of HAI may be exacerbated by the shortage of isolation facilities and preponderance of infectious diseases in LMIC settings. There is however no reported literature from African settings regarding utilization of paediatric isolation facilities.

Hypothesis 4. TCH has insufficient provision and/or inappropriate utilization of paediatric isolation facilities.

The risk of pathogen transmission following ineffective environmental cleaning of isolation facilities is well-recognized.³⁸⁻⁴² Many studies demonstrate that improved environmental cleaning can reduce transmission risk or curb hospital outbreaks.^{40,43,44} Several methods for assessing efficacy of environmental cleaning have been evaluated including quantitative microbiological cultures, fluorescent markers and ATP bioluminescence. These techniques are useful not only to evaluate cleaning adequacy, but also as a means to provide training and ongoing feedback to cleaning personnel.⁴⁵⁻⁴⁸ Adequacy of environmental cleaning of paediatric isolation rooms and its potential role in HAI transmission at TCH has not been previously evaluated.

Hypothesis 5. Inadequate cleaning of paediatric isolation facilities may contribute to HAI transmission at TCH.

Knowledge, attitudes and practices regarding HAI (Chapter 5)

Several studies have documented infection prevention-related knowledge among LMIC healthcare providers demonstrating deficits or misconceptions of standard precautions,

personal protective equipment use and hand hygiene methods.⁴⁹⁻⁵² There are fewer data describing healthcare providers' knowledge, attitudes and reported IPC practices (KAP) regarding HAI^{53,54}, although several surveys of medical students have been conducted.⁵⁵⁻⁵⁷ A single study of African paediatric healthcare providers' HAI-related KAP was identified from an Egyptian PICU.⁵⁸ Robust data on the knowledge, attitudes and practices of TCH paediatric staff regarding HAI will inform development of targeted IPC training interventions.

Hypothesis 6. Paediatric healthcare providers at TCH underestimate HAI burden and may demonstrate attitudes and clinical practices which influence HAI development.

Chapter 2

Burden and impact of paediatric healthcare-associated infection

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Healthcare-associated infection (HAI) complicates between 4-8% of paediatric hospitalization episodes in high-income countries.^{5,6,59-61} Ironically, very little is known about the frequency, spectrum and impact of paediatric HAI in low-resource, high infectious disease burden settings. A systematic review of HAI data from low-middle income countries (LMIC) identified no studies reporting paediatric HAI data from Sub-Saharan Africa between 1995 and 2008.⁹

Given the extreme paucity of information on paediatric HAI epidemiology in Africa, we conducted prospective clinical HAI surveillance at Tygerberg Children's Hospital using 2013 Centers for Disease Control criteria. We documented extremely high HAI incidence rates (with a quadrupling of infection rates in the paediatric intensive care unit [PICU]). Predominant infection types were hospital-acquired pneumonia, bloodstream and urinary tract infections, although device-associated infections were an important contributor to HAI in the PICU. A novel finding of this study was the increased risk of developing HAI among HIV-exposed and HIV-infected children (a previously undescribed risk factor for HAI of relevance in Sub-Saharan Africa). Two-thirds of all in-patient mortality occurred in association with HAI; patients with any HAI event had a 6-fold increase in crude mortality rate. Patients experiencing HAI also had 3-fold higher rates of hospital readmission within 30 days. We provided the first economic evaluation of HAI-related costs at our institution, as well as the impact on hospital stay, antimicrobial and laboratory investigation use in paediatric wards.

This study highlights the substantial but underappreciated burden of HAI in hospitalized African children and provides strong motivation for the establishment of HAI surveillance and prevention programmes in Sub-Saharan Africa.



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 methicillin-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 1
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 $\times 1000$); (5) device use ratios (total device-days/total patient-days); (6) average device-days per

patient. HCAs 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 \times median excess length of stay for that HCAI type \times 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-affected 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 1). 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%)

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).

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 (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

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

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; $P < 0.001$).

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)					
<i>Klebsiella pneumoniae</i> (ESBL)	5 (5)	2 (2)	24 (22)	2 (0)	2 (2)
<i>Enterobacter cloacae</i>	4	—	—	1	—
<i>Escherichia coli</i> (ESBL)	5 (2)	—	7 (2)	4 (0)	—
<i>Acinetobacter</i> spp. (MDR)	3 (1)	—	—	—	—
<i>Pseudomonas aeruginosa</i> (MDR)	2 (0)	—	1 (1)	3 (1)	—
<i>Serratia marcescens</i>	1	—	—	—	1
<i>Salmonella</i> non-typhi	1	—	—	—	—
<i>Morganella morganii</i>	—	—	—	2	—
<i>Bordetella pertussis</i>	—	—	—	—	1
<i>Stenotrophomonas maltophilia</i>	—	—	—	—	1
Gram-positives (N = 25)					
<i>Staphylococcus aureus</i> (MRSA)	6 (1)	1 (1)	2 (0)	4 (1)	—
<i>Enterococcus faecium</i>	3	—	1	—	—
<i>Enterococcus faecalis</i>	1	—	1	—	—
CoNS	4	—	—	—	—
<i>Leuconostoc</i> spp.	—	1	—	—	—
<i>Streptococcus agalactiae</i>	1	—	—	—	—
Fungi (N = 18)					
<i>Candida albicans</i>	3	1	6	—	—
<i>Candida glabrata</i> (azole-resistant)	—	2 (2)	1	—	—
<i>Candida parapsilosis</i>	2	1	—	—	—
<i>Candida lusitanae</i>	—	—	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, methicillin-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 HABS and death from HABS 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 sub-components 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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Conflict of interest statement

None declared.

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Dramowski A, Cotton MF, Rabie H, Whitelaw A. Trends in paediatric bloodstream infections at a South African referral hospital. BMC Pediatr. 2015(2);15:33.

Bloodstream infections (BSI) are a leading contributor to the spectrum of paediatric HAI, in contrast to adult populations where surgical site infections predominate.^{2,5,6} Despite the major sequelae of these infections for both patients and the healthcare system, few African institutions have reported on the epidemiology of nosocomial BSI in children.^{29,30} Another major knowledge gap is the impact of expanded immunization programmes and the evolving HIV epidemic on nosocomial BSI epidemiology.

We retrospectively analyzed microbiology laboratory blood culture data from paediatric wards at Tygerberg Childrens' Hospital (2008-2013) to determine BSI rates (community- versus hospital-acquired) and trends in pathogen spectrum, antimicrobial resistance (AMR) and patient outcome. We demonstrated declining BSI rates and pathogen yield, but significant increases in blood culture contamination, suggesting a need for quality improvement in blood culture sampling practices. Nosocomial BSI was frequent (404 [47%] vs 460 [53%] episodes of community-acquired BSI) with an infection rate exceeding the only other published data on paediatric nosocomial BSI²⁹ from a low HIV-prevalence cohort (1.6 vs 1.0 episodes/1000 patient days). BSI-related mortality was high (20.4%), and associated with HIV-infection (OR 1.7), HA-BSI (OR 1.4), fungal (OR 2.1) and Gram-negative pathogens (OR 1.9).

Gram-negative BSI (primarily Enterobacteriaceae) predominated (60%), with significantly increased odds of exhibiting an AMR phenotype (OR 3.7). Among Gram-positive pathogens, *S. aureus* remained dominant, whereas *S. pneumoniae* BSI rates declined significantly. AMR rates were significantly higher among HA- vs community-acquired BSI isolates for *S. aureus* and *A. baumannii*, whereas extended spectrum β -lactamase (ESBL) carriage rates were similar among HA- and community-acquired *K. pneumoniae* and *E. coli* BSI isolates; there was no significant change in overall AMR prevalence during the study period. Analysis of HA-BSI antibiotic susceptibility demonstrated greatest in vitro coverage with a regimen including meropenem and amikacin.

This study provided the first detailed analysis of paediatric BSI epidemiology and trends at our institution, demonstrating the impact of improved vaccination coverage and ongoing advancement in HIV prevention and treatment programmes.

RESEARCH ARTICLE

Open Access

Trends in paediatric bloodstream infections at a South African referral hospital

Angela Dramowski^{1*}, Mark F Cotton¹, Helena Rabie¹ and Andrew Whitelaw²

Abstract

Background: The epidemiology of paediatric bloodstream infection (BSI) in Sub-Saharan Africa is poorly documented with limited data on hospital-acquired sepsis, impact of HIV infection, BSI trends and antimicrobial resistance.

Methods: We retrospectively reviewed paediatric BSI (0–14 years) at Tygerberg Children's Hospital between 1 January 2008 and 31 December 2013 (excluding neonatal wards). Laboratory and hospital data were used to determine BSI rates, blood culture contamination, pathogen profile, patient demographics, antimicrobial resistance and factors associated with mortality. Fluconazole resistant *Candida* species, methicillin-resistant *Staphylococcus aureus* (MRSA), multi-drug resistant *Acinetobacter baumannii* and extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* were classified as antimicrobial resistant pathogens.

Results: Of 17001 blood cultures over 6 years, 935 cultures isolated 979 pathogens (5.5% yield; 95% CI 5.3–5.7%). Contamination rates were high (6.6%, 95% CI 6.4–6.8%), increasing over time ($p = 0.003$). Discrete BSI episodes were identified ($n = 864$) with median patient age of 7.5 months, male predominance (57%) and 13% HIV prevalence. BSI rates declined significantly over time (4.6–3.1, overall rate 3.5 per 1000 patient days; 95% CI 3.3–3.7; Chi square for trend $p = 0.02$). Gram negative pathogens predominated (60% vs 33% Gram positives and 7% fungal); *Klebsiella pneumoniae* (154; 17%), *Staphylococcus aureus* (131; 14%) and *Escherichia coli* (97; 11%) were most prevalent. Crude BSI mortality was 20% (176/864); HIV infection, fungal, Gram negative and hospital-acquired sepsis were significantly associated with mortality on multivariate analysis. Hospital-acquired BSI was common (404/864; 47%). Overall antimicrobial resistance rates were high (70% in hospital vs 25% in community-acquired infections; $p < 0.0001$); hospital-acquired infection, infancy, HIV-infection and Gram negative sepsis were associated with resistance. *S. pneumoniae* BSI declined significantly over time (58/465 [12.5%] to 33/399 [8.3%]; $p = 0.04$).

Conclusion: Although BSI rates declined over time, children with BSI had high mortality and pathogens exhibited substantial antimicrobial resistance in both community and hospital-acquired infections. Blood culture sampling technique and local options for empiric antimicrobial therapy require re-evaluation.

Keywords: Bloodstream infection, Sepsis, Community-acquired infection, Hospital-acquired infection, Healthcare-associated infection, paediatrics, antimicrobial resistance, vaccination, HIV

Background

The epidemiology of paediatric bloodstream infection (BSI) in Africa is poorly documented. A meta-analysis of prospective studies of community-acquired BSI [1] identified 22 eligible studies (four in Southern Africa) [2–5], where non-typhoidal *Salmonella*, *E. coli*, *S. aureus* and *S. pneumoniae* infection predominated. Despite published

descriptions of community-acquired sepsis in African children [1–9] data on hospital-acquired BSI are extremely limited [10,11]. It is estimated that healthcare-associated BSI may be responsible for 25000 deaths in African children annually [12]. Overall, incidence rates of healthcare-associated infection in developing countries are thought to be at least double that of high-income settings [13]. Further research on the epidemiology of hospital-acquired BSI in African children is needed to quantify the burden and better understand contributory factors.

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Significant changes in BSI epidemiology among African children are expected, given increasing access to HIV prevention programmes, paediatric antiretroviral therapy and inclusion of pneumococcal conjugate vaccine (PCV) in the immunisation schedule [14,15]. In light of globally increasing antimicrobial resistance [12], regional antimicrobial resistance prevalence and the efficacy of empiric antibiotic therapy for paediatric BSI in Sub-Saharan Africa also require evaluation. Descriptions of increasing prevalence of *Enterobacteriaceae* BSI isolates producing extended-spectrum beta-lactamases (ESBL) are concerning given the limited availability of appropriate antibiotics in many African countries [16].

The difficulties in obtaining paediatric blood culture specimens and the increased yield with higher volume blood inoculum are well described [8]. Of concern in our region are two recent audits [17,18] reporting low pathogen yields and high blood culture contamination rates (exceeding accepted rates of < 3%) [19]. We examined trends in paediatric BSI epidemiology over six years at a single academic institution, determining rates of bacteraemia, blood culture yield and contamination, BSI-associated mortality and prevalence of antimicrobial resistance. We also investigated the association between bacteraemia, antimicrobial resistance and HIV infection.

Methods

Setting

We retrospectively reviewed paediatric BSI at Tygerberg Children's Hospital (TCH) in Cape Town, South Africa between 1 January 2008 and 31 December 2013 (excluding neonatal wards). The TCH admits sick infants and children (0–14 years) requiring general (70%) or specialised (30%) paediatric care (haematology/oncology, nephrology, gastroenterology, infectious diseases, cardiology, neurology, pulmonology, paediatric surgery, endocrinology) to one of six wards (153 beds; 85% occupancy rate in 2013). The 10-bedded medical/surgical paediatric intensive care unit (PICU) has an 89% occupancy rate (2013). Critically-ill children requiring ventilation or inotropic support are preferentially managed in the PICU but also on the wards when PICU is full.

The antenatal HIV prevalence in the Western Cape Province was 16.9% in 2012 (versus 29.5% nationally) [20]. Among children aged 2–14 years, HIV prevalence in the Western Cape Province was 0.7% in 2012 (versus 2.4% nationally) [21]. Antiretroviral therapy has been available since 2004, including prevention of mother-to-child HIV infection transmission, with transmission rates of 3.9% in 2010 [22]. HIV testing with informed consent is performed if the child's status is unknown, using an HIV PCR if < 18 months and HIV Elisa if > 18 months. If the HIV status is already known, no laboratory sample is submitted. Thus for this study only HIV tests taken at

the time of hospitalisation, or taken at prior hospital visits were accessible.

Immunisation coverage in the Cape Metropolitan area in 2011/12 was 87.5% among the population < 1 year of age (including BCG, polio, diphtheria/tetanus/pertussis, hepatitis B and measles vaccines; rotavirus was introduced in 2009) [23]. *Haemophilus influenzae* serotype B (Hib) conjugate vaccine was introduced in 1995 and PCV for *S. pneumoniae* in 2009 (7-valent) and 2011 (13-valent) [15].

Investigation and management of BSI

Blood cultures are obtained from all children with suspected sepsis or severe infection with a focal site (e.g. pneumonia, cellulitis). Empiric antibiotic therapy for community-acquired sepsis depends on the presumed site of infection, but usually includes either ceftriaxone or ampicillin and gentamicin. Empiric treatment of hospital-acquired infection usually includes meropenem, or ertapenem if *Pseudomonas aeruginosa* is considered unlikely and meningitis is excluded. Vancomycin is added if MRSA is considered a likely pathogen e.g. with suspected central line sepsis or soft tissue infection in hospital.

Blood culture sampling and analysis

A single blood culture sample (one bottle) is submitted from most patients, unless infective endocarditis is suspected. Local guidelines recommend inoculation of at least 2 mL of blood into paediatric blood culture bottles, however for older children, larger blood inoculums of 5 – 10 ml are encouraged. Blood cultures are taken at the discretion of attending clinicians and transferred to the on-site National Health Laboratory Service (NHLS) microbiology laboratory for processing in an automated system. Prior to April 2011 the Bactec system (Becton Dickinson, New Jersey, United States) was used; and thereafter the BacT/Alert system (BioMerieux, Marcy l'Etoile, France), in line with NHLS policy. For both systems, paediatric-specific culture bottles were used (Becton Dickinson BACTEC Peds Plus/F and thereafter BacT/ALERT® PF bottles). Both contain specialized media that accommodate small-volume samples (≤3 mL of blood) and resin for antibiotic neutralization. If bacterial growth is detected in the bottles, a Gram stain is performed, the sample sub-cultured onto appropriate media based on the Gram stain and incubated overnight. Further identification and antimicrobial susceptibility testing of clinically significant isolates is performed with the automated Vitek II system (BioMerieux, Marcy l'Etoile, France), using annually published Clinical and Laboratory Standards Institute (CLSI) breakpoints [24]. Pneumococcal isolates were considered non-susceptible to penicillin at minimum inhibitory concentrations (MICs) ≥0.12 mg/L using the meningitis breakpoints for parenteral penicillin [24].

Data analysis

All positive blood cultures from the paediatric wards over the six year study period were extracted from the computerised laboratory database; demographic data was obtained from the laboratory and hospital admissions database. BSI rates, blood culture contamination, pathogen profile, patient demographics and factors associated with antimicrobial resistance and BSI mortality were determined. Organisms were categorised using the United States Centers for Disease Control (US CDC) list of pathogens and contaminants; common commensals defined by the CDC include diphtheroids [*Corynebacterium* spp. not *C. diphtheriae*], *Bacillus* spp. [not *B. anthracis*], *Propionibacterium* spp., coagulase-negative staphylococci [including *S. epidermidis*], viridans group streptococci, *Aerococcus* spp., and *Micrococcus* spp [25]. Positive blood cultures obtained < 72 hours after admission were classified as community-acquired sepsis. Those obtained >72 hours after admission were considered hospital-acquired sepsis. All positive blood cultures isolating the same pathogen within 14 days were considered a single episode of BSI. Fluconazole resistant *Candida* species, methicillin-resistant *Staphylococcus aureus* (MRSA), multi-drug resistant *Acinetobacter baumannii* (resistant to at least 3 classes of antimicrobials) and extended spectrum B-lactamase (ESBL)-producing *Enterobacteriaceae* were classified as antimicrobial resistant pathogens using proposed standard definitions [26].

Statistical analysis

The BSI rate was calculated by dividing the total number of BSI episodes by the total inpatient days accumulated during the 6 year period. The pathogen and contamination rates were calculated by dividing the number of blood cultures yielding pathogens and contaminants respectively by the total number of blood culture requested. Continuous and categorical variables were compared using student t tests and Chi square analysis respectively. A Chi square test for linear trend was used to assess change in rates over the study period. To determine factors associated with mortality from BSI and antimicrobial resistance, binary logistic regression analyses were performed. A p-value below 0.05 was considered statistically significant. Stata Statistical Software version 13.0 IC (College Station, TX: StataCorp LP) was used.

Ethical approval

Ethical approval and waiver of individual informed consent was obtained from the Human Health Research Ethics committee of Stellenbosch University (S13/09/171).

Results

For 63209 children hospitalized over the study period, 17001 blood culture specimens were submitted; 1 blood

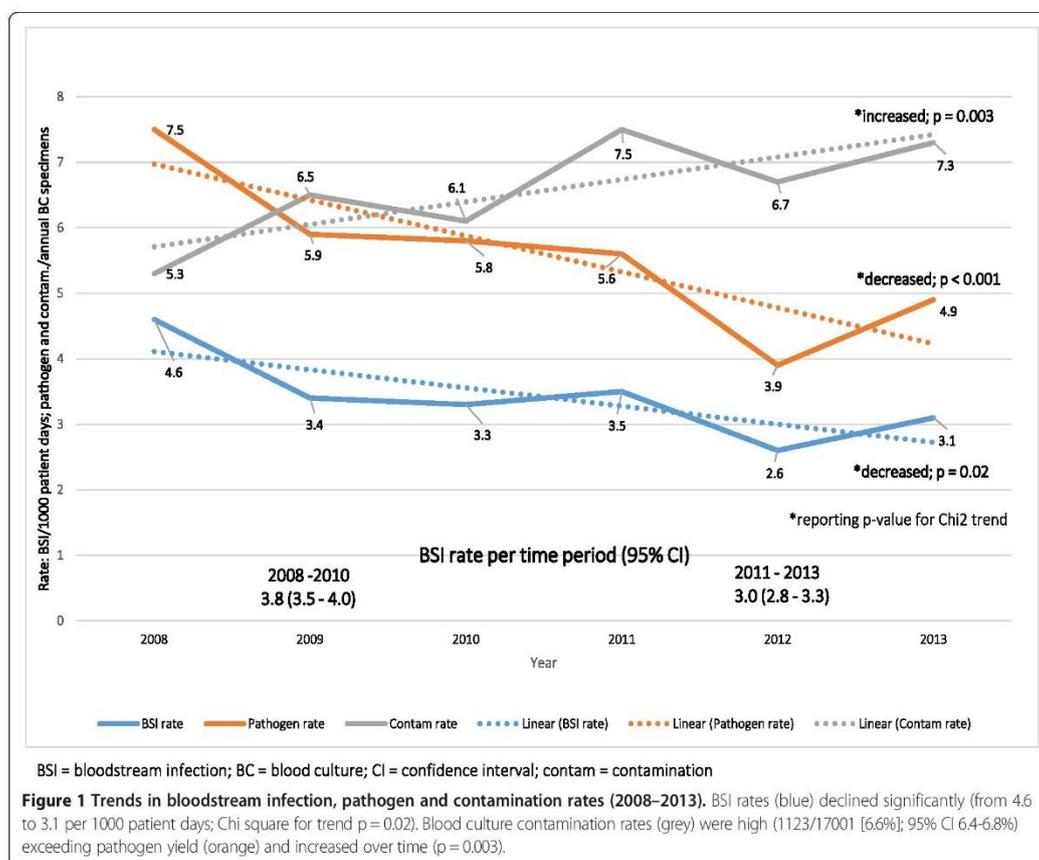
culture per 3.7 admissions or 68.6 specimens/1000 patient days. From 935 culture-positive specimens, 979 BSI pathogens were isolated (5.5% yield; 95% CI 5.3–5.7%). Blood culture contamination rates were high (1123 contaminated blood cultures from 17001 blood culture specimens submitted [6.6%]; 95% CI 6.4–6.8%), increasing over time ($p = 0.003$) (Figure 1). Coagulase-negative staphylococci (CoNS) were the most commonly isolated contaminant (650/1123; 57.9%), followed by non-pathogenic streptococci (75/1123; 6.7%), *Bacillus* species (74/1123; 6.6%), *Micrococcus* species (63/1123; 5.6%) and diphtheroids (61/1123; 5.4%).

Of 864 discrete BSI episodes, 818 (94.7%) were mono-microbial infections and 46 (5.3%) were polymicrobial (42 with 2 pathogens; 4 with 3 pathogens). The overall BSI rate was 3.5 per 1000 patient days (95% CI 3.3–3.7). A significant decline in the BSI rate from 4.6 in 2008 to 3.1 in 2013 (Chi square for trend $p = 0.02$; Figure 1) was noted despite substantial increases in hospitalizations (7537 to 11201 [49%]) and number of blood cultures (7816 vs 9185 [17%]) submitted between 2008 and 2013.

The median age of patients with BSI episodes was 7.5 months with male predominance (57.4%) and 13.4% HIV prevalence (however the test positivity rate was 20.6% [116/564], when children of unknown HIV [$n = 299$] status were excluded) (Table 1). Most patients (679; 78.6%) had blood cultures submitted from general paediatric wards i.e. were not yet in the PICU. Nearly half of all BSI episodes were hospital-acquired (404; 46.8%), with a median hospital stay of 17 days (IQR = 8 – 33.5 days) before onset of BSI. The overall rate of hospital-acquired BSI was 1.63 episodes per 1000 patient days (404/247969; 95% CI 1.49 – 1.78) and declined between 2008–2010 and 2011–2013 (from 1.79 to 1.49/1000 patient days; $p = 0.06$). The risk of developing hospital-acquired BSI during hospitalisation was 6.4 per 1000 admissions (95% CI 5.8 – 7.0).

Gram negative organisms predominated (60.2%) followed by Gram positives (32.4%) and fungi (7.4%). *Klebsiella pneumoniae* (154; 17%), *Staphylococcus aureus* (131; 14%) and *Escherichia coli* (97; 11%) were most prevalent (Table 2). The profile and proportional representation of pathogens varied markedly by location (ward vs PICU) and by place of onset. Gram positive pathogens were more prevalent in community-acquired isolates and Gram negative and fungal pathogens in hospital-acquired sepsis. The spectrum and ranking of BSI pathogens among children known to be HIV infected was similar to that of HIV uninfected patients, except for *S. pneumoniae* which was more common in HIV infected children (20/116 [17.2%] vs 30/448 [6.7%]; $p < 0.001$).

While *H. influenzae* BSI episodes increased between 2008–2010 and 2011–2013 (7/465 [1.5%] to 15/399 [3.8%]; $p = 0.05$), the proportion of *H. influenzae* serotype B isolates remained similar (3/7 [42.9%] vs 5/15



[33.3%]; $p=0.65$). However, *S. pneumoniae* BSI declined significantly (58/465 [12.5%] to 33/399 [8.3%]) ($p=0.04$). Pneumococci as a percentage of all Gram positive pathogens declined from a pre-vaccine high of 43.5% (27/62) in 2008 to 13.1% (8/61) in 2013 [$p<0.001$]. The proportion of pneumococcal BSI due to vaccine-serotypes (accounting for PCV7 and PCV13) did not decrease significantly over the two time periods, despite PCV-13 giving broader coverage (20/68 [29.4%] vs 6/23 [26%], $p=0.99$). The proportion of pneumococcal BSI exhibiting penicillin-resistance remained unchanged between 2008–2010 and 2011–2013, (18/58 [31%] vs 10/33 [30.3%]; $p=1.0$).

Overall crude BSI mortality was 20.4% (176/864); patients with hospital-acquired BSI experienced higher mortality than community-acquired BSI (25% [101/404] vs 16.3% [75/460]; $p=0.002$). The pathogen associated with the highest BSI mortality was *Acinetobacter* spp ($p=0.03$) at 38% (30/78), followed by *Candida* species (31%; 20/65) and *E. coli* BSI (24%; 23/97). HIV, fungi, Gram negative organisms and hospital-acquired sepsis were significantly associated with BSI mortality on multivariate analysis (Table 3).

Prevalence of antimicrobial resistance was assessed among a subset of pathogens, focussing on fluconazole resistant *Candida* species and four bacterial pathogens: MRSA, multi-drug resistant *Acinetobacter baumannii* and ESBL-producing *E. coli* and *K. pneumoniae* (Figure 2). No carbapenem resistant Enterobacteriaceae (CRE) or vancomycin resistant Enterococci (VRE) were isolated. For the four selected bacterial pathogens, antimicrobial resistance prevalence among community isolates was 25% compared with 70% among hospital-acquired isolates ($p<0.001$). For *A. baumannii* and MRSA, resistance rates were significantly higher among hospital-acquired isolates, whereas *E. coli* and *K. pneumoniae* isolates had similar prevalence of ESBLs among hospital- and community-acquired isolates. Among the 65 *Candida* species, all 21 *C. albicans* isolates were fluconazole susceptible, while 22 of the 44 (50%) non-*albicans* *Candida* species were fluconazole resistant. The prevalence of antimicrobial resistance did not differ significantly between 2008–2010 and 2011–2013 for the selected pathogens [Chi square for trend $p=0.24$ and $p=0.14$ respectively]. Factors associated with antimicrobial resistance on multivariate analysis included

Table 1 Demographic profile of paediatric patients with bloodstream infection

Variable	Number (n)	Percentage (%)	Age	Age	Age	p-value
			<1 yr (n; %)	1 - 5 yrs (n; %)	5 - 14 yrs (n; %)	
Laboratory confirmed-BSI episodes*	864	100%	506 (58.6)	206 (23.8)	152 (17.6)	-
Median age (months)	7.5	IQR 2.9-23.8	3.2	18.2	96	-
Male	496	57.4	298 (58.9)	111 (53.9)	89 (58.5)	0.41
HIV status						
- Positive	116	13.4	68 (13)	31 (15)	17 (11)	
- Negative	448	52	271 (54)	101 (49)	76 (50)	0.57
- Unknown	299	34.6	167 (33)	74 (36)	59 (39)	
Onset of BSI[#]						
- Community-acquired	460	53.2	244 (53)	133 (29)	83 (18)	<0.001
- Hospital-acquired	404	46.8	262 (65)	73 (18)	69 (17)	
Ward at BSI diagnosis						
- Intensive care	185	21.4	140 (28)	33 (16)	12 (8)	<0.001
- General ward	679	78.6	366 (72)	173 (84)	140 (92)	
BSI outcome						
- Died	176	20.4	109 (22)	45 (22)	22 (14)	0.13
- Survived	688	79.6	397 (78)	161 (78)	130 (86)	
Crude mortality rate by age	-	20.4	21.5	21.8	14.5	-

*BSI episodes: blood culture sampling episodes that yielded a pathogen, excluding blood cultures that isolated the same organism within 14 days of the original sampling episode; IQR = interquartile range; [#]CA-BSI = BC submitted within first 72 hours of admission; HA-BSI = BC submitted > 72 hours after admission. Continuous and categorical variables were compared using student t tests and Chi square analysis respectively; p < 0.05 was considered statistically significant.

hospital-acquired infection, infancy, HIV-infection and Gram negative sepsis (Table 4).

Susceptibility to different combinations of empiric antimicrobial therapy for hospital-acquired BSI was determined for all BSI isolates from 2012 and 2013 (Table 5). The combination of meropenem and amikacin was the most active against both ward and ICU BSI isolates, based on the *in-vitro* susceptibility test results (overall 82/133; 83.6% of isolates susceptible to one or both agents).

Discussion

In keeping with previous studies from Africa, gram negatives predominated in our study. *E. coli* and *Klebsiella* spp. were the most prevalent *Enterobacteriaceae*. Nontyphoidal salmonellae, a prominent BSI pathogen in malaria-endemic regions [27], was uncommon in our study. *S. pneumoniae* (the most common isolate in community-acquired BSI in African children [1]), was also prominent in our cohort. In addition, the profile of gram positive isolates changed significantly over time owing to reduced frequency of *S. pneumoniae* detection. The proportion of vaccine-serotype pneumococcal BSI isolates remained stable over time suggesting that the

dramatic decline in pneumococcal sepsis rates is not solely attributable to vaccine. However, a study of invasive pneumococcal disease in South Africa did demonstrate a substantial reduction of 89% in disease caused by PCV7 serotypes in children <2 years old [28]. Other factors such as increasing antiretroviral uptake and decreasing HIV prevalence probably contributed. Fungi (especially hospital-acquired) and gram negatives were significantly associated with BSI mortality, as in other African studies [6,10,11].

The burden of paediatric BSI was concentrated among infants (58.6% of the cohort). Young age was not associated with mortality from BSI but was significantly associated with antimicrobial resistant pathogens. Overall BSI mortality in our cohort (20.4%) was higher than that reported for high income settings (11 - 14%) [29,30], but lower than other African settings (27 - 38%) [6,10,11]. Access to intensive care was not reported for the other African BSI studies and likely contributed to the lower case fatality in our cohort, although PICU facilities at our institution are very limited (only 1 in 5 patients was admitted in PICU at BSI diagnosis).

As previously reported [10], HIV-infected children were at increased risk for BSI-associated mortality and

Table 2 Microbiological profile of paediatric bloodstream infection episodes (n = 864)

BSI episodes	n	%	Total pathogens isolated from 864 BSI episodes*		
Monomicrobial	818	94.7	914		
Polymicrobial					
- 2 pathogens	42	4.8			
- 3 pathogens	4	0.5			
Gram negatives	Organism	n = 550	% of Gram negatives	Organism rank*	
Enterobacteriaceae	<i>K. pneumoniae</i>	154	28%	1	
	<i>E. coli</i>	97	18%	3	
	<i>E. cloacae</i>	30	5%	7	
	<i>S. marcescens</i>	19	3%	10	
	<i>Salmonella</i> spp (non-typhi)	18	3%		
	<i>Klebsiella</i> spp	12	2%		
	Other (9 different genera)	30	5%		
	Total	360	65%		
	Non-fermenting Gram negative bacilli	<i>A. baumannii</i>	78	14%	5
		<i>P. aeruginosa</i>	20	4%	9
<i>Acinetobacter</i> spp		16	3%		
<i>S. paucimobilis</i>		9	2%		
Other (9 different genera)		20	4%		
Total		143	26%		
Other Gram negative organisms	<i>H. influenzae</i>	23	4%	8	
	<i>N. meningitidis</i>	11	2%		
	Other (6 different genera)	13	3%		
	Total	47	9%		
Gram positives	Organism	n = 296	% of Gram positives	Organism rank*	
Staphylococci	<i>Staphylococcus aureus</i>	131	44%	2	
Streptococci	<i>Streptococcus pneumoniae</i>	91	31%	4	
	Group B <i>Streptococcus</i>	19	6%	10	
Enterococci	<i>Enterococcus</i> spp	46	16%	6	
Other Gram positive organisms	Other (4 different genera)	9	3%		
Fungi	Organism	n = 68	% of Fungi	Organism rank*	
Candida spp	<i>Candida albicans</i>	21	31%	9	
	<i>Candida tropicalis</i>	12	18%		
	<i>Candida parapsilosis</i>	9	13%		
	<i>Candida glabrata</i>	3	4%		
	<i>Candida krusei</i>	2	3%		
	All other <i>Candida</i> spp	18	27%		
	Other fungi	<i>Aspergillus</i> spp,	1	4%	
<i>Trichosporon</i> spp,		1			
unidentified yeast		1			

Table 2 Microbiological profile of paediatric bloodstream infection episodes (n = 864) (Continued)

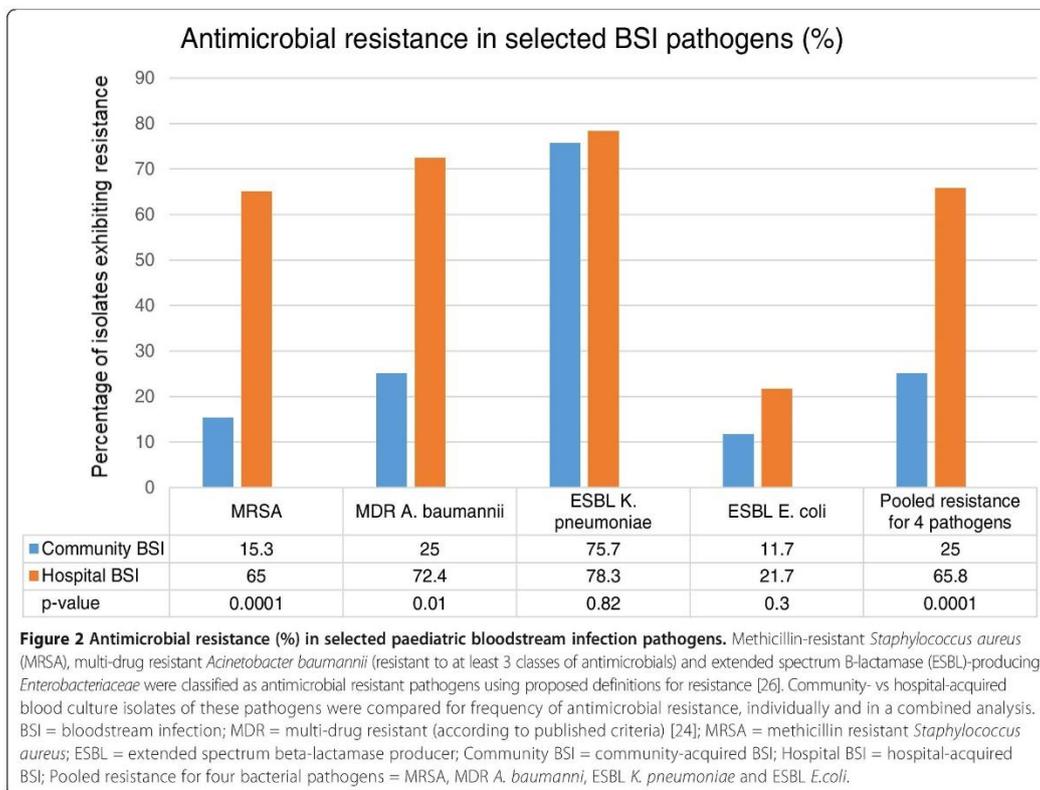
BSI pathogens (n = 914) by type and place of infection onset for 864 BSI episodes					
Community-acquired (CA-BSI) pathogens n = 477			Hospital-acquired (HA-BSI) pathogens n = 437		
CA-BSI ward pathogens [#]	n = 433	%	HA-BSI ward pathogens [#]	n = 275	%
- <i>Staphylococcus aureus</i>	90	21	- <i>Klebsiella pneumoniae</i>	86	31
- <i>Streptococcus pneumoniae</i>	81	19	- <i>Candida spp</i>	28	10
- <i>Escherichia coli</i>	67	15	- <i>Acinetobacter baumannii</i>	26	10
- Other	195	45	- Other	135	49
CA-BSI ICU pathogens [#]	n = 44	%	HA-BSI ICU pathogens [#]	n = 162	%
- <i>Escherichia coli</i>	9	21	- <i>Acinetobacter baumannii</i>	42	26
- <i>Klebsiella pneumoniae</i>	7	16	- <i>Klebsiella pneumoniae</i>	33	20
- <i>Staphylococcus aureus</i>	5	11	- <i>Candida spp</i>	22	14
- Other	23	52	- Other	65	40

*Total pathogens isolated from 864 BSI episodes = 914 pathogens (818 monomicrobial + polymicrobial 42 × 2 isolates + 4 × 3 isolates) [#]CA-BSI = BC submitted within first 72 hours of admission; HA-BSI = BC submitted > 72 hours after admission; ICU = intensive care unit; *Organism rank reported for the top ten isolates only.

Table 3 Bloodstream infection-associated mortality

BSI-associated mortality	Number (n)	Percentage (%)	p-value	
Total BSI-associated deaths	176	100	-	
Male	97	55.1	0.49	
Median age (months) IQR	7.2	IQR 3–14.7	-	
HIV status				
- Positive	34	19.3		
- Negative	87	49.4		0.03
- Unknown	55	31.3		
Onset of BSI[#]				
- Community-acquired	75/460	16.3		0.002
- Hospital-acquired	101/404	25		
Factors associated with mortality from BSI				
Variable assessed	Univariate analysis (p-value)	Multivariate analysis (p-value)	Odds ratio	95% CI
Length of stay prior to BSI onset	<0.001	0.11	-	-
Age category	0.13	0.44	-	-
Gender	0.49	0.32	-	-
HIV status (positive)	0.03	0.02	1.74	1.1 – 2.8
Year of BSI	0.89	0.78	-	-
Place of BSI onset (hospital-acquired)	0.002	0.04	1.43	1.1 – 2.0
Type of BSI pathogen	0.001	0.03		
- Fungal			2.10	1.1 – 4.2
- Gram negative			1.88	1.2 – 2.9
Mono- vs poly-microbial BSI	0.72	0.6	-	-
ICU vs general ward at BSI onset	<0.001	0.001	2.93	1.9 – 4.4
Antimicrobial resistance	0.06	0.83	-	-

BSI = bloodstream infection; ICU = intensive care unit; [#]CA-BSI = BC submitted within first 72 hours of admission; HA-BSI = BC submitted > 72 hours after admission. To determine factors associated with mortality from BSI and antimicrobial resistance, binary logistic regression analyses were performed. A p-value below 0.05 was considered statistically significant.



more likely to have antimicrobial resistant pathogens. Bacterial colonisation is a risk factor for later invasive infection with high rates of colonisation with antimicrobial resistant pathogens described among HIV-infected children in Cape Town [31]. It was not possible (given the study design) to compare the relative risk for BSI among HIV-infected versus HIV-uninfected children or the

effect of antiretroviral therapy. A prospective study is underway at our institution to determine the relative risk for hospital-acquired infection (including BSI) among HIV-infected children.

Hospital-acquired BSI was common (nearly half of all BSI episodes), more prevalent among infants and significantly associated with mortality. The profile of hospital-acquired

Table 4 Factors associated with antimicrobial resistance

Variable assessed	Univariate analysis (p-value)	Multivariate analysis (p-value)	Odds ratio	95% CI
Length of stay prior to BSI onset	<0.001	0.53	-	-
Age category (infants)	<0.001	0.003	1.92	1.2 – 3.1
Gender	0.8	0.92	-	-
HIV status (positive)	<0.001	<0.001	2.64	1.7 – 4.2
Year of BSI	0.4	0.19	-	-
Place of BSI onset (hospital-acquired)	<0.001	<0.001	3.68	2.7 – 5.1
Type of BSI pathogen				
- Gram negative	<0.001	<0.001	1.99	1.4 – 2.9
Mono- vs poly-microbial BSI	0.18	0.84	-	-
ICU vs general ward at BSI onset	<0.001	0.06	-	-

BSI = bloodstream infection; ICU = intensive care unit; Hospital-acquired BSI = BC submitted > 72 hours after admission. To determine factors associated with antimicrobial resistance, binary logistic regression analyses were performed. A p-value below 0.05 was considered statistically significant.

Table 5 Coverage achieved for hospital-acquired bloodstream infections with empiric antimicrobial regimens (2012–2013)*

Antibiotic susceptibility	OVERALL n = 159		WARD n = 92		PICU n = 67		Ward vs PICU	
	SUSCEPTIBLE							
	Number (n)	Percentage (%)	Number (n)	Percentage (%)	Number (n)	Percentage (%)		p-value
piperacillin tazobactam + amikacin	122	76.7	71	77.2	50	74.6	0.7	
ertapenem	110	69.1	71	77.2	40	59.7	0.02	
meropenem	112	70.4	70	76	42	62.7	0.08	
meropenem + amikacin	133	83.6	82	89.1	51	76	0.03	
meropenem + vancomycin	119	74.8	73	79.3	46	68.7	0.14	

PICU = paediatric intensive care unit; *only pathogens isolated in 2012 and 2013 were included in this analysis in order to determine recent antimicrobial resistance patterns.

pathogens was distinct from that of community-acquired BSI with *Klebsiella*, *Acinetobacter* and *Candida* species predominating. In keeping with the only prospective study of hospital-acquired bacteraemia in African children, *Acinetobacter* sepsis had the highest case fatality rates in our cohort. The rate of hospital-acquired BSI in our study exceeded the rate of nosocomial bacteraemia in rural Kenya (1.63 versus 1.0 episodes per 1000 patient days), however our cohort had a substantially higher HIV prevalence (13.4% vs 2%) [11]. Unsurprisingly, hospital isolates exhibited significantly greater antimicrobial resistance. Unlike the Tanzanian cohort [10], antimicrobial resistance was not associated with BSI mortality, possibly due to our use of carbapenems for empiric treatment of hospital-acquired sepsis.

A worrying observation is the high rate of antimicrobial resistance among community-acquired pathogens, especially *E.coli* and *Klebsiella* spp. Inappropriate empiric antimicrobial therapy (due to ESBL-producing and multi-resistant pathogens) predicted death in the Tanzanian cohort (OR 12.9) [10]. It is possible that pre-hospital antibiotic administration in our cohort may have falsely elevated antimicrobial resistance rates for community-acquired pathogens, by decreasing the frequency of isolation of susceptible pathogens. However our data are in keeping with pooled laboratory data (2010–2012) from public sector hospitals in South Africa demonstrating ESBL-carriage in 68% of 2774 *K. pneumoniae* BSI isolates [32]. Ongoing surveillance of antimicrobial resistance in community BSI (and monitoring of clinical outcomes among children given ineffective antibiotic therapy) is needed to determine if antibiotic guidelines need revision.

Among hospital-acquired BSI in the last two years of the study period, isolates exhibited highest susceptibility (83.6%) to meropenem plus amikacin, not currently our recommended empiric regimen. A prospective review, which includes clinical data on response to therapy is urgently needed to inform our guidelines for treatment of hospital-acquired sepsis. However, given the need for antimicrobial stewardship (and restriction of carbapenem use), it is also important to assess the efficacy of narrower-

spectrum regimens (such as piperacillin-tazobactam and amikacin).

Our review of temporal trends in paediatric BSI epidemiology identified targets for quality improvement. Although not unique to our setting, blood culture contamination rates were high (double the international norm [19]) and increased over time (exceeding the rate of pathogen isolation). The annual pathogen yield declined significantly over time and in 2013 (4.9%; 95% CI 3.9 – 5.2) was substantially lower than blood culture yields from a systematic review in Africa (8.2%; 95% CI 7.9 – 8.4) [1]. There are several explanations for these findings including poor aseptic technique during specimen collection with failure to isolate pathogens because of overgrowth by contaminants, low sensitivity of paediatric blood cultures and sub-optimal blood volumes from children [8]. Prior administration of antibiotics also contributes to low blood culture yield: local management guidelines [33] recommend that critically-ill children referred in from primary care receive a single dose of intramuscular ceftriaxone prior to transfer.

Between the two study time periods, BSI rates declined significantly despite a substantial increase in hospitalization (measured by increased inpatient days) and despite an increase in actual numbers of blood culture specimens submitted. We suspect that improvements in PMTCT programmes, paediatric antiretroviral coverage and PCV introduction between 2008 and 2013 are partly responsible. However, declining pathogen yields (as described above) may also have artificially reduced BSI rates.

This study has several limitations, most importantly the possibility that some healthcare-associated BSI (re-admission within 30 days of hospital discharge) may have been misclassified as community-acquired, owing to the retrospective study design. We chose 72 hours as a more conservative cut-off for hospital-acquired bacteraemia (many authorities use 48 hours) to avoid possibly including some community bacteraemias as hospital-acquired. The time of blood culture collection and the time of developing symptoms/signs of infection (as opposed to blood culture collection) were not routinely

available. The use of 72 hours as a cut-off, may have slightly underestimated the nosocomial bacteraemia rate. We were unable to evaluate the appropriateness of empiric therapy for community-acquired BSI, as the locally recommended treatment regimen depends on the child's clinical presentation. Lack of standardized patient selection or technique for blood culture, lack of comprehensive clinical data or information on recent antibiotic use and/or hospitalisation are also limitations. Many patients had unknown HIV status, but were likely tested at a different facility.

Although BSI rates declined over time, we could not determine which factors and practices contributed to this trend. In addition, the BSI rates may have been significantly underestimated owing to pre-hospital antibiotic administration and inadequate blood volumes submitted for culture. We believe that change in the laboratory culturing system and average volume of blood inoculum are less likely explanations for the decline in BSI rate, since the blood culture contamination rate increased significantly over time. However, differences in pathogen yield between the two systems have been described, and the impact of a different blood culture system on the BSI rate cannot be completely discounted [34-36].

Given the relatively good resources and care at our institution (including an infection prevention and control service and PICU facilities), these findings may be more generalizable to better-resourced African settings. Recommendations for local practice arising from this study include urgent review of paediatric blood culture practice (emphasizing aseptic technique and adequate blood inoculum) and review of empiric antibiotic therapy for both community and hospital-acquired BSI.

Conclusions

Children with BSI experienced high mortality, particularly for hospital-acquired infection. *S. pneumoniae* BSI declined after introduction of PCV and increasing antiretroviral coverage. Pathogens (both community- and hospital-acquired) exhibited substantial antimicrobial resistance. Although BSI rates declined, blood culture contamination rates increased; blood culture sampling technique and local options for empiric antimicrobial therapy require re-evaluation.

Abbreviations

BSI: Bloodstream infection; CI: Confidence interval; ESBL: Extended-spectrum beta-lactamase; HIV: Human immunodeficiency virus; MRSA: Methicillin-resistant *Staphylococcus aureus*; PCV: Pneumococcal conjugate vaccine; PICU: Paediatric intensive care unit; PMTCT: Prevention of mother to child transmission of HIV.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors (AD, MC, HR, AW) contributed to study design and critical review of the manuscript. AD carried out the data collection, data cleaning (assisted by AW) and statistical analysis. All authors read and approved the final manuscript.

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Chapter 3

Surveillance methods for paediatric healthcare-associated infection

Dramowski A, Cotton M, Whitelaw A. *Surveillance of healthcare-associated infection in hospitalized South African children: which method performs best? S Afr Med J.* 2017;107(1):56-63.

Accurate surveillance estimates of HAI burden in low-middle income countries are lacking, partly because of the significant resources and skills required.^{9,10} In 2012, HAI surveillance became mandatory at all South African healthcare facilities, but no recommendations of surveillance method/s were provided by the Department of Health.⁶² We compared the performance of three HAI surveillance methods (repeated point prevalence surveys [PPS], laboratory surveillance and tracking of antimicrobial prescriptions) using the prospectively collected HAI dataset (chapter 2) as the reference standard.

PPS are an attractive, low-cost method of HAI surveillance, which can provide estimation of HAI trends when repeated at regular intervals. We found, however that PPS (repeated monthly) had poor sensitivity for HAI detection in our setting. Laboratory surveillance for HAI episodes performed better but missed all suspected or “culture-negative” HAI episodes; in addition, sensitivity of laboratory surveillance depends on the utilization rate of investigations and adequacy of clinical samples submitted. Surveillance of antimicrobial prescriptions showed highest sensitivity overall, largely owing to detection of HAI episodes that were culture-negative or instances where laboratory specimens were not submitted. However, a combination of laboratory surveillance with antimicrobial prescription tracking achieved best sensitivity (85%) and positive predictive value (97%), and required fewer resources to perform.

Although all three methods are potentially suitable for HAI surveillance on South African paediatric wards, the most suitable method for each facility will vary depending on clinical practices and available resources. In resource-limited settings, where prospective, patient-based surveillance is difficult to conduct, PPS, laboratory, antimicrobial prescription or combinations thereof, are acceptable alternative HAI surveillance methods.

Surveillance of healthcare-associated infection in hospitalised South African children: Which method performs best?

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Background. In 2012, the South African (SA) National Department of Health mandated surveillance of healthcare-associated infection (HAI), but made no recommendations of appropriate surveillance methods.

Methods. Prospective clinical HAI surveillance (the reference method) was conducted at Tygerberg Children's Hospital, Cape Town, from 1 May to 31 October 2015. Performance of three surveillance methods (point prevalence surveys (PPSs), laboratory surveillance and tracking of antimicrobial prescriptions) was compared with the reference method using surveillance evaluation guidelines. Factors associated with failure to detect HAI were identified by logistic regression analysis.

Results. The reference method detected 417 HAIs among 1 347 paediatric hospitalisations (HAI incidence of 31/1000 patient days; 95% confidence interval (CI) 28.2 - 34.2). Surveillance methods had variable sensitivity (S) and positive predictive value (PPV): PPS S = 24.9% (95% CI 21 - 29.3), PPV = 100%; laboratory surveillance S = 48.4% (95% CI 43.7 - 53.2), PPV = 55.2% (95% CI 50.1 - 60.2); and antimicrobial prescriptions S = 66.4% (95% CI 61.8 - 70.8%), PPV = 88.5% (95% CI 84.5 - 91.6). Combined laboratory-antimicrobial surveillance achieved superior HAI detection (S = 84.7% (95% CI 80.9 - 87.8%), PPV = 97% (95% CI 94.6 - 98.4%)). Factors associated with failure to detect HAI included patient transfer (odds ratio (OR) 2.0), single HAI event (OR 2.8), age category 1 - 5 years (OR 2.1) and hospitalisation in a general ward (OR 2.3).

Conclusions. Repeated PPSs, laboratory surveillance and/or antimicrobial prescription tracking are feasible HAI surveillance methods for low-resource settings. Combined laboratory-antimicrobial surveillance achieved the best sensitivity and PPV. SA paediatric healthcare facilities should individualise HAI surveillance, selecting a method suited to available resources and practice context.

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Healthcare-associated infections (HAIs) are the most common complication of hospitalisation, resulting in adverse patient outcomes and increased healthcare costs.^[1] The burden of HAIs in most high-income settings is well established by national internet-based reporting systems or repeated national/facility-level HAI point prevalence surveys (PPSs).^[2-5]

In sub-Saharan Africa, most healthcare facilities are unable to perform HAI surveillance because they lack trained infection prevention (IP) staff, data analysts and information technology (IT) infrastructure.^[6] The situation in South Africa (SA), a country with greater resources than many of its neighbours, is similar, with no national HAI surveillance programme and extremely limited data on the paediatric and adult HAI burden.^[7,8] A single study in 2005 estimated a prevalence of 9.7% for four major HAI types, with higher prevalence among children (16.5%) and patients in intensive care units (ICUs) (28.5%).^[9,10]

In 2012, SA introduced National Core Standards for Healthcare Establishments,^[11] with a patient safety domain mandating HAI surveillance, but lacking recommendations for HAI surveillance methods. Prospective clinical (patient-based) surveillance is considered the reference method or 'gold standard' for HAI surveillance, but requires substantial resources.^[12,13] HAI surveillance is conventionally conducted by IP staff applying technically complex

definitions to their inpatient population (most often using the Centers for Disease Control's National Healthcare Safety Network (CDC/NHSN) definitions^[14]). Even in well-resourced settings, so-called 'whole-house' clinical surveillance for all HAI event types is seldom done. Instead, targeted HAI surveillance is more commonly performed, focusing on specific clinical units (e.g. ICUs), types of HAI (e.g. device-associated infection) or procedures (e.g. surgical site infection (SSI) after caesarean section). Less resource-intensive HAI surveillance methods that still allow for monitoring of HAI trends and benchmarking are required, especially in resource-limited settings.^[3,5]

Electronic detection of HAIs has many advantages over conventional clinical surveillance: patient data abstraction is automated, and several data sources can be combined. This method increases objectivity, reliability and efficiency of HAI identification.^[15] However, automated surveillance may be a poor proxy for conventional HAI surveillance (particularly when utilising the 10th revision of the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10) coding), with both false positives and missed HAI events reported.^[16-18] Computerised HAI identification algorithms that use multiple sources of information (e.g. laboratory data, ICD-10 coding and inpatient prescriptions) can achieve better sensitivity and positive predictive values (PPVs).^[19]

However, lack of IT infrastructure and electronic health records precludes the use of automated HAI surveillance in most low- and middle-income countries (LMICs), including SA.

Data on device-associated infection rates in the private SA healthcare sector were recently published,^[20] highlighting the challenges associated with active HAI surveillance even in a comparatively well-funded setting. Alternative, passive HAI surveillance methods that could be utilised in low-resource settings include laboratory surveillance (for selected hospital-acquired pathogens) and review of pharmacy prescriptions (identifying antimicrobials used to treat HAIs). In addition, repeated PPSs may be feasible in LMIC healthcare facilities, particularly if a targeted population/clinical unit is selected, e.g. ICUs or neonatal wards.^[21,22] The feasibility and sensitivity of HAI detection using different surveillance strategies has not been evaluated in SA. We compared the performance of three HAI surveillance methods in an SA children's hospital using the CDC framework^[23] for evaluating public health surveillance programmes (reporting sensitivity, PPV, simplicity, flexibility, timeliness, acceptability and representativeness).

Methods

Setting

Tygerberg Children's Hospital (TCH) in Cape Town, SA, has 300 paediatric beds within a 1 384-bed academic hospital complex. Sick neonates, infants and children (0 - 14 years) are admitted to 13 neonatal and paediatric wards (including surgical wards, medical generalist wards, medical specialty wards, e.g. infectious diseases, haematology and oncology, and intensive care facilities); critically ill children requiring ventilation or inotropic support are managed in the 10-bed medical/surgical paediatric intensive care unit (PICU). There are approximately 17 000 neonatal and paediatric admissions to TCH annually, with bed occupancy rates of 93%, 92% and 87% in the PICU and general and subspecialist wards, respectively, in 2015. The burden of infectious diseases is high, with HIV, tuberculosis, lower respiratory tract infections (RTIs) and gastroenteritis predominating. In 2013, the antenatal HIV prevalence in the Western Cape Province of SA was 19% (v. 30% nationally), and in 2012 the HIV prevalence in children (2 - 14 years) was 0.7% (v. 2.4% nationally).

Investigation and management of HAIs at TCH

Blood cultures are obtained from all children with suspected sepsis or severe infection in a focal site (e.g. pneumonia, cellulitis). Other laboratory samples are submitted at the discretion of attending clinicians, e.g. urine, pus or endotracheal aspirates. Empirical antibiotic therapy for HAIs usually includes meropenem, or ertapenem if *Pseudomonas aeruginosa* is considered unlikely and meningitis is excluded. Vancomycin is added if methicillin-resistant *Staphylococcus aureus* (MRSA) is a likely pathogen, e.g. suspected central-line sepsis or soft-tissue infection. Colistin, ciprofloxacin, fluconazole and amphotericin B are occasionally used empirically, although the hospital antimicrobial stewardship (AS) programme encourages use of narrower-spectrum, targeted therapy if culture results are available.

Routine HAI surveillance at Tygerberg Hospital (including TCH)

The Unit for Infection Prevention and Control (IPC) utilises laboratory surveillance of selected bacterial 'alert' pathogens from blood culture, urine, pus, endotracheal aspirates and sputum samples to calculate hospital-acquired bloodstream infection and other selected HAI rates. This targeted surveillance differs from the expanded laboratory surveillance method utilised in the present study, which included all

pathogenic bacteria, fungi and selected viral pathogens. The only prospective clinical HAI surveillance at TCH has been conducted by neonatal ICU staff since 2013, reporting central line-associated bloodstream infection (CLABSI) rates (a type of device-associated HAI accounting for just 1.5% of paediatric HAI at our institution).^[24] Utilising laboratory surveillance data and individual patient referrals from clinicians, the IP practitioners conduct daily ward rounds to advise on transmission-based precautions, patient isolation, and other IPC-related management and staff education.

Study design

Prospective clinical surveillance (the reference method) was conducted in three paediatric wards (general paediatrics, paediatric surgery, infectious diseases/gastroenterology) and the PICU on weekdays from 1 May 2015 to 31 October 2015, documenting HAI events, microbiology/virology laboratory data and antimicrobial prescriptions among inpatients admitted for ≥ 48 hours or transferred from another facility. Data on incident HAI events, laboratory data and antimicrobial prescriptions occurring over weekends were collected on the Monday ward rounds. CDC/NHSN definitions for HAI^[14] were used for both the reference method and the monthly HAI PPS. The CDC/NHSN defines an HAI in acute-care settings as 'a localized or systemic condition resulting from an adverse reaction to the presence of an infectious agent(s) or its toxin(s) that was not present or incubating' at the time of hospitalisation (bacterial colonisation and inflammation from non-infectious causes are excluded). HAI is confirmed when all elements of the CDC/NHSN criteria 'were first present together on or after the 3rd hospital day', and each HAI type has so-called 'site-specific criteria', e.g. SSI, skin and soft-tissue infection. 'Presumed' HAI infection events (not part of the CDC/NHSN classification) were defined as episodes of clinically diagnosed HAI without an identified source or positive laboratory tests, where broad-spectrum antimicrobials were initiated and continued for at least 5 calendar days. Each surveillance type was considered to have correctly identified an HAI event (identified by the reference method) if the HAI event was 'active' on the day of the PPS, any microbiology/virology investigation for suspected HAI yielded a pathogen, or any new prescription was boarded for meropenem, ertapenem, ciprofloxacin, vancomycin or colistin. The updated CDC guideline for public health surveillance programme evaluation^[23] was used to compare each surveillance method's performance for sensitivity, PPV, simplicity, flexibility, timeliness, acceptability and representativeness.

Statistical analysis

HAI events identified by the reference method were used to calculate HAI incidence (HAI events/1 000 patient days) and HAI prevalence (one or more HAI event/100 admissions). HAI incidence (in wards and the PICU) and overall HAI prevalence estimates obtained by the three comparator surveillance methods were calculated with 95% confidence intervals (CIs). The sensitivity of each comparator surveillance method was calculated as number of HAI events detected/total events detected by the reference method. PPV was calculated as the proportion of 'HAI cases' detected by the comparator method that were confirmed by the reference method. Potential factors influencing HAI detection rates for each surveillance method were entered into a logistic regression model. A *p*-value of < 0.05 was considered statistically significant. Stata statistical software version 13.0 (StataCorp, USA) was used.

Ethical approval

Research approval and waiver of individual informed consent were obtained from the Human Health Research Ethics Committee of

Stellenbosch University (ref. no. S13/09/171), and institutional approval was obtained from Tygerberg Hospital (no reference number).

Results

During the 6-month surveillance period, 1 347 children were transferred in and/or admitted for ≥ 48 hours to the three wards and the PICU, generating 13 401 patient days. The reference method detected 417 HAI events during 324 patient admission episodes for 296 discrete patients (1.4 HAI events per affected patient). The overall HAI incidence rate was high at 31/1 000 patient days (95% CI 28.2 - 34.2), with a period prevalence of 22/100 admissions (95% CI 28.2 - 34.2) (Table 1). HAI rates were highest among children admitted to the PICU (94.4/1 000 patient days (95% CI 80.6 - 109.8)).

Sensitivity of alternative HAI surveillance methods was highest for antimicrobial prescriptions at 66.4% (95% CI 61.8 - 70.8), followed by laboratory surveillance at 48.4% (95% CI 43.7 - 53.2) (Table 1). Repeated PPSs were significantly less sensitive than antimicrobial and laboratory surveillance (24.9 (95% CI 21.0 - 29.3); $p < 0.001$). Combining antimicrobial and laboratory surveillance improved sensitivity to 84.7% (95% CI 80.9 - 87.8).

PPVs were 100% for PPS, 55.2% (95% CI 50.1 - 60.2) for laboratory surveillance and 88.5% (95% CI 84.5 - 91.6) for antimicrobial prescriptions. Reasons for 'misidentification' of the 164 false positives identified by laboratory surveillance included pathogens representing colonisation only ($n=21$), community-acquired pathogens ($n=129$), duplicate laboratory specimens ($n=5$), and pathogens identified from more than one sample site, e.g. bloodstream and urine ($n=9$). Few false positives were identified by antimicrobial prescription surveillance ($n=36$), with resistant community-acquired infections and complicated intra-abdominal infections as the main indications for carbapenem or ciprofloxacin use in these cases. Combining antimicrobial and laboratory surveillance substantially reduced false-positive HAI

identification ($n=11$) and resulted in an improvement of the PPV to 97% (95% CI 94.6 - 98.4).

The alternative surveillance methods performed variably for detecting the four main HAI types: hospital-acquired pneumonia (HAP) ($n=185$), urinary tract infection (UTI) ($n=45$), laboratory-confirmed bloodstream infection (LC-BSI) ($n=41$), and SSI ($n=20$) (Fig. 1). Compared with the reference method, repeated PPS detected $< 30\%$ of the four main HAI types other than SSI, whereas laboratory surveillance achieved the highest proportional detection rates for UTI, SSI and LC-BSI. Antimicrobial prescriptions achieved the highest detection rates for HAP. Combining antimicrobial and laboratory surveillance substantially improved detection of SSI and HAP events, and to a lesser extent UTI and LC-BSI detection.

Table 2 summarises the pathogens associated with four main HAI types. *Klebsiella pneumoniae* (33/68, 48.6%) and *S. aureus* (13/25, 52.0%) were the leading Gram-negative and Gram-positive

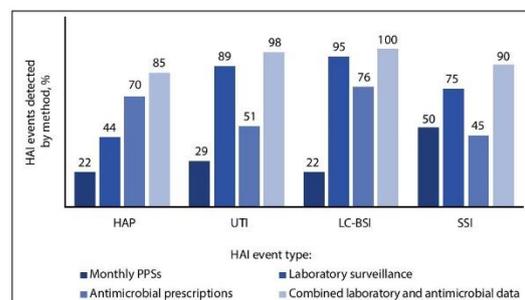


Fig. 1. Comparative HAI detection by surveillance method and HAI event type. The proportion of HAI events detected by alternative surveillance methods (when compared with the reference method's assumed HAI detection rate of 100%) is shown for four frequent HAI event types: HAP ($n=185$), UTI ($n=45$), LC-BSI ($n=41$) and SSI ($n=21$).

Table 1. Comparative performance of HAI surveillance methods

Measure	Reference method	PPSs	Laboratory surveillance	Antimicrobial prescriptions	Combined laboratory-antimicrobial surveillance
HAI 'cases' detected by method, n	417	104	202	277	353
HAI incidence, /1 000 patient days* (95% CI)					
Overall (wards + PICU)	31.1 (28.2 - 34.2)	7.8 (6.3 - 9.4)	15.1 (13.1 - 17.3)	20.7 (18.3 - 23.2)	26.3 (23.7 - 29.2)
PICU	94.4 (80.6 - 109.8)	20.5 (14.1 - 28.7)	56.5 (45.7 - 68.9)	72 (59.9 - 85.8)	88.8 (75.4 - 103.8)
Paediatric wards	22.5 (19.9 - 25.3)	6 (4.7 - 7.6)	9.4 (7.8 - 11.3)	13.7 (11.6 - 15.9)	17.8 (15.5 - 20.4)
HAI prevalence, [†] /100 admissions (95% CI)	22 (19.9 - 24.3)	7.4 (6.1 - 9)	12 (10.3 - 13.8)	16.1 (14.2 - 18.2)	20.5 (18.5 - 22.8)
Sensitivity, [‡] % (95% CI)	Reference standard	24.9 (21.0 - 29.3)	48.4 (43.7 - 53.2)	66.4 (61.8 - 70.8)	84.7 (80.9 - 87.8)
PPV, [§] % (95% CI)	Reference standard	100 (50.1 - 60.2)	55.2 (50.1 - 60.2)	88.5 (84.5 - 91.6)	97 (94.6 - 98.4)

*Patient days: sum of patients on each ward at 08h00 every day during the 6-month study period (13 401 patient days = 1 610 paediatric ICU + 11 791 three paediatric wards).
[†]HAI prevalence: discrete patients with one or more HAI event/100 patient admissions to the four selected wards (reference method = 296/1 347; PPS = 100/1 347; laboratory surveillance = 161/1 347; antimicrobial prescriptions = 217/1 347; combined laboratory + antimicrobial data = 277/1 346).
[‡]Sensitivity of the surveillance method: number of HAI events detected by the alternative method/total events detected by the reference method, e.g. HAI events detected by PPS/reference method = 104/417 (24.9%).
[§]PPV: the proportion of detected 'cases' who actually had an HAI event confirmed by the reference method, e.g. for antimicrobial prescriptions = true positives (277)/(true positives (277) + false positives (36)) (88.5%).

Table 2. Pathogens associated with selected HAI types (N=299)

Pathogen	LC-BSI (N=41)	CLABSI* (N=7)	UTI (N=45)	SSI (N=21)	HAP† (N=185)
Gram-negatives (N=72)					
<i>Klebsiella pneumoniae</i>	5	2	24	2	2
<i>Enterobacter cloacae</i>	4	0	0	1	0
<i>Escherichia coli</i>	5	0	7	4	0
<i>Acinetobacter</i> spp.	3	0	0	0	0
<i>Pseudomonas aeruginosa</i>	2	0	1	3	0
<i>Serratia marcescens</i>	1	0	0	0	1
<i>Salmonella</i> non-typhi	1	0	0	0	0
<i>Morganella morganii</i>	0	0	0	2	0
<i>Bordetella pertussis</i>	0	0	0	0	1
<i>Stenotrophomonas maltophilia</i>	0	0	0	0	1
Gram-positives (N=25)					
<i>Staphylococcus aureus</i>	6	1	2	4	0
<i>Enterococcus faecium</i>	3	0	1	0	0
<i>Enterococcus faecalis</i>	1	0	1	0	0
Coagulase-negative staphylococci	4	0	0	0	0
<i>Leuconostoc</i> spp.	0	1	0	0	0
<i>Streptococcus agalactiae</i>	1	0	0	0	0
Fungi (N=18)					
<i>Candida albicans</i>	3	1	6	0	0
<i>C. glabrata</i>	0	2	1	0	0
<i>C. parapsilosis</i>	2	1	0	0	0
<i>C. lusitanae</i>	0	0	2	0	0
Viruses (N=93)					
Respiratory syncytial virus	-	-	-	-	38
Adenovirus	-	-	-	-	25
Parainfluenza virus	-	-	-	-	14
Influenza virus	-	-	-	-	5
Coronavirus OC43	-	-	-	-	4
Human metapneumovirus	-	-	-	-	4
Rhinovirus	-	-	-	-	2
Bocavirus	-	-	-	-	1
No pathogen isolated	-	-	-	3 (14.2%)	69 (37.3%)
No specimen sent	-	-	-	2 (9.6%)	34 (18.4%)

*One patient had polymicrobial infection, hence 8 pathogen isolates for 7 CLABSI episodes.

†HAP 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 isolates, respectively, for LC-BSI, UTI and SSI events. Of the 61 Enterobacteriaceae isolated, 35 (57.4%) were ESBL producers, and 3/13 (23.1%) *S. aureus* isolates were MRSA. Viral pathogens (particularly respiratory syncytial virus (RSV) and adenovirus) predominated in HAP events, with 82/151 patients (54.3%) investigated yielding one or more RTI pathogens.

Factors associated with failure to detect an HAI (Table 2) were as follows: for PPSs, patient transfer (OR 2.0; 95% CI 1.01 - 3.1) and a single HAI event (OR 2.8; 95% CI 1.5 - 5.1); for laboratory surveillance, admission to a general ward (OR 2.3; 95% CI 1.5 - 3.5) and age group 1 - 5 years (OR 2.1; 95% CI 1.1 - 3.9), and for

antimicrobial prescriptions, admission to a general ward (OR 1.8; 95% CI 1.1 - 2.9). Death was associated with significantly less chance of a 'missed' HAI event for the antimicrobial prescription surveillance method (OR 0.3; 95% CI 0.1 - 0.9) (Table 3). Table 4 compares data on the qualitative elements of the CDC surveillance programme evaluation, and summarises the advantages, disadvantages and recommended settings for use of each surveillance method.

Discussion

The reference method measured HAI prevalence at 22%, far exceeding rates of 4 - 5% reported in hospitalised children in high-

Table 3. Factors associated with failure to detect HAI*

	Surveillance method											
	Repeated PPSs				Laboratory surveillance				Antibiotic prescriptions			
	Uni- variate analysis (p-value)	Multi- variate analysis (p-value)	Odds ratio	95% CI	Uni- variate analysis (p-value)	Multi- variate analysis (p-value)	Odds ratio	95% CI	Uni- variate analysis (p-value)	Multi- variate analysis (p-value)	Odds ratio	95% CI
Ward type	0.248	-	-	-	<0.001	<0.001	2.28	1.48 - 3.51	0.001	0.017	1.81	1.11 - 2.97
Length of stay	0.023	0.24	0.99	0.97 - 0.99	0.90	-	-	-	0.016	0.27	0.99	0.98 - 1.00
Outcome: Death	<0.001	0.06	1.87	0.95 - 8.8	0.147	-	-	-	0.002	0.03	0.36	0.14 - 0.93
Outcome: Transfer	<0.001	0.04	2.0	1.01 - 3.07	0.147	-	-	-	0.002	0.30	0.77	0.47 - 1.26
Single HAI event	0.001	0.001	2.8	1.53 - 5.09	0.074	-	-	-	0.192	-	-	-
Patient risk factor/s for HAI	0.987	-	-	-	0.321	-	-	-	0.803	-	-	-
HIV status	0.419	-	-	-	0.72	-	-	-	0.241	-	-	-
Age category: 1 - 5 years	0.654	-	-	-	0.002	0.03	2.07	1.08 - 3.98	0.619	-	-	-

- = variables that were not entered into the multivariate analysis because the univariate p-value was >0.1.
*To determine factors associated with not identifying ('missing') an HAI event, binary logistic regression analyses were performed for each surveillance method. A p-value of <0.05 was considered statistically significant. HAI type was omitted from the multivariate analysis because there were too many infection groups to analyse.

income settings.^[24,25] Our study prevalence (including all HAI types) is similar (16.5%) to that established for four HAI types (SSI, UTI, LC-BSI and RTIs) in a paediatric ward in Gauteng, SA, in 2005.^[9] Given the extreme paucity of data^[1,26] on paediatric HAI in Africa, we could not benchmark our HAI prevalence against other inpatient settings. The high HAI rate in our ICU (v. paediatric wards) is in keeping with published data for both LMICs and high-income countries (albeit three- to four-fold higher than their published HAI rates).^[1] Prevalence and incidence estimates produced by the combined laboratory-antimicrobial surveillance method were not significantly different (overlapping CIs) from those measured by the reference method, suggesting that combined laboratory-antimicrobial surveillance provides the most accurate approximation of the true HAI burden in our setting.

Repeated PPSs showed poorer sensitivity than laboratory and antimicrobial prescription surveillance. Monthly PPSs would have missed many infection events, including HAI-attributable mortality. This limitation of the PPS methodology can be partially mitigated by using period prevalence (infections occurring during a predefined period before the survey day) rather than point prevalence (which only includes HAIs present on the survey day). Zingg *et al.*^[27] established a 32% greater HAI yield when using period prevalence (HAI within 7 days of the survey date), with the additional cases attributed largely to identification of short-duration HAIs, e.g. lower RTIs and UTIs. This phenomenon may partly explain why our

monthly PPSs performed better at detecting SSI events than other HAIs, as SSIs prolonged hospitalisation disproportionately to other HAI types, increasing the likelihood of being surveyed. We also identified that transfer out was associated with failure to detect HAI on PPS, reflecting the lower likelihood of a patient with HAI being present on a PPS day if they had been transferred out to complete antibiotic therapy at another facility.

Another limitation of PPSs is the inability to quantify the influence of seasonal fluctuations in community-acquired viral infections with potential for nosocomial spread. We documented very few healthcare-associated gastroenteritis events, possibly owing to the surveillance period (May - October are low-prevalence months for rotaviral disease in SA). Conversely, HAP events may have been over-represented in our cohort, as the surveillance months included the peak winter hospitalisations for community-acquired RTIs.^[28]

The perfect performance of PPSs at identifying true HAI is probably due to use of the same HAI case definitions and data collection tool as the reference method. The PPV achieved by antimicrobial prescription surveillance was similarly high, indicating that ultra-broad-spectrum antibiotics, e.g. carbapenems, were reserved mostly for HAIs. This finding can be ascribed in part to institutional AS interventions targeting clinicians, e.g. antimicrobial restriction policies and weekly AS ward rounds. The PPV of laboratory surveillance was poor, mainly because of difficulty in excluding community-acquired and colonising pathogens in

Table 4. Comparison of HAI surveillance methods

	Reference method*	PPSs	Laboratory surveillance	Antimicrobial prescriptions
Simplicity [†]	Most complex	Moderately complex	Less complex	Least complex
Activities	Daily ward rounds, data capture + validation	Monthly ward rounds, data capture + validation	Laboratory data and hospital admissions, data extraction + validation	Pharmacy data and hospital admissions, data extraction + validation
Resources	IP data collector, data capturer, hospital IT	IP data collector, data capturer, hospital IT	Laboratory database/s, hospital IT	Pharmacy database, hospital IT
Time (hours/month) [‡]	120	30	10	5
Flexibility [§]	Moderately flexible	Moderately flexible	Moderately flexible	Very flexible
Timeliness [¶]	High	Moderate	Low (unless using real-time surveillance)	Low
Acceptability	Low	Moderate	Moderate to high	Moderate to high
Representativeness**	High	Moderate	Moderate to low (influenced by frequency and quality of laboratory sampling)	Moderate to low (influenced by availability of and ability to extract additional clinical data)
Advantages	Detects more HAI events than other methods; collects clinical data simultaneously; establishes whether infection is HA v. HCA	Less labour intensive; if repeated regularly may be helpful in establishing trends; collects clinical data simultaneously	Less labour intensive; additional data on pathogen profile and antibiotic susceptibility patterns of the institution	Least labour intensive; additional data on antibiotic consumption patterns for HAI at the institution; can identify HAI events even if rates of laboratory sampling or pathogen yields are low
Disadvantages	Labour intensive	Misses many HAI events; detection rate could be improved if include all HAI events occurring within 7 days preceding the PPS ^[26]	Sensitivity depends on frequency and quality of laboratory samples collected; difficult to distinguish colonisation from infection; cannot distinguish HA from HCA infection events	Additional data on HAI type and indication for antibiotic and patient demographics may not be available
Suitable contexts	Hospital settings with experienced IP practitioners, IT analyst + epidemiology support	Hospital settings with experienced IP practitioner/s + some IT analyst support	Hospitals with high use of laboratory tests for investigation of HAI and available IT/data analyst assistance	Hospitals with insufficient resources to perform other surveillance, moderate IT support/searchable pharmacy database

ID = infectious disease; HA = hospital acquired; HCA = healthcare associated.
[†]Clinical surveillance conducted on weekdays only.
[‡]Time calculations were based on surveillance conducted in 1 PICU (10 beds) and 3 paediatric wards (bed complement = 83).
[§]Simplicity includes the surveillance method structure, method of data collection and analysis, resources needed and ease of operation.
[¶]Flexibility includes the system's ability to adapt to changing information or operating conditions with minimal changes to time, personnel or operational costs, e.g. changes to HAI case definitions and use of standard data formats allowing easy integration with other systems.
^{||}Timeliness is the time interval between the onset of the HAI event and its reporting to those in charge of prevention and control efforts.
^{||}Acceptability is a subjective measure of the willingness and ability of individuals on whom the surveillance method depends to provide the required data accurately, consistently and on time.
^{**}Representativeness is the degree to which the system accurately reflects occurrence, distribution and demographic characteristics of persons experiencing HAI events.^[25]

the absence of clinical information. Combining antimicrobial and laboratory surveillance achieved a very high PPV, suggesting that it is an efficient way to monitor HAI events (with few false positives that would need folder review to exclude from HAI estimates).

Laboratory surveillance performed well for three of the four main HAI types (LC-BSI, SSI and UTI), but failed to detect over half of HAP events. However, combined laboratory-antimicrobial

surveillance resulted in improved detection of all main HAI types (particularly SSI and HAP events, which were poorly detected by individual surveillance methods). The poor sensitivity of laboratory surveillance for HAP may be due to low rates of laboratory testing for viral pathogens with polymerase chain reaction (PCR) outside the PICU and failure to detect bacterial respiratory pathogens with standard laboratory investigations.

The influence of viral pathogens on paediatric HAI rates is probably grossly underestimated. In a 3-month study of hospitalised children in Soweto, 15/130 (11.6%) clinically diagnosed with 'nosocomial sepsis' had confirmed nosocomial RSV infection.^[29] At Red Cross War Memorial Children's Hospital in Cape Town, 22/226 RSV infections (9.5%) were nosocomially acquired in 2012.^[30]

It is notable that laboratory surveillance (our institution's current surveillance method) was less sensitive than antibiotic prescription and combined laboratory-antimicrobial surveillance. This finding has implications for institutions with low rates of laboratory investigation of suspected HAI events; in such settings, laboratory surveillance may miss an even greater proportion of HAIs, which would still be detected by surveillance of antimicrobial prescriptions. In addition, laboratory surveillance was two times less likely to identify HAI in children aged 1 - 5 years, possibly because they undergo fewer laboratory investigations than infants who have nonspecific clinical presentation of sepsis necessitating more extensive diagnostic testing.

In keeping with previous SA studies, *K. pneumoniae* and *S. aureus* were the most frequently isolated HAI pathogens with a high prevalence of antimicrobial-resistant phenotypes.^[28] Viral pathogens were identified in over 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 18.4% of HAP events, no respiratory pathogen testing was performed, representing missed opportunities for identification and isolation of patients with transmissible pathogens.

The decision on which antimicrobials to include in prescriptions surveillance should be determined by the institution's empirical antimicrobial recommendations for HAI. The degree to which these antimicrobials are reserved for HAI treatment and the extent of resistant community-acquired infections will influence the HAI detection rate, potentially generating false-positive HAI events. Conversely, a prescription of antimicrobial/s other than the institution's empirical HAI therapy agents may result in 'missed' HAI events or false negatives.

We identified that hospitalisation in a ward (as opposed to the PICU) doubled the odds of failure to detect HAI (for both laboratory and antimicrobial surveillance methods). This finding is explained by the less frequent use of and lower yield of laboratory investigations in the wards as well as lower carbapenem utilisation rates. Death was associated with significantly less chance of 'missing' an HAI event by antimicrobial prescription surveillance, possibly because most critically ill children hospitalised for >48 hours would be prescribed a carbapenem antibiotic empirically.

Given the failure of alternative methods to achieve high HAI detection rates, combining surveillance methods may achieve superior sensitivity (as demonstrated by combination of our antimicrobial and laboratory data to produce test sensitivity of 85%). Another possible strategy would be use of antimicrobial prescriptions to monitor certain HAI types with low laboratory testing rates and pathogen yield (e.g. HAP) and to use laboratory surveillance for HAI events with higher pathogen isolation rates (e.g. UTI, LC-BSI and SSI). This would, however, require the pharmacy to record clinical indications for HAI therapy (which was recently implemented at some institutions through a dedicated antimicrobial prescription chart designed by the South African Antimicrobial Stewardship Programme).^[31] Furthermore, increased use of appropriate laboratory tests for viral pathogens in cases of presumed HAI should be encouraged to assist with AS efforts. This strategy would avoid empirical antibiotic

treatment of presumed HAI based only on clinical suspicion, and limit antibiotic duration in cases where viral pathogens are identified or presumed HAI events where no pathogens are identified, after appropriate laboratory investigations.

Repeated PPSs should not be discounted in low-resource settings, although in our cohort this method had the lowest sensitivity and required the greatest resources (time and labour). A distinct advantage of the PPS methodology is that a standardised, validated data collection tool can be used regionally or nationally, reducing inter- and intra-observer variability and facilitating benchmarking of individual facilities. Greater inter-institution variability in HAI rates would be expected using laboratory and/or antimicrobial prescription surveillance owing to variable specimen collection practices, laboratory methods and prescribing practices. Another advantage of PPSs is the possibility of collecting patient demographic data to identify patients at highest risk of HAI, allowing for targeting of HAI prevention interventions.

Using the CDC guidelines for evaluating surveillance systems, we identified wide variability in performance attributes of each surveillance method. Although the resources required to implement the reference surveillance method at our institution are not currently available, prospective, continuous HAI surveillance would provide timely (in real time) and representative ('whole-house') data. Laboratory and antimicrobial prescription surveillance methods appear the most attractive, most flexible and least resource-intensive options, but would provide less frequent HAI reports (weekly or monthly) and less complete data (not every case of HAI will be detected) in our context. Real-time laboratory data surveillance (if combined with additional clinical data collection) could, however, provide more accurate, timely and representative data.

Limitations of our study include the single study site, selection of four 'representative' wards, with exclusion of neonatal wards and the neonatal ICU, the study period sampled (May - October), which may have underestimated seasonal fluctuations in HAI (from nosocomial propagation of community-acquired viral infections), the use of antibiotic prescription data from patient records rather than from pharmacy databases, and microbiology/virology laboratory testing at clinicians' discretion with possible underdiagnosis of HAI events by laboratory surveillance (although this could also be construed as a strength, in that it represents the performance of laboratory surveillance in a 'real-world', current-practice setting).

In LMICs where the burden of HAIs is greatest, many healthcare facilities are poorly equipped to conduct prospective clinical HAI surveillance. Consequently, published data on the epidemiology of HAIs in developing countries are scant, but could be increased through use of simpler, less resource-intensive surveillance methods than the reference standard of prospective, clinical HAI surveillance. No single method will approximate the reference method or perform uniformly in all settings. Individualisation of HAI surveillance recommendations is therefore needed, considering available resources and the practice context. Nevertheless, our study suggests that laboratory surveillance, antimicrobial prescriptions, PPSs or combinations thereof are feasible alternatives to conventional clinical HAI surveillance.

Conclusions

SA paediatric wards should select an HAI surveillance method based on available resources, expertise and technology infrastructure. Where clinical HAI surveillance is not possible, monitoring of antimicrobial prescriptions in combination with laboratory data analysis appears a reasonable alternative.

Author contributions. All the authors contributed to study design and critical review of the manuscript. AD carried out the data collection, data cleaning and statistical analysis (with assistance from Ms Tonya Esterhuizen of the Stellenbosch University Biostatistics Unit, Centre for Evidence-based Healthcare). All the authors read and approved the final manuscript.

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Chapter 4

Utilization and terminal cleaning of paediatric isolation facilities

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In many high-income countries, paediatric wards are purposively designed with single room, en-suite facilities to reduce the risk of infection transmission. Ironically in resource-limited settings where infection burden is highest, few or no patient isolation facilities exist.^{10,31,32} Although several studies from high-income countries report data on paediatric isolation facility utilization⁶³⁻⁶⁵, we identified no publications on this topic from African settings.

We prospectively observed isolation room utilization patterns at Tygerberg Children's Hospital over 6 months to estimate and characterize demand for isolation facilities and identify missed opportunities for isolation. A surprisingly low proportion of children were admitted to isolation (6% vs 14-17% reported from studies in high-income settings), with most (78%) isolated for infection prevention (IP) indications. In contrast to high-income settings, our main isolation requirement was for airborne precautions (52%) in children with tuberculosis (26% with drug-resistant TB disease).

Demand for isolation beds fluctuated (peaking in mid-winter), although observed isolation occupancy averaged only 66%. Potential missed opportunities for isolation were identified by cross-referencing isolation room occupants' identifying information against laboratory data of patient specimens with antibiotic-resistant bacteria, *M. tuberculosis* and selected viral pathogens. When taking into account missed isolation opportunities and syndromic indications for isolation, bed demand would have exceeded available bed capacity for 5/6 observed months. In most instances, alcohol handrub (89%) and appropriate personal protective equipment (74%) were available at isolation rooms. However levels of hand hygiene compliance (65%) and adherence to transmission-based precautions (58%) among staff caring for children in isolation, were substantially lower.

This is the first publication from Africa to characterize paediatric isolation room utilization, quantify demand for isolation beds and identify airborne precautions for TB as the predominant isolation indication. In addition we identified major shortcomings and opportunities for improved utilization of this scarce resource at Tygerberg Children's Hospital.

RESEARCH

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Utilization of paediatric isolation facilities in a TB-endemic setting

Angela Dramowski^{1*}, Mark F. Cotton¹ and Andrew Whitelaw²**Abstract**

Introduction: In hospital settings, patient isolation is used to limit transmission of certain pathogens (e.g. *M. tuberculosis* [TB], antibiotic-resistant bacteria and viruses causing respiratory and enteric infection). Data is lacking on utilization of paediatric isolation facilities in low-resource, TB-endemic settings.

Methods: Prospective weekday observation of 18 paediatric isolation rooms at Tygerberg Children's Hospital, Cape Town, South Africa, was conducted between 1 May 2014 and 31 October 2014 documenting: occupancy rate; indication for isolation; duration of isolation; application of transmission-based precautions and infection prevention (IPC) behaviour of personnel. Potential under-utilization of isolation rooms was determined by cross-referencing isolation room occupancy with laboratory isolates of antibiotic-resistant bacteria, *M. tuberculosis* and selected viral pathogens.

Results: Six percent (335/5906) of hospitalized children were isolated: 78 % (260/335) for IPC purposes. Most IPC-isolated patients had community-acquired infections (213/260; 82 %), including tuberculosis (130/260; 50 %) and suspected viral infections (75/260; 29 %). Children (median age 17 months [IQR 6–50]) spent 4 days (IQR 2–8) in isolation. Isolation occupancy was 66 % (2172/3294 occupied bed days), but varied significantly by month. Laboratory data identified an additional 135 patients warranting isolation with 2054 extra bed-days required. Forty patients with 171 patient days of inappropriate isolation were identified. During 1223 weekday visits to IPC-isolated patient rooms: alcohol-based handrub was available (89 %); transmission-based precautions were appropriately implemented (71 %); and personal protective equipment was provided (74 %). Of 358 observed interactions between paediatric staff and isolated patients, hand hygiene compliance was 65 % and adherence to transmission-based precautions was 58 %.

Conclusion: Patients isolated for TB (under airborne precautions) accounted for more than half of all isolation episodes. Missed opportunities for patient isolation were common but could be reduced by implementation of syndromic isolation. Demand for isolation facilities was seasonal, with projected demand exceeding available isolation beds over winter months.

Keywords: Paediatrics, Healthcare-associated infection, Nosocomial infection, Infection control, Patient isolation, Transmission-based precautions, Tuberculosis

Background

Standard and transmission-based precautions (contact, droplet and airborne) [1] are used to interrupt pathogen transmission in healthcare settings. Patient isolation is a key component of these precautions, targeting pathogens such as *M. tuberculosis* (TB), antibiotic-resistant bacteria and certain viruses. Despite widespread implementation of these precautions in high-income countries, the resources

to effectively apply patient isolation and transmission-based precaution recommendations are lacking in many low and middle income countries [2, 3].

In paediatric wards, where infectious disease related-admissions predominate, the demand for isolation beds may be ten-fold greater than for hospitalized adults [4]. Not only are hospitalized children more likely to transmit infection, they are also at elevated risk for healthcare-associated infection (HAI) owing to immunological immaturity, underdeveloped mucosal barriers and increased handling by healthcare staff [5]. Studies of isolation facility usage in high-income settings report that 5-17 % of

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paediatric patients need isolation for IPC purposes, mostly for community-acquired infections (60–75 %) [4, 6–8]. Marked seasonality in demand for paediatric isolation beds (with demand often exceeding supply) is reported even from facilities with more single rooms than cohort beds [4, 6, 7]. The most common precaution type implemented in paediatric studies [5, 8, 9] is contact precautions (80–90 %) followed by droplet precautions [6]. A single study [6] measured correct use of isolation room precaution signage (93 %) and availability of personal protective equipment (100 %). Staff compliance with hand hygiene and transmission-based precautions recommendations in paediatric isolation rooms was not evaluated in these studies.

The impact of absent or limited paediatric isolation facilities in low-middle income settings is unquantified, but undoubtedly promotes infection transmission, along with adverse health system factors like overcrowding and lack of IPC provisions [3]. Data on rates of patient isolation, indications for and utilization patterns of paediatric isolation facilities in Africa is lacking. We evaluated isolation facility utilization and transmission-based precaution implementation at a paediatric referral hospital in a TB-endemic setting in Cape Town, South Africa.

Methods

Setting and patient profile

The Tygerberg Children's Hospital (TCH) in Cape Town, South Africa has 300 paediatric beds within the 1384-bed academic hospital complex. Sick neonates, infants and children (0–14 years) from Cape Town's Metropole East are hospitalized in 13 neonatal and paediatric wards (including surgical, general medical, sub-specialty wards and intensive care). Admissions reflect a high burden of infectious disease with TB, lower respiratory tract infections and gastroenteritis predominating. HIV prevalence in paediatric inpatients is approximately 15 %; antiretroviral therapy is widely available and improved access to prevention of mother-to-child HIV infection transmission programmes (PMTCT) has reduced national vertical HIV transmission rates to 2.4 % in 2012 [9]. Immunisation coverage rates were 88 % in infants under 12 months of age in 2012 [10].

Patient isolation in our context implies placement of a patient in a single room with application of transmission-based precautions based on clinical indication. Five paediatric wards have 18 single rooms available for patient isolation (9 under negative pressure; only 3 with en-suite bathrooms; none have ante-rooms). This represents 14 % of the available beds on the five wards: 1 room in acute admissions, 3 in paediatric surgery, 2 in general paediatrics, 2 in pulmonology/neurology and 10 in the infectious diseases/gastroenterology ward. The paediatric intensive

care unit (PICU) has 10 beds in 2 cohort rooms with no single room or isolation facilities available. PICU patients were eligible for study inclusion if transferred to any of the specified wards.

Each ward's medical and nursing personnel determine which patients are placed in isolation. Although there is no formal policy guiding isolation room utilization, preference is given to patients requiring airborne precautions e.g. pulmonary TB, measles and varicella. Where possible, children are accompanied by a caregiver (who may also require isolation e.g. for pulmonary TB). Syndromic isolation for suspected viral diseases is infrequently implemented, owing to clinician unfamiliarity with the practice and limited isolation space. In contrast, syndromic isolation for suspected TB is actively practiced, based on compatible symptoms and signs, history of TB contact and/or a suggestive chest radiograph appearance. The hospital's Unit for Infection Prevention and Control (IPC) conducts laboratory surveillance for selected bacterial "alert" pathogens and makes recommendations for patient isolation on an ad-hoc basis. Infectious patients are usually isolated until discharge (with the exception of meningococcal disease with de-isolation after 24 h of therapy).

Study design and data collection

Prospective observation of paediatric isolation rooms was conducted on weekdays from 1 May 2014 to 31 October 2014 documenting: occupancy rates; indication for isolation; duration of patient isolation and application of transmission-based precautions using the 2007 CDC patient isolation indications [1]. During weekday visits, observed interactions between personnel and isolated patients were documented including compliance with hand hygiene and transmission-based precautions. Hand hygiene was scored as compliant if all potential opportunities for hand hygiene were followed, or non-compliant if all or some opportunities for hand hygiene were missed. Transmission-based precautions were scored as compliant if all recommendations and appropriate personal protective equipment was applied, or non-compliant if all or some recommendations were not followed. Alcohol handrub and personal protective equipment was scored as available, if the handrub and equipment items needed (based on the appropriate precautions) were supplied at the entrance to the isolation room.

Estimation of isolation room under-utilization

Two datasets were created: "patient isolation room utilization data" was collected on weekday ward rounds using Microsoft Access 2013 and "patients with pathogens warranting isolation" was extracted from Microbiology and Virology laboratory databases. Pathogens warranting isolation [1] included: multidrug-resistant (MDR) bacteria [11] from any clinical specimen (blood culture, urine,

tissue, pus, wound swab and catheter tip) including methicillin-resistant *S. aureus* [MRSA], carbapenem-resistant *A. baumannii* [CRAB], MDR *P. aeruginosa* [MDR PA] and extended spectrum B-lactamase producing Enterobacteriaceae [ESBL]; *M. tuberculosis* both drug-susceptible (DS) and drug-resistant (DR) isolated from any respiratory sample (gastric washing and/or induced sputum) on GeneXpert, smear microscopy or TB culture; and viruses including enteric (rota and adenovirus, hepatitis A virus) and respiratory pathogens (respiratory syncytial virus, adenovirus, human rhinovirus, parainfluenza 1/2/3, influenza A/B and human metapneumovirus) identified by rapid assays, enzyme-linked immunosorbent assays (ELISA) or polymerase chain reaction (PCR) panel testing. All laboratory investigations were taken at the discretion of attending clinicians. Repeated isolates of the same pathogen from one or more sites counted as a single infection episode warranting patient isolation.

The laboratory pathogen dataset was cross-referenced against the patient isolation room utilization dataset. Several measures of isolation room utilization were calculated: missed isolation (patients with pathogens warranting isolation who were not isolated), delayed isolation (patients with late imposition of isolation precautions), inappropriate isolation (no clinical indication for isolation; failure to de-isolate after no pathogens or pathogens not warranting isolation were identified and failure to de-isolate after appropriate therapy) and syndromic isolation requirement (patients with suspected viral infections who were not isolated and had a negative laboratory test results for viral

pathogens by day four of hospitalisation). Additional isolation bed days required were calculated by adding the length of stay for each patient who was identified as having a missed indication for IPC-isolation. Additional syndromic bed-days were calculated by adding the number of days from hospital admission to a negative test result for specified viral pathogens for each patient (mean interval was 3.5 days). Additional days of pathogen exposure were calculated as days of missed isolation plus days of delayed isolation.

Statistical analysis and ethical approval

Descriptive statistical analyses were performed using Stata Statistical Software version 13.0 IC (College Station, TX: StataCorp LP). Median length of stay was compared using the Mann–Whitney test. A p-value below 0.05 was considered statistically significant. Ethical approval and waiver of individual informed consent was obtained from the Human Health Research Ethics committee of Stellenbosch University (S13/09/171).

Results

Six percent (335/5906) of children admitted during the study period were placed in isolation. Most isolation episodes (260/335; 78 %) were for IPC indications. Community-acquired infections were the predominant reason for isolation (213/260; 82 %), including TB disease (130/260; 50 %) and suspected viral infections (75/260; 29 %) (Table 1). Non-IPC indications for isolation included nursing considerations (post-operative care or

Table 1 Paediatric isolation room utilization

Variable	Total	Percentage	Interquartile range
Discrete patient isolation episodes	335	100	-
Median patient age (months)	17	-	6–50
Median stay in isolation room (days)	4	-	2–8
Indication for isolation			
- infection control (IPC) purposes	260	78	
- nursing care	46	14	-
- palliation/privacy	13	4	
- other ^a	16	4	
Transmission-based precautions ^b applied			
- airborne precautions	136	52	-
- droplet precautions	57	22	
- contact precautions	67	26	
	Mean	Minimum	Maximum
Isolation room occupancy rate ^c	2172/3294	225/540	487/558
	(66 %)	(42 %)	(87 %)

IPC = infection prevention and control

^aother = no obvious reason for isolation ($n = 11$), behavioural isolation ($n = 3$), protective isolation ($n = 2$)

^bUsing the 2007 CDC isolation guidelines[1]

^cCalculated as the sum of days when isolation rooms ($n = 18$) were occupied divided by [total isolation bed capacity x number of days in the observation period] i.e. 6 months to calculate mean or 1 month to calculate minimum and maximum occupancy rates

provision of total parenteral nutrition), palliation, behavioral or protective isolation. In 11/335 (3 %) episodes, no indication for isolation was identified. Children (median age 17 months; IQR 6–50) were isolated for a median of 4 (IQR 2–8) days. Patients isolated for suspected or confirmed TB stayed longer than patients with other infectious indications for isolation (median of 5 versus 3.5 days; $p = 0.006$). Overall isolation room occupancy was 66 % (2172 occupied/3294 available bed days), but varied significantly by month with peak usage in winter months (June [76 %], July [77 %], August [87 %]).

TB disease (130/260; 50 %) was the most frequent admission diagnosis in IPC-isolated patients [Table 2]. In 55 children (42 %) microbiological confirmation was obtained; twelve children (9 %) had smear-positive tuberculosis (1–99 acid-fast bacilli per high power field) and 12/45 (26 %) children with culture-positive TB had drug-resistant disease.

The remaining 130/260 (50 %) patients isolated for IPC indications included suspected or confirmed: viral respiratory infection (49; 19 %), viral gastrointestinal infection (20; 8 %), varicella or measles (6; 2.5 %), nosocomial sepsis (29; 11 %), skin/soft tissue infection (13; 5 %), hepatitis A (7; 3 %) and meningococcal infection (6; 2.5 %). In some patients (isolated on clinical suspicion of infection), laboratory tests revealed no pathogen or a pathogen not requiring isolation/transmission-based precautions (Table 2).

Cross-referencing of patient isolation and laboratory data identified an additional 135 patients warranting isolation (i.e. missed isolation episodes), with an additional 2054 required isolation bed-days. Of patients with missed isolation episodes, 43 (32 %) had MDR bacteria [1167 extra bed-days], 16 (12 %) had newly-diagnosed, microbiologically confirmed drug-susceptible TB [116 extra bed-days] and 76 (56 %) had viral pathogens [771 extra bed-days] (Table 3).

Of 395 laboratory investigations for viral pathogens warranting isolation: 103 patients with a positive test were identified (26 % yield). Of these 103 patients, 19 (18 %) had been isolated from admission, 8 (8 %) had delayed isolation (mean of 6 days delay) and 76 (74 %) were never isolated. The eight delayed isolation episodes had a combined 51 days of additional pathogen exposure on the ward (including hepatitis A, adenovirus, respiratory syncytial virus, parainfluenza 3 and rhinovirus.) A further 226 patients (with 292 negative laboratory tests for viral pathogens warranting isolation) would have qualified for syndromic isolation on admission. Implementing syndromic isolation for these patients would add an additional 990 days of isolation bed demand, increasing the months where demand would outstrip bed availability from 3 to 5 months in the study period (Fig. 1).

Forty patients with 171 patient days of inappropriate isolation were identified (29 days with no apparent reason for isolation and 142 days where IPC isolation was unwarranted i.e. no pathogens were isolated by day 4 of admission). Overall inappropriate isolation days accounted for 5 % of the available bed days (171/3294). Although total projected isolation bed-days reflected a deficit of 761 days (or 123 % projected occupancy) for missed isolation episodes, the deficit was confined to the first 3 months of the study period during the winter season (Fig. 1). The percentage of paediatric admissions requiring isolation increases from 6 % to 8 % when patients with missed isolation episodes are included and to 12 % when including missed isolation and children investigated for viral pathogens.

During 1223 weekday visits to isolation rooms used for IPC: alcohol-based handrub was generally available (89 %); transmission-based precautions were appropriately implemented (71 %) and personal protective equipment was provided (74 %). Of 358 observed interactions between personnel and isolated patients, hand hygiene compliance was 65 % and adherence to transmission-based precautions was 58 %.

Discussion

In our study of paediatric isolation room utilization, only 6 % of hospitalized children were placed in isolation. This contrasts with reported isolation rates of 14–17 % in high-income countries, where more single rooms and favourable staffing ratios facilitate greater use of isolation precautions. However, even in high income countries, isolation facilities may be under-utilised. Failure to implement syndromic isolation for suspected viral infections may also explain our institution's lower isolation rates, supported by the finding of many missed isolation opportunities (particularly among children investigated for viral respiratory and enteric infections). Another explanation for our apparently "low" isolation room occupancy and many "missed" episodes, may be a mismatch between theoretical availability of isolation beds and actual availability of beds. At times of peak isolation demand, even with overall 66 % occupancy, clinicians may struggle to find an open isolation bed at the time that the patient requires it.

In keeping with published reports, community-acquired infections predominated, although TB was the most frequent diagnosis among isolated patients at our institution. Consequently airborne precautions were the predominant precaution type implemented, in stark contrast to studies from high-income settings [4, 6–8]. Since our institution is a referral centre for complicated and/or drug-resistant TB, the findings may over-estimate requirement for airborne isolation facilities in other low-middle income paediatric settings. However, South African TB incidence

Table 2 Microbiological isolates^a from patients in isolation for IPC purposes

Category	Variable	Total (%)	
All suspected TB (n = 130)	pulmonary TB	118 (91)	
	extra-pulmonary TB ^b	12 (9)	
TB smear microscopy (n = 130)	not tested (diagnosis confirmed at referral hospital)	10 (8)	
	smear-negative	108 (83)	
	smear-positive (1–10 AFB/field)	8 (6)	
	smear-positive (11–99 AFB/field)	4 (3)	
Confirmed TB ^c (n = 55)	TB diagnosis confirmed at referral hospital	10	
	GeneXpert positive	43	
	TB culture positive	45	
Drug-susceptibility profile of culture positive cases (n = 45)	Drug-susceptible (DS)	33 (74)	
	Multidrug-resistant (MDR)	9 (20)	
	Rifampicin mono-resistant (RMR)	2 (4)	
	Extensively drug-resistant (XDR)	1 (2)	
	Total (number DR)		
All ^g bacterial/fungal isolates cultured from patients in isolation (n = 46)	Gram positives		
	<i>S. aureus</i> total (methicillin-resistant)	7 (2)	
	Other gram positives ^d	4	
	Gram negatives: Enterobacteriaceae		
	<i>K. pneumoniae</i> (extended-spectrum B-lactamase)	11 (10)	
	<i>E. coli</i> (extended-spectrum B-lactamase)	5 (1)	
	<i>E. cloacae</i> (inducible B-lactamase)	4 (2)	
	Other Enterobacteriaceae ^e	4	
	Gram negatives: Non-fermenters		
	<i>A. baumannii</i> (multi-drug resistant)	4 (4)	
	<i>P. aeruginosa</i> (multi-drug resistant)	5 (3)	
	Others		
	<i>N. meningitidis</i>	2	
	<i>B. pertussis</i> (PCR positive)	1	
	<i>C. albicans</i>	2	
	Viral pathogens confirmed among patients in isolation (n = 51)	Gastrointestinal viruses	
		Hepatitis A	6
Rotavirus		4	
Enteric adenovirus		2	
Respiratory viruses			
Respiratory syncytial virus		15	
Adenovirus		12	
Rhinovirus		4	
Parainfluenza virus		2	
Other respiratory viruses ^f		3	

Table 2 Microbiological isolates^a from patients in isolation for IPC purposes (*Continued*)

Other	
Varicella	2
Rubella	1

^aSome patients were isolated on clinical suspicion of sepsis or suspicion of a pathogen warranting isolation, but laboratory tests subsequently confirmed a pathogen which did not warrant isolation or transmission-based precautions by CDC guidelines[1] e.g. *Candida albicans*; TB = tuberculosis

^bExtra-pulmonary TB: disseminated (7), TB lymphadenitis (3), TB meningitis (2)

^cconfirmed TB = geneXpert positive or culture positive for mTB; DR = drug-resistant

^dOther gram positives: *C. difficile* (1), *S. pyogenes* (1), *S. pneumoniae* (1), *E. faecium* (1)

^eOther Enterobacteriaceae: *S. typhi* (1), *S. non-typhi* (1), *C. freundii* (1), *P. mirabilis* (1)

Other respiratory viruses^f: Influenza virus (1), Bocavirus (1), Human metapneumovirus (1)

rates are among the highest worldwide (at 860 per 100 000 population) [12] and therefore a strong argument could be made for provision of airborne isolation at all inpatient facilities.

Paediatric TB is often considered low-risk for nosocomial transmission, but our cohort of 130 patients had substantial rates of smear-positive and/or drug-resistant disease. Children with TB also stayed significantly longer (increasing TB exposure time on the wards), despite expedited transfer to a regional TB treatment facility. Another consideration in TB-endemic settings is the

presence of undiagnosed or recently diagnosed pulmonary TB in caregivers accompanying hospitalized children, with several documented instances of nosocomial TB transmission [13–17]. Paediatric wards in TB-endemic settings should implement routine symptom screening of adult caregivers and make allowance for additional isolation space for infectious adults, whenever possible.

Most isolation episodes were for IPC purposes, although nursing considerations also influenced isolation room use. Five percent of isolation bed-days were inappropriately used, highlighting the need for a written guideline on

Table 3 Missed opportunities^a for patient isolation (May – October 2014)

Pathogen type and species	Missed isolation (Non-isolated patients with pathogens warranting isolation)						
	May	June	July	August	Sept.	Oct.	Study period
^b MDR bacteria							
Methicillin-resistant <i>S. aureus</i> (MRSA)	3	0	0	1	2	1	7
Carbapenem-resistant <i>A. baumannii</i> (CRAB)	0	1	0	0	0	2	3
MDR <i>P. aeruginosa</i> (MDR PA)	0	0	0	1	2	1	4
Extended spectrum B-lactamase producing (ESBL) Enterobacteriaceae	8	8	5	4	1	3	29
^c <i>M. tuberculosis</i>							
Drug-susceptible (DS)	2	0	3	3	3	5	16
Drug-resistant (DR)	0	0	0	0	0	0	0
Enteric viruses							
Hepatitis A	3	4	5	7	2	2	23
Rotavirus and/or enteric Adenovirus	0	2	2	1	0	0	5
Respiratory viruses							
Respiratory syncytial virus A/B	9	5	2	2	0	1	19
Adenovirus	2	2	3	3	3	1	14
^d Other respiratory viruses	0	3	4	2	2	4	15
Missed patient isolation episodes ^a	27	25	24	24	15	20	135
Inappropriate isolation room use (days) ^e	29	77	7	30	27	1	171

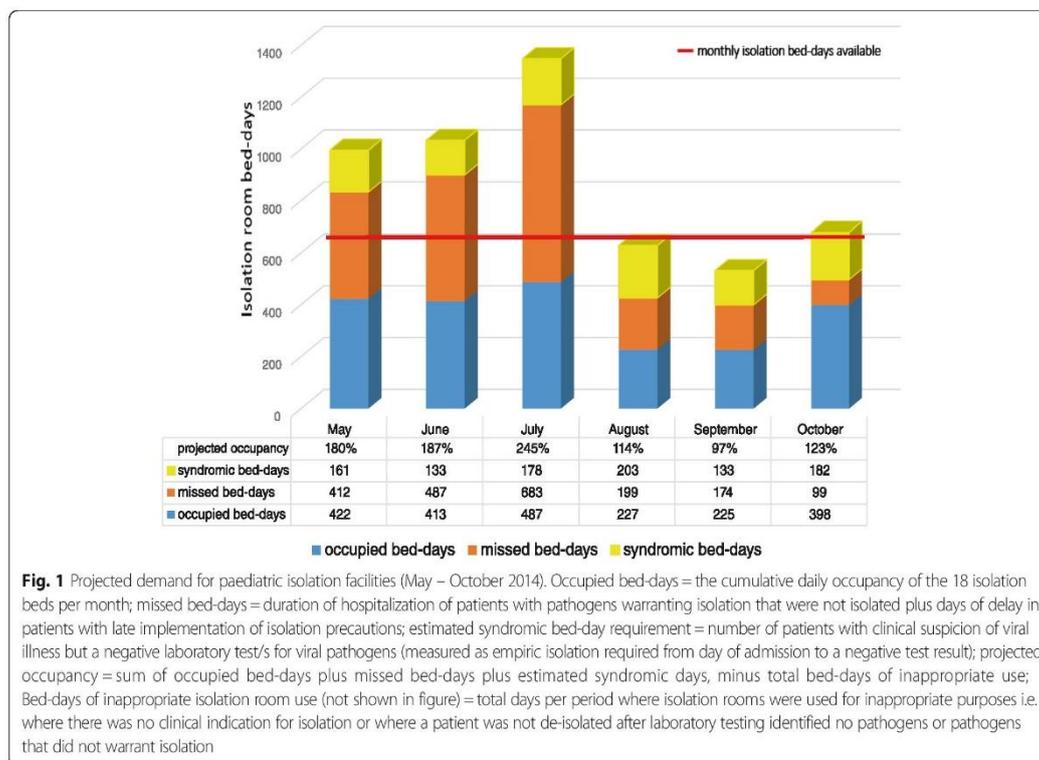
^aMissed patient isolation opportunities = patients with pathogens warranting isolation that were not isolated plus days of delay in patients with delayed isolation; multiple laboratory isolates of the same pathogen from 1/more sites was considered a single infection episode warranting patient isolation

^bMultidrug-resistant (MDR) bacteria isolated from a clinical specimen (blood culture, urine, tissue, pus, wound swab, catheter tip) as per proposed definitions [12] (including methicillin-resistant *S. aureus* [MRSA], carbapenem-resistant *A. baumannii* [CRAB], MDR *P. aeruginosa* [MDR PA] and extended spectrum B-lactamase producing Enterobacteriaceae [ESBL])

^c*M. tuberculosis* (*M.tb*) = any form of drug-susceptible (DS) or drug-resistant (DR) *M.tb* isolated on GeneXpert, smear microscopy or TB culture; Viruses included gastrointestinal and respiratory pathogens identified by rapid assays, ELISA or PCR panels

^dOther respiratory viruses warranting isolation and transmission-based precautions = human rhinovirus, parainfluenza 1/2/3, Influenza A/B and human metapneumovirus

^eInappropriate isolation room use = total days when isolation rooms were used for inappropriate purposes i.e. without a clinical indication, failure to de-isolate after laboratory testing identified no pathogens or pathogens that did not warrant isolation



isolation room usage and better staff education about indications for isolation. More importantly, at least 135 opportunities for patient isolation were missed (mostly for MDR bacterial and viral infections). Notably, there were few missed isolation episodes for TB, possibly owing to heightened awareness of isolation recommendations for TB among clinicians.

If patients with missed isolation episodes had been appropriately isolated, an overall shortage of 761 isolation bed-days would have been experienced during the study period (i.e. 123 % projected occupancy). However, missed isolation episodes also showed seasonal fluctuation with greatest projected demand over winter (peaking at 208 % or a deficit of 608 bed-days in June 2014). The true need for isolation beds (actual usage, missed episodes and syndromic episodes) is underestimated by the laboratory cross-referencing methodology used, which only identifies children who had appropriate laboratory investigation/s requested and whose specimens had a positive yield.

In contrast to a Canadian study [6] with almost universally correct use of precaution signage and reliable availability of personal protective equipment (PPE), our rates of 71 % and 74 % respectively were lower. Ongoing in-service training of staff and a standardized isolation policy should improve these rates. Encouragingly, alcohol-

based handrub was consistently available (89 %), although hand hygiene compliance was lower at 65 %. Concurrently collected hand hygiene audit data on the same wards using the “secret shoppers” method, recorded compliance rates of only 41 % (personal communication, Marina Aucamp, Professional Nurse). The Hawthorne effect (where individuals modify or improve behaviour in response to awareness of being observed) may have resulted in our “higher” compliance rate, but these rates are concerning given that staff knew they were handling infectious patients.

Paediatric staff at our institution [18] self-report high rates of adherence (80 %) to transmission-based precaution recommendations, but observed compliance was low (58 %). Although appropriate PPE was sometimes unavailable, when it was reliably supplied staff either took no precautions or applied only certain aspects. The additional time and effort required to nurse patients under isolation precautions is well-described [19] and may discourage compliance, together with staff shortages and a lack of education about isolation recommendations.

Limitations of this study include: the short duration (6-months) with inability to estimate annual isolation bed demand and evaluate impact of seasonal disease fluctuations; the tertiary hospital setting (with 18

isolation beds) which differs from most “open-plan” paediatric wards in low-middle income settings; the observation process (Hawthorne effect) which may have increased staff compliance; the method for identification of missed isolation episodes based on laboratory isolation of specific pathogens, potentially underestimating the true demand for isolation (particularly if syndromic isolation were to be implemented).

Notwithstanding these limitations, this study of paediatric isolation utilization has relevance for our own institution and paediatric wards in other low-resource, TB-endemic settings. To accommodate for peaks in demand and facilitate implementation of syndromic isolation, we propose that new paediatric facilities in our setting have a minimum of 40 % of available beds as single or double cohort isolation rooms. Provision for airborne precautions (needed for half of all isolation episodes in this setting), should be prioritised in new facilities and for renovations of existing paediatric wards in TB-endemic settings. Sufficient provision should be made for administrative/office space during design of new wards or facilities, to avoid isolation rooms being inappropriately utilized for non-clinical activities. Syndromic isolation for suspected infection should be implemented (with prompt de-isolation after negative laboratory tests), to reduce risk of infection transmission on children’s wards in low-resource settings. To ensure rational and co-ordinated use of isolation beds in our 300-bedded children’s hospital, nursing or infection control practitioners could be trained as isolation bed managers. Staff education, written policies and active management of scarce paediatric isolation resources are required.

Conclusion

Most children admitted to isolation facilities in our TB-endemic setting require airborne precautions. Missed opportunities for patient isolation are common, and could be reduced by implementation of syndromic isolation. Actual and projected demand for isolation facilities exceeds available capacity over the winter season.

Abbreviations

CRAB: Carbapenem-resistant *Acinetobacter baumannii*; DS: Drug-susceptible; DR: Drug-resistant; ESBL: Extended spectrum B-lactamase producing Enterobacteriaceae; HAI: Healthcare-associated infection; HIV: Human immunodeficiency virus; IPC: Infection prevention and control; IQR: Interquartile range; LMIC: Low-middle income country; MDR: Multidrug-resistant; MDR PA: Multidrug-resistant *Pseudomonas aeruginosa*; MRSA: Methicillin-resistant *Staphylococcus aureus*; M.tb: *Mycobacterium tuberculosis*; PMTCT: Prevention of mother to child transmission of HIV; PICU: Paediatric intensive care unit; PPE: Personal protective equipment; TB: Tuberculosis; TCH: Tygerberg Children’s Hospital.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

All authors contributed to study design and critical review of the manuscript. AD carried out the data collection, data cleaning and statistical analysis. All authors read and approved the final manuscript.

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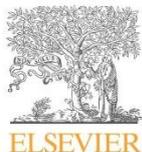


Dramowski A, Whitelaw A, Cotton MF. *Assessment of terminal cleaning in pediatric isolation rooms: options for low-resource settings*. Am J Infect Control. 2016 (in press)

Ineffective terminal cleaning of patient isolation rooms has been implicated in transmission of infection to next room occupants.³⁸⁻⁴² The near-patient hospital environment acts as a reservoir for bacteria, viruses and spores, with viable pathogens persisting on surfaces for up to 30 months.³⁹ Globally, there is renewed interest in the subject of environmental cleaning in healthcare, although published data from Africa is scarce. In addition, few African healthcare facilities have guidelines on environmental cleaning and even fewer perform routine assessment of cleaning adequacy.

We investigated the adequacy of isolation room terminal cleaning and the impact of verbal feedback on cleaning staff performance at Tygerberg Children's Hospital. Three methods of cleaning assessment were utilized (quantitative bacterial surface cultures, adenosine triphosphate [ATP] bioluminescence assays and fluorescent high-touch markers). Of the 25 isolation room terminal cleaning episodes evaluated, 98% and 90% were considered adequately cleaned by ATP assay and aerobic colony counts (ACC) respectively, with few potential bacterial pathogens cultured. All rooms showed significant reduction in ATP relative light units and ACC between pre- and post-cleaning evaluations. The most heavily contaminated surfaces post-cleaning were sinks and mattresses. Fluorescent markers showed sub-optimal cleaning of high touch surfaces, with a 50% overall removal rate post-cleaning.

Cleaning staff performance improved significantly between 'first' and 'subsequent' terminal cleaning episodes following provision of verbal feedback. The sustainability of improved cleaning performance was not assessed owing to the short study duration. Cost, time and resources required for cleaning assessment using ATP and surface cultures far exceeded that needed for fluorescent markers. In low-resource settings, fluorescent markers are an inexpensive option for cleaning evaluation and have the additional benefit of providing immediate visual feedback when training cleaning personnel.



Major Article

Assessment of terminal cleaning in pediatric isolation rooms: Options for low-resource settings

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Key Words:

Patient isolation
Health care-associated infection
Infection control
ATP bioluminescence
Fluorescent markers
Surface cultures

Background: Few studies have evaluated terminal cleaning in low-resource settings.**Methods:** Adequacy of pediatric isolation room terminal cleaning was evaluated using quantitative bacterial surface cultures, ATP bioluminescence assays, and fluorescent high-touch surface markers at Tygerberg Children's Hospital in South Africa (August 1, 2014–October 31, 2015). Cleaning adequacy was assessed by comparing pre- and postcleaning measurements. Influence of verbal feedback was determined by comparing cleaners' first and subsequent cleaning episodes. Cleaning methods were compared for cost, time, and feasibility.**Results:** Adequacy of terminal cleaning was evaluated in 25 isolation rooms after hospitalization for pulmonary tuberculosis (n = 13), respiratory (n = 5) and enteric viruses (n = 5), pertussis (n = 1), and methicillin-resistant *Staphylococcus aureus* (n = 1). Mean aerobic colony counts and mean ATP relative light units declined between pre- and postcleaning evaluations (39 ± 41 to 15 ± 30 [$P < .001$] and 72 ± 40 to 23 ± 11 [$P < .001$]). Fluorescent marker removal was initially poor, but improved significantly at subsequent cleaning episodes (17 out of 78 [22%] to 121 out of 198 [61%]; $P < .001$); mean aerobic colony counts and ATP values also declined significantly following feedback. Cost, time, and resources required for ATP and surface cultures far exceeded that required for fluorescent markers.**Conclusions:** Adequacy of isolation room cleaning improved following feedback to cleaning staff. Fluorescent markers are an inexpensive option for cleaning evaluation and training in low-resource settings.

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BACKGROUND

Health care facilities in low-middle income countries (LMICs) are challenged by a large infectious disease burden, insufficient infrastructure, and limited infection prevention (IP) resources.¹ In particular, hospital isolation facilities are severely limited, impeding implementation of patient isolation for containment of *Mycobacterium tuberculosis* (TB), multidrug-resistant bacteria, and viruses.² Pathogen contamination of the near-patient environment

(ie, surfaces and equipment) occurs by shedding of bacteria-laden skin cells and settling of exhaled droplet nuclei on surfaces. Pathogens are then transmitted by indirect transfer on health care workers' hands or shared equipment, or via direct contact by the next room occupant.³ Experimental studies modeling pathogen transmission routes show rapid contamination of clinical environments through direct and indirect contact. In a study using plant DNA as a marker of contamination, spread from a single contaminated point source (a telephone handle) was confirmed to all clinical areas on a neonatal intensive care unit within 4 hours.⁴

Pathogen transmission from infected or colonized patients establishes an environmental reservoir of bacteria, viruses, and spores that remains a potential source of infection even after the affected patient is discharged.⁵ Prolonged survival of multidrug-resistant (MDR) bacteria and spores in hospital environments is well described; viable *Acinetobacter*, *Pseudomonas*, *Klebsiella*, *Enterococcus*, and *Staphylococcus aureus* species have been isolated from dry hospital surfaces at up to 12–30 months.^{5,6} Persistence of these pathogens in the hospital environment is particularly concerning for LMIC and other settings where environmental cleaning is suboptimal and/or nonstandardized.^{7–9}

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Conflicts of interest: None to report.

All authors contributed to study design and critical review of the manuscript. AD carried out the data collection, data cleaning, and statistical analysis. All authors read and approved the final manuscript.

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Renewed interest in environmental cleaning for health care-associated infection (HAI) prevention has been generated by studies linking nosocomial infection risk to contamination of patient environments.¹⁰⁻¹³ The role of a contaminated hospital environment in pathogen acquisition has been established through prior room occupancy studies. Isolation of the same pathogen from a prior room occupant and a new patient (with no epidemiologic link) implicates the near-patient environment as an important source for pathogen transmission. Next room occupants have an estimated 1.5-4.5 fold increased risk of acquiring a bacterial pathogen that caused infection in the prior room occupant.^{7,14,15} This mode of infection has been demonstrated for a variety of organisms, including *Clostridium difficile*,¹⁵ methicillin-resistant *S aureus* (MRSA),¹⁶ and multidrug-resistant gram-negative bacilli.¹⁷ Further compelling evidence for the role of the hospital environment in infection transmission is reduced HAI incidence when frequency and/or adequacy of environmental cleaning is increased.^{7,18,19} Enhanced environmental cleaning is also frequently implemented as part of a multimodal outbreak control intervention, highlighting the hospital environment as a reservoir for pathogen persistence.^{5,11}

Given the elevated risk for HAI with suboptimal environmental cleaning, effective and evidence-based guidelines for terminal or postdischarge cleaning of isolation facilities are needed. Although widely available and implemented in high-income settings,²⁰⁻²² standard and terminal cleaning guidelines are lacking in many resource-constrained hospitals. A further challenge is the lack of standardized definitions and methods to determine whether surfaces are in fact clean, because visual assessment of cleanliness does not correlate with microbiologic evidence of reduced contamination.²³

Environmental surface cultures, fluorescent marker removal,^{23,24} and ATP bioluminescence assays^{25,26} are the most commonly employed cleaning evaluation methods in high-income settings.^{7,27} Data on adequacy of terminal cleaning in low-resource health care facilities is lacking, with no guidance for suitable and cost-effective cleaning evaluation methods. We conducted a multimodal evaluation of isolation room terminal cleaning and measured influence of verbal feedback to cleaners on the adequacy of terminal cleaning at a pediatric referral hospital in Cape Town, South Africa.

METHODS

Setting

The Tygerberg Children's Hospital (TCH) has 300 pediatric beds within a large (1,384-bed) academic hospital complex. Sick neonates, infants, and children (aged 0-14 years) are admitted to 13 neonatal and pediatric wards (including surgical, medical generalist, specialty, and intensive care facilities). The burden of infectious diseases is high, with HIV and TB disease, lower respiratory tract infections, gastroenteritis, and bacterial infections predominating. Among pediatric bloodstream infection (BSI) isolates, gram-negative pathogens predominate and overall rates of antimicrobial resistance are high. Among hospital-acquired BSI pathogens, 78% of *Klebsiella pneumoniae* are extended spectrum β -lactamase producers, 22% of *Escherichia coli* produce extended spectrum β -lactamase, 72% of *Acinetobacter baumannii* exhibit MDR, and 65% of *S aureus* are methicillin-resistant.²⁸ Among children isolated for culture-confirmed TB, drug-resistant isolates are common (20% MDR, 2% extensively drug-resistant, and 4% rifampicin monoresistant).²⁹ Five pediatric wards have 18 single rooms available for patient isolation (50% with negative pressure ventilation), with priority given to patients requiring airborne or droplet precautions. Isolation bed demand²⁹ is high, especially in winter, with staff required to rapidly turn over rooms for admission of new patients requiring isolation.

Each ward averages 28 beds serviced by 1 permanent cleaning staff member, under direct supervision of the ward nursing managers.

Terminal cleaning

Indications for isolation room terminal cleaning (after patient discharge) include any patient isolated under transmission-based precautions; for example, airborne (TB), droplet (respiratory and gastrointestinal viruses), and contact (MDR bacterial infections).² The hospital's unit for infection prevention and control gives annual training in cleaning methods, but without routine evaluation of terminal cleaning adequacy. The recommended method for terminal cleaning at our institution includes disposal of all nonfixed items followed by cleaning of surfaces and furniture with water and detergent. Once dry, surfaces are wiped with disinfectant (usually 70% alcohol; sodium hypochlorite is only used for patients with *Clostridium difficile* infection).

Study design

Contamination of pediatric isolation rooms on patient discharge was evaluated (before and after terminal cleaning) between August 1, 2014, and October 31, 2015. Three methods were used: fluorescent markers, ATP bioluminescence assays (CleanTrace swabs and a portable luminometer from 3M Health Care), and bacterial surface cultures. Adequacy of cleaning was established by comparing pre- and postcleaning measurements for each room. Following first measurement of cleaning adequacy, each cleaner received individual verbal feedback. The influence of verbal feedback to cleaners was determined through comparison of measurements for cleaners' first and subsequent cleaning episodes (each cleaner was assigned a unique code). The cost (including consumables and labor), time, and equipment required for each cleaning evaluation method was documented.

Sample collection

Surface swabs (using a cotton swab premoistened with sterile water) were collected from 5 surfaces (ie, bedrail, bedside table, sink, door handle, and mattress) before and after terminal cleaning. ATP relative light unit (RLU) readings were measured on 4 surfaces (ie, bedrail, bedside table, sink, and mattress) using CleanTrace swabs before and after terminal cleaning. For this study, surfaces measuring <100 RLU were considered clean, although there is considerable disagreement in published literature regarding cutoffs for cleanliness.²⁷ We applied the ultraviolet (UV) disclosing lotion GlitterBug Potion (Brevis Corp, Salt Lake City, UT) to flat surfaces using a cotton bud in a circular motion, creating a UV marker diameter of approximately 3 cm. Between 10 and 13 fluorescent marks were placed on high-touch surfaces in each room before cleaning (eg, bedrail, bedside table, sink tap, light switch, and door handle); the proportion of marks removed postcleaning was recorded.

Laboratory methods for surface cultures

Cotton swabs premoistened with sterile water were used to sample a prestandardized area of the bedrail, bedside table, sink, door handle, and mattress. In the laboratory, swabs were immersed in 1 ml sterile water and vortexed for 30 seconds; a new sterile swab was used to inoculate a blood agar plate that was incubated at 37°C for 48 hours. Aerobic colony count (ACC) was recorded for each plate and each unique colony was Gram stained. Gram-positive cocci were identified as being *S aureus*, coagulase-negative staphylococci, enterococci, or streptococci through catalase testing, pyrrolidonyl aminopeptidase activity, and/or latex

agglutination (Pastorex Staph-Plus; Bio-Rad, Redmond, WA). Gram-negative isolates were identified using the automated Vitek-2 system³⁰ (BioMerieux, Marcy-l'Étoile, France). Agar plates with common commensals (as defined by the Centers for Disease Control and Prevention)³¹ were classified as "normal flora"; agar plates with any other organisms (such as *S aureus*, enterococci, and gram-negative bacilli) were classified as "potential pathogens."

Statistical analysis and ethical approval

Descriptive statistical analyses were performed using Stata Statistical Software version 13.0 IC (StataCorp LP, College Station, TX). The proportion of surfaces considered clean pre- and postcleaning was compared using the χ^2 test. ACC and ATP RLU readings (pre- vs postcleaning) were compared using a Student *t* test, and entered into a multivariate model to assess effect of cleaner code and cleaning indication. Mean colony counts, ATP RLU readings, and proportion of fluorescent marks removed postcleaning were compared for cleaning personnel's first and subsequent cleaning episodes. A *P* value below .05 was considered statistically significant. Figures were designed using SPSS Statistics for Windows, version 21.0 (IBM-SPSS Inc, Armonk, NY) and Graphpad Prism 6 (GraphPad Software Inc, La Jolla, CA). Ethical approval was obtained from the Human Health Research Ethics committee of Stellenbosch University (S13/09/171).

RESULTS

Adequacy of terminal cleaning was measured in 25 pediatric isolation rooms. Indications for isolation were pulmonary TB (*n* = 13), adenovirus (*n* = 3), hepatitis A (*n* = 4), rotavirus (*n* = 1), varicella zoster (*n* = 1), paramyxovirus (*n* = 1), pertussis (*n* = 1), and MRSA (*n* = 1). The 25 isolation rooms underwent terminal cleaning by 7 cleaners (an average of 3.6 terminal cleaning episodes observed per cleaner), generating data on 7 first and 18 subsequent cleaning episodes.

Mean ACC declined significantly between pre- and postcleaning evaluations (39 vs 15; *P* < .001) (Table 1). Bacterial growth from isolation room surfaces before cleaning (mean ACC) varied from most contaminated (sinks [*n* = 85], bedside tables [*n* = 37], and mattresses

[*n* = 35]) to least contaminated (bedrails [*n* = 22] and door handles [*n* = 15]). Postcleaning, sinks and mattresses remained the most contaminated surfaces (mean ACC, 49 and 10, respectively). For all cleaning personnel, mean postcleaning ACC values declined significantly between first and subsequent cleaning episodes (*P* < .001). Few potential pathogens were cultured (*n* = 27; 19 out of 27 [70%] from sinks), including *Stenotrophomonas maltophilia* (*n* = 6), *Pseudomonas* species (*n* = 5), *Enterobacter cloacae* (*n* = 4), *Brevundimonas diminuta* (*n* = 3), *Acinetobacter* species (*n* = 3), *Enterococcus* species (*n* = 2), *Sphingomonas paucimobilis* (*n* = 2), *Chryseomonas indologenes* (*n* = 1), and *Shewanella putrefaciens* (*n* = 1). Coagulase-negative staphylococci and environmental flora predominated on all surfaces, including *Micrococcus*, *Bacillus*, fungal species, and *Delftia acidovorans* (Table 1).

Mean ATP RLU values for 4 surfaces (ie, bedrail, bedside table, sink, and mattress) were low before cleaning (72 ± 40) and decreased further postcleaning (23 ± 11) (*P* < .001) (see Fig 1). Similarly, the number of surfaces considered clean (<100 RLU) increased significantly postcleaning (*P* < .001). Levels of contamination before cleaning did not vary significantly between different surfaces with mean ± standard deviation ATP RLU values for bedside tables of 94 ± 83, sinks 84 ± 72, mattresses 72 ± 86, and bedrails 60 ± 40. There was no difference in ATP reduction pre- and postcleaning by indication for terminal cleaning (TB vs non-TB; *P* = .62) or by cleaner code (*P* = .74). For all cleaning personnel, mean ATP RLU declined significantly between first and subsequent room cleaning episodes, after receiving verbal feedback on cleaning adequacy (*P* < .001) (Fig 2).

Of the 276 fluorescent (UV) marks placed on high-touch surfaces in the 25 isolation rooms, 138 (50%) were removed postcleaning. However, adequacy of fluorescent marker removal improved following verbal feedback (Fig 3), with an increased proportion removed between first and subsequent room cleaning episodes (17 out of 78 [22%] vs 121 out of 198 [61%]; *P* < .001). Some surfaces (ie, toilet seats, flush handles, paper towel dispensers, and door handles) showed no or marginal improvement in marker removal; these were also the least frequently cleaned surfaces in the first cleaning episode.

Cost, time, and resources to conduct ATP bioluminescence and surface cultures (ACC) far exceeded that required for fluorescent markers (Table 2). In addition, cleaners responded better to visual and verbal feedback provided from the fluorescent markers than

Table 1
Multimodal assessment of isolation room terminal cleaning (*n* = 25)

Cleaning assessment method	Precleaning	Postcleaning	<i>P</i> value
Agar plates* exhibiting no growth	17/125 (14)	72/125 (58)	<.001
Agar plates exhibiting growth of normal flora	88/125 (70)	46/125 (36)	<.001
Agar plates exhibiting growth of potential pathogens [†]	20/125 (16)	7/125 (6)	.01
Pooled (all surfaces) aerobic colony count	39 ± 41	15 ± 30	<.001
Sink	85	49	-
Bedside table	37	8	-
Mattress	35	10	-
Bedrail	22	5	-
Door handle	15	2	-
ATP RLU (mg/L)	72 ± 40	23 ± 11	<.001
Proportion of surfaces with ATP RLU < 100	28/100 (28)	98/100 (98)	<.001
Proportion of fluorescent markers removed	n/a	138/276 (50)	n/a

NOTE. Values are presented as *n* (%), mean ± standard deviation, or *n*. *n/a*, not applicable; RLU, relative light units.

*Each isolation room had 5 surfaces cultured pre- and postcleaning (hence 125 agar plates).

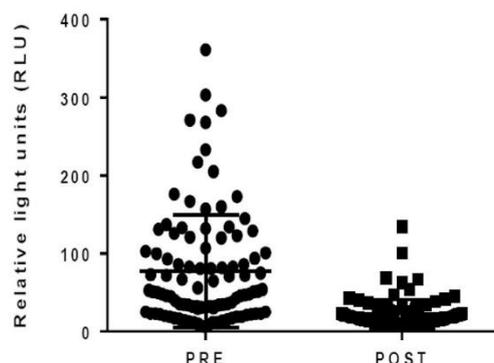
[†]Agar plates with common commensals (as defined by the Centers for Disease Control and Prevention)³¹ were classified as "normal flora"; agar plates with any other organisms (such as *Staphylococcus aureus*, enterococci, and gram-negative bacilli) were classified as "potential pathogens."

Table 2
Comparison of cost, time, and resources required for evaluation of terminal cleaning

Variable assessed	Bacterial surface cultures	ATP bioluminescence	Fluorescent surface markers
Mean time to final evaluation result	52-96 h	10 min	10 min
Average cost* per isolation room cleaning evaluation (\$)	43	21	0.4
Laboratory facilities required	Yes	No	No
Specialized equipment needed	Laboratory facilities	Luminometer and ATP swabs	Fluorescent gel and ultraviolet light
Real-time feedback possible	No	Yes	Yes

*The average cost for cleaning evaluation per isolation room was calculated as follows: bacterial surface cultures (10 × blood agar plates, Gram stains, microscopy, biochemical tests and VitekID (BioMerieux, Marcy-l'Étoile, France) culture identification for Gram-negative isolates); ATP bioluminescence (8 × UXL100 Clean-Trace surface ATP test swabs from 3M Health Care, St. Paul, MN); fluorescent surface markers (total cost of UV disclosing lotion [GlitterBug Potion, Brevis Corp, Salt Lake City] and one handheld UV light source/25 rooms).

Comparison of surface contamination as measured by ATP levels



ATP levels of isolation room surfaces pre- vs post-terminal cleaning

Fig 1. Decline in ATP relative light unit readings after terminal cleaning of isolation rooms.

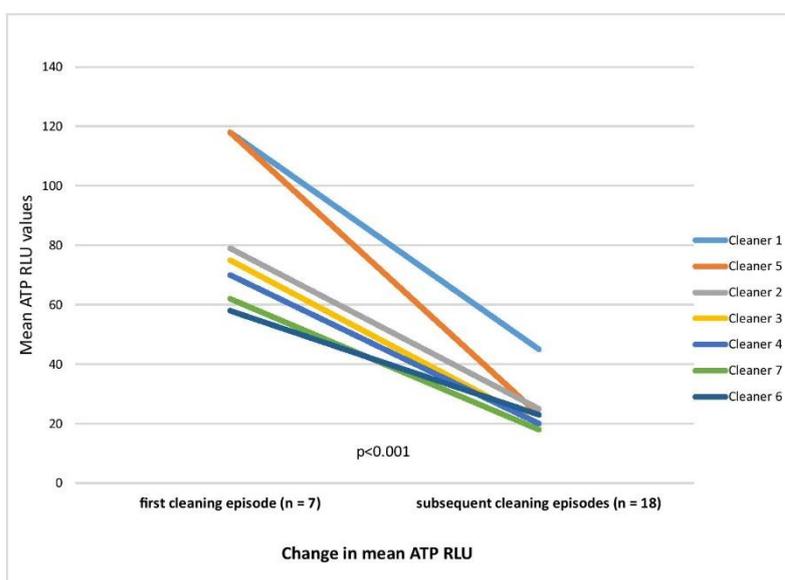


Fig 2. Decline in ATP relative light unit readings, by cleaner.

demonstration of the ATP RLU readings or ACC data. Two cleaners who were observed over 9 months achieved sustained improvement in marker removal.

DISCUSSION

This study measured adequacy of pediatric isolation room terminal cleaning and evaluated 3 cleaning assessment methods available in our setting. Unlike nonteaching hospitals in South Africa, our institution has significantly greater IP resources, policies, and procedures (including a terminal cleaning policy, room cleaning checklist, and annual training of cleaning personnel). However, even in this relatively well-resourced facility there are no guidelines for cleaning evaluation and adequacy of terminal cleaning is not as-

sessed. Given that visual inspection of cleanliness is unsatisfactory, LMIC health care facilities require guidance on objective, affordable, and standardized methods for evaluating environmental cleaning quality. Additional barriers to improving environmental cleaning (although not unique to LMIC), include rapid turnover of cleaning personnel and shortage of qualified IP staff for training and evaluating cleaning programs.

Our study isolated few bacterial pathogens from surfaces, possibly implying low risk of transmission to subsequent occupants of pediatric isolation rooms. We did identify several gram-negative bacilli (*Acinetobacter*, *Pseudomonas*, and *Enterobacter*) and enterococci, which are among the top-10 BSI pathogens in our pediatric wards.²⁸ Despite our study's low measured ACC of surface cultures, infectious dose for some pathogens is very low (eg, MRSA at

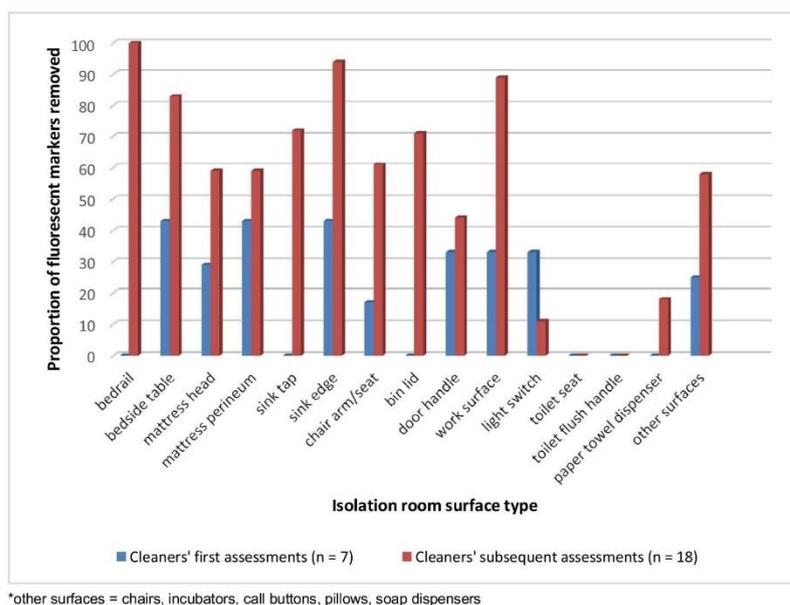


Fig 3. Fluorescent marker removal at first versus subsequent cleaning assessments.

4 CFU and norovirus at 20 virions) implying that even low-level environmental contamination may pose a risk to the next room occupant.¹¹ In addition, we isolated other bacteria (environmental flora and coagulase-negative staphylococci) that may cause opportunistic infections in severely immunocompromised hosts (eg, those with HIV, malnutrition, and prematurity). Possible explanations for the low yield of pathogens on surface swabs may be truly low contamination of the surfaces, suboptimal sampling volume, poor standardization of swabbing technique (ie, pressure and contact time), poor viability of bacteria on the cotton swabs, and variable release of bacteria on the cotton swab into the diluent.³²

Postterminal cleaning, sinks and mattresses remained the most bacterially contaminated surfaces in our pediatric isolation rooms probably due to promotion of bacterial growth in moist environments. Outbreaks arising from contaminated water sources (particularly hospital sinks) are commonplace in the literature,³³⁻³⁶ and interventions aimed at eliminating water from the patient environment or disinfecting sinks have been effective at reducing HAI and/or colonization with gram-negative pathogens.^{37,38}

Of the 25 terminal cleaning episodes evaluated, 98% of rooms were considered adequately cleaned by ATP assay and 90% by bacterial surface cultures (ACC). The low mean ATP RLU readings and bacterial surface ACC (even before cleaning) was surprising, given recently published data on contamination of mattresses in our institution.³⁹ These mattresses were located mostly in wards with high patient turnover and high potential for bodily fluid contamination (maternity and casualty wards with average length of stay <48 hours). An explanation for the low contamination rate of our pediatric isolation rooms may be that there was comparatively little body fluid surface contamination. Although low ATP RLU readings may reflect minimal organic matter on the sampled surfaces, other problems with this method include poor sensitivity, major variability between ATP measurement systems, or even interference by residual disinfectants.¹¹ Even with a very stringent ATP threshold level (<100 RLU), we achieved a total of 98% of surfaces that were considered clean after terminal cleaning.

Compared with bacterial ACC and ATP RLU readings, cleaners' performance at fluorescent marker removal from high touch surfaces was suboptimal (only 50% of fluorescent markers on high touch surface were removed by cleaning). This is not dissimilar to high-touch surface marker removal rates reported from a high-income setting (49%).⁴⁰ Despite initially low marker removal rates, all 7 cleaners in our study achieved substantial improvement after feedback on which high touch surfaces had been missed. However, improvement of proportion of marker removal was minimal for light switches, toilets, and flush and door handles, which is worrying given the potential for contamination of these surfaces. A study evaluating cleaning in 23 US acute-care hospitals found similar variation in removal of UV marks on toilet handholds, light switches, and door-knobs (mean cleaning rate, <30% for these surfaces).⁴⁰

Hospitals in high-income settings have benefited from enhanced monitoring of environmental cleaning, although most studies show decline in cleaning performance after monitoring is discontinued.^{7,13,23,24} Given the universal difficulty in sustaining improvement in environmental cleaning, a randomized trial piloting an environmental cleaning bundle is underway at 11 Australian hospitals to inform best practice in hospital cleaning training, policy, and practice.⁴¹ Although the duration and number of observations in our study was limited, 2 cleaners observed for more than 9 months achieved sustained improvement in mark removal. In the absence of other changes to cleaning personnel training during the study period, the improved cleaning adequacy is likely related to immediate feedback on cleaning performance after each first cleaning episode. The study provided an additional opportunity for one-on-one training of cleaning personnel, with suggestions for improved cleaning tailored to initial performances. A secondary benefit of sharing the environmental cleaning evaluation results with cleaning personnel and nursing managers was increased awareness of the hospital environment's role in health care-associated infection. This realization will hopefully also lead to improved recognition of cleaning personnel's contribution to patient safety. Despite the resource limitations in LMIC (ie, financial, IP personnel, and

laboratory services), the inexpensive and easy-to-use fluorescent marker method for cleaning evaluation is suitable (with appropriate training and guidelines). As an environmental cleaning quality improvement tool, fluorescent markers could also be of value in nonisolation patient areas.

Limitations of this study include that no environmental sampling was performed for *Mycobacterium tuberculosis*, fungi, or viruses; to reduce laboratory costs only gram-negative isolates underwent formal identification; only surfaces and permanent room fixtures were tested (ie, cleaning of portable equipment such as saturation monitors and infusion pumps was not assessed); a relatively small number of isolation rooms were evaluated owing to the fact that many patient discharges and terminal cleaning episodes occurred after hours; although luminometer calibration was performed before each test, only a single ATP surface swab was obtained from each surface type pre- and postcleaning; and given the short study duration, sustainability of improvements in cleaning adequacy were not assessed.

Nevertheless, this study of pediatric isolation room terminal cleaning has relevance for our own and similar institutions. Fluorescent surface markers for assessing adequacy of high-touch surface cleaning are inexpensive, easy-to-use, and can provide visual demonstration and feedback to cleaners in real time. Given the utility of this method and the risk of pathogen transmission to subsequent isolation room occupants, IP practitioners in low-resource settings should strongly consider use of fluorescent markers both to evaluate environmental cleaning and to train cleaning personnel.

CONCLUSIONS

There are limited data to inform best practice for terminal cleaning evaluation in resource-limited settings. Our study confirms that fluorescent markers are a feasible and inexpensive cleaning assessment method. In addition, UV markers provided visual feedback of cleaning efficacy, with improved cleaning performance of staff following verbal feedback.

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Chapter 5

Healthcare workers' knowledge, attitudes and practices regarding paediatric healthcare-associated infection

Dramowski A, Whitelaw A, Cotton MF. *Healthcare-associated infections in children: knowledge, attitudes and practices of paediatric healthcare providers at Tygerberg Hospital, Cape Town. Paediatr Int Child Health. 2016; 36(3);225-231.*

Publications reporting paediatric healthcare providers' infection prevention (IP) and healthcare-associated infection (HAI) knowledge, attitudes and practices (KAP) are extremely limited; a single publication of IP knowledge and attitudes in an Egyptian paediatric intensive care unit was identified.⁵⁸ We conducted a KAP study regarding paediatric HAI to better understand the IP training needs of Tygerberg Children's Hospital staff. Two-thirds of paediatric staff participated including nursing, medical, allied health staff and health science students.

Several important misconceptions regarding infection transmission routes and hand hygiene methods were documented in the knowledge survey. Substantial differences in attitudes and reported practices regarding IP and HAI were demonstrated for nursing versus medical personnel, with nurses generally having more favourable attitudes and reportedly greater adherence to IP recommendations. Regression analysis highlighted that: younger staff members were more likely to be influenza vaccinated (although overall annual uptake was only 25%); presenteeism was 19 times more prevalent among medical staff; nursing staff were 3 times more likely to adhere to precautions and 19-fold more likely to use personal protective equipment, although N95 respirator fit-testing rates were lowest among nurses (21%). There was surprisingly widespread support for use of punitive measures for staff who disregard IP recommendations and for the suggestion to report all paediatric HAI as adverse events.

Our study contributes to the limited literature on HAI KAP of African healthcare workers and identifies opportunities for improved IP training and practice among staff at Tygerberg Children's Hospital.

Original Research Paper

Healthcare-associated infections in children: knowledge, attitudes and practice of paediatric healthcare providers at Tygerberg Hospital, Cape Town

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Background: Healthcare (HC) providers' knowledge, attitudes and practices with regard to infection control (IC) may positively or adversely affect rates of institutional healthcare-associated infection (HAI).

Objectives: To determine paediatric HC providers' knowledge, attitudes and practices regarding HAI and guide IC interventions in a resource-limited setting.

Methods: Paediatric HC providers at Tygerberg Children's Hospital, Cape Town, South Africa completed an anonymous, self-administered, 37-item questionnaire.

Results: Questionnaires (201, 66.6% participation rate) were completed by medical (90, 44.7%), allied health (16, 8%) and nursing providers (95, 47.3%). Median age was 34 years (IQR 27–43), and 84% were female. Knowledge scores were low [57% correct, mean (SD) 7.7 (1.7)/14 questions] but higher in the medical/allied category ($P \leq 0.001$) and those qualified for ≥ 10 years ($P = 0.008$). Providers lacked knowledge of the main routes of infection transmission and misunderstood hand hygiene and terminal cleaning recommendations. Nurses scored higher for attitude questions [63% desired responses, mean 5 (1.2)/8 questions] ($P = 0.02$). Only 38% reported adequate undergraduate teaching on HAI and most (93%) wanted more in-service IC training. Providers agreed with punitive measures for colleagues ignoring IC recommendations (89%). Nurses scored higher for practice questions [53% desired responses, mean 3.2 (1.2)/6 questions] ($P \leq 0.001$). Self-reported adherence to IC recommendations was high, 88% for hand hygiene and 74% for use of personal protective equipment. However, there was poor uptake of annual influenza vaccination (25%) and N95 respirator fit-testing (28%), and many felt obliged to report for work when sick (67%).

Discussion: Expanded in-service and undergraduate training in IC should emphasize methods of hand hygiene and routes of infection transmission. Paediatric providers support mandatory reporting of HAI events and stricter enforcement of IC recommendations.

Keywords: Paediatrics, Healthcare-associated infection, Infection prevention and control, Nosocomial infection, KAP survey

Abbreviations: HAI, healthcare-associated infection, HC, healthcare, IC, infection control, IQR, interquartile range, IPC, infection prevention and control, KAP, knowledge attitudes and practice, NS, not significant, PPE, personal protective equipment, TBP, transmission-based precautions, TCH, Tygerberg Children's Hospital

Introduction

Healthcare-associated infection (HAI) is the most common complication of hospitalization, increasing healthcare costs, morbidity and mortality.¹ Hospitalized children are at increased risk for HAI due to immunological immaturity,

underdeveloped mucosal barriers and increased handling by healthcare staff.² In low-resource settings, children face additional risks for HAI including host factors (malnutrition, HIV) and health system factors [overcrowding, poor infrastructure and lack of provision for infection control (IC)].³ In the largest paediatric surveillance study to date, the European Centres for Disease Control (ECDC) estimated an HAI point prevalence of 4.2% (95% CI 3.9–4.5)

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in hospitalized children in 29 countries.⁴ Although prevalence data from African children are lacking, HAI prevalence rates are estimated to be at least double that of high-income countries.^{3,5,6}

Understanding the influence of institutional culture and attitudes on healthcare provider behavior is key to the appropriate selection of HAI prevention strategies. Many educational and other interventions for HAI prevention are simple and affordable,⁷ but adaptation to local circumstances, cultures and patient populations is needed. In addition, knowledge gain alone has limited impact on healthcare provider practice.^{8,9} Knowledge, attitudes and practice (KAP) surveys can provide useful baseline data to inform IC programmes and guide interventions for HAI reduction.

Several KAP studies of healthcare providers in low-resource settings have been published about IC^{10–13} and HAI,^{14,15} but KAP studies of paediatric healthcare providers are scarce.¹⁶ To identify deficits in knowledge, attitude and practice and guide future IC interventions in Cape Town, a survey of hospital-based paediatric HC providers' KAP regarding HAI was conducted.

Methods

Setting and patient profile

The Tygerberg Children's Hospital (TCH), Cape Town, South Africa has 300 beds and is located within a large academic hospital (1384-bed capacity). Sick neonates, infants and children (0–14 years) from Cape Town's Metropole East are admitted to 13 dedicated neonatal and paediatric wards (including surgical and medical generalist, specialist and intensive care facilities). HC providers (medical and nursing) are dedicated to the paediatric platform. Allied health providers (dietitians, occupational therapists and physiotherapists) provide hospital-wide services.

The hospital has an on-site Unit for Infection Prevention and Control (IPC). Routine microbiology laboratory data are used for surveillance of selected HAI types and specified bacterial 'alert' pathogens. Four infection prevention nurse practitioners are employed (1:350 patients), with one dedicated to paediatric disciplines. A recently established IPC 'link nurse' programme facilitates sharing HAI data and IC best practice with ward nursing staff. An on-site Occupational Health Service offers free annual influenza vaccination to HC providers. A national healthcare quality improvement plan¹⁷ was launched in 2012, with the inclusion of minimum IPC standards; IPC compliance was measured at 50% in the baseline nationwide audit.¹⁸

The profile of children admitted to TCH is varied. Neonates account for 35% of all admissions with 6000 births annually, a 37% low-birthweight rate and an antenatal maternal HIV prevalence of 16.9% in 2012.¹⁹ Among paediatric inpatients, lower respiratory tract infection, gastro-enteritis and malnutrition are the most common diagnoses. Paediatric antiretroviral therapy is widely available, and improved access to vertical transmission

prevention programmes had reduced HIV transmission rates to $\leq 4\%$ by 2010.²⁰ Immunisation coverage in the Cape Metropolitan area in 2011/12 was 87.5% for infants ≤ 1 year of age.²¹

Study design and participants

The anonymous KAP questionnaire was completed between 1 May and 31 July 2014. Paediatric medical staff [including interns, medical officers, registrars (residents) and consultants (attending paediatricians)] were invited to complete the survey electronically via an online link to our university-hosted REDCap²² server. Medical staff who did not respond to the original request to participate received a second electronic invitation after 30 days. A convenience sample of paediatric nurses (staff, enrolled and professional) and allied health providers completed the questionnaire manually. Investigators visited each of the 13 paediatric and neonatal wards three times during the study period. All nursing and allied health providers on duty on the wards during each day-time visit were approached and personally invited to participate, after an explanation of the study's purpose. Written informed consent was obtained and the questionnaires (which were completed in the providers' language of choice, English or Afrikaans) were collected immediately after completion.

Data management and statistical analysis

Data from the manually completed questionnaires were added to the electronic responses from the medical staff in the REDCap database. Data were analysed using Stata Statistical Software version 13.0 IC (StataCorp LP, College Station, TX). Frequencies were used to describe the study population demographics. Mean scores for knowledge (K), attitudes (A) and practice were compared by job category (nursing vs medical) using a two-sample *t*-test and for years of experience using one-way ANOVA. Individual question scores were compared by job category using the Pearson χ^2 test. $P \leq 0.05$ was considered statistically significant. The following possible predictors were included in a linear regression model evaluating their association with K and A scores (reporting adjusted co-efficients), and in a logistic regression model evaluating their association with self-reported practices (reporting adjusted odds ratios): job category (nursing vs medical); age; gender; professional vs student status and years of work experience. Responses to the open-ended questions were coded using Atlas.ti version 7.0 software (Berlin, Scientific Software Development, 1999) and categorised by framework analysis²³ into emerging themes.

Ethics approval

Approval was obtained from the Human Health Research Ethics committee of Stellenbosch University (S13/09/171) and all survey participants provided individual electronic or written, informed consent.

Results

Of 302 eligible paediatric HC providers, 201 (66.6%) completed questionnaires either manually (111, 55.3%) or electronically (90, 44.7%); there was no difference in response rates by method of questionnaire completion ($P=0.39$). Participants were young (median 34 y, IQR 27–43), predominantly female (84%) and included the following provider categories: nursing (95, 47.3%), medical (90, 44.7%) and allied health (16, 8%) (Table 1). The medical providers were younger and included more males than the nursing providers ($P\leq 0.0001$ and $P=0.04$, respectively).

Knowledge

Overall K scores were low [57% correct, mean 7.7 (1.7) of 14 questions] but higher in the medical/allied category and those qualified for ≥ 10 years ($P\leq 0.0001$, $P=0.008$, respectively). Many providers (particularly nurses, $P\leq 0.0001$) were unfamiliar with the definition of HAI, but most correctly identified young age and invasive procedures as important HAI risk factors (Table 2). Knowledge of routes of infection transmission was poor, with most nurses (85%) incorrectly identifying the environment as the predominant source of HAI. Less than half of the participants (48%) believed that alcohol hand-rub was an acceptable alternative to hand-washing with soap and water. Providers misunderstood indications for terminal cleaning, with 84% believing it should be performed in all areas after patient discharge. They were also unfamiliar with the HAI reporting format used in our institution (rate/1000 inpatient days), and 86% erroneously believed that the IC service performed active surveillance for all types of HAI.

Attitudes

Attitude questions received 63% desired responses overall [mean 5 (1.2) of 8 questions] with higher scores among nurses ($P=0.02$) (Table 3) and students (Table 4). Few providers (38%) believed they had received adequate undergraduate teaching on HAI. Almost half (48%) considered HAI an inevitable part of healthcare. Only 22% of medical vs 56% of nursing staff thought that the paediatric

wards had adequate patient isolation facilities ($P\leq 0.0001$). The idea of punitive measures for colleagues who ignored IC recommendations received widespread support (89%). More doctors (86%) than nurses (64%) agreed with the suggestion that HAIs should be reported as adverse events ($P\leq 0.0001$). Most participants (93%) wanted in-service IC training and reported a positive attitude to IC (72%).

Practice

Practice questions received 53% desired responses overall [mean 3.2 (1.2) of six questions] with higher scores among nurses ($P\leq 0.0001$) (Table 3). Self-reported adherence to IC best practice was high: hand hygiene (88%), use of personal protective equipment (74%) and transmission-based precaution recommendations (80%). For all three measures, nurses reported higher adherence rates ($P\leq 0.0001$) (Table 4). However, providers had poor uptake of annual influenza vaccination (25%) and most (especially doctors, $P\leq 0.0001$) felt obliged to report for work when sick (95% vs 55%). Uptake of N95 respirator fit-testing was poor (28%).

Qualitative data

Two open-ended questions were posed to participants: what factors contribute to HAI development in the paediatric wards, and what can be done to reduce paediatric HAI at our institution?

Poor IC practices emerged as a major theme with participants citing low hand-hygiene compliance and low use of protective equipment, sharing of equipment between patients, poor aseptic technique for procedures, unnecessary indwelling devices and antibiotic overuse. Participants noted that although IC policies and protocols were in place, they were seldom followed. Infrastructural and system challenges were another prominent theme and included overcrowded wards, understaffing, lack of isolation facilities, poor use of triage/patient cohorting strategies and inadequate ventilation. Some participants noted insufficient provisions for IC (hand-hygiene consumables and personal protective equipment) on the wards. The lack of education/training in IC and a perceived lack of an institutional culture of patient safety emerged as major themes. Providers also noted the absence of screening procedures for illness (e.g. undiagnosed tuberculosis) and basic IC education for caregivers/parents as a possible cause of infection transmission.

Three themes for potential interventions to reduce paediatric HAI emerged: resources, practices and education with feedback. Participants highlighted the need for additional human resources (especially nurses) to increase the staff-to-patient ratio. Other key resources requested were provision of alcohol hand-rub at every bedside and additional patient isolation beds. The best practices advocated for reducing HAI were: rapid patient triage/cohorting, early discontinuation and reduction of broad-spectrum

Table 1 Demographics of paediatric healthcare providers (n=201)

Variable	Frequency	%
Age, yrs, median, IQR	34	IQR 27–43
Gender (female)	169	84.1
Job category		
Medical doctor	90	44.8
Nurse	95	47.2
Allied health professional*	16	8
Healthcare experience, yrs		
0 (healthcare student)	43	21.4
≤5	18	9
5–10	51	25
≥10	89	44.6

IQR, interquartile range; * allied health professional: dietician, occupational therapist, physiotherapist

Table 2 Knowledge of healthcare-associated infection (HAI)

Knowledge questions (maximum score 14)	Total n = 201	Nursing n = 95	Medical* n = 106	P-value
Mean score (SD)	7.7 (1.7)	7.2 (1.5)	8.2 (1.7)	≤0.001
True/false questions (correct response)			Correct responses, n (%)	
1. The environment (air, surfaces, water) is the major source of bacteria causing HAI (nosocomial) infections (false)	49 (24)	14 (15)	35 (33)	0.003
2. Invasive procedures (drips, catheters, mechanical ventilation) increase the risk of developing HAI (true)	187 (93)	82 (86)	105 (99)	≤0.001
3. Less than 2% of patients in South African hospitals develop HAI (false)	157 (78)	64 (67)	93 (88)	≤0.001
4. Very young age (≤3 months) increases the risk of HAI (true)	182 (91)	81 (85)	101 (95)	0.02
5. HAI are infections occurring after at least 7 consecutive days in hospital (false)	111 (55)	35 (37)	76 (72)	≤0.001
6. Adequate hand hygiene can be achieved using alcohol hand rub instead of soap and water (true)	96 (48)	48 (51)	48 (45)	0.46
7. Care bundles† can be used to reduce the risk of device-associated infections (true)	171 (85)	84 (88)	87 (82)	0.15
8. The Tygerberg Hospital Unit for Infection Prevention and Control performs active surveillance for all types of HAI (false)	28 (14)	3 (3)	25 (24)	≤0.001
9. Patients colonised with antibiotic-resistant bacteria require the same infection control precautions as patients infected with antibiotic resistant bacteria (true)	126 (63)	59 (62)	67 (63)	0.87
10. HAI rates are most commonly reported as number of infections per 100 patients discharged (false)	97 (48)	43 (45)	54 (51)	0.42
11. Terminal cleaning and disinfection of the hospital room is required after discharge for all patients (false)	32 (16)	11 (12)	21 (20)	0.11
12. Surveillance of HAI is mandatory for all South African healthcare facilities (true)	176 (88)	92 (97)	84 (79)	≤0.001
13. <i>Neisseria meningitidis</i> (meningococcus) is spread by the airborne route (false)	79 (39)	42 (44)	37 (35)	0.18
14. Alcohol hand rub should be used for hand decontamination during rotavirus outbreaks (false)	62 (31)	24 (25)	38 (36)	0.11

HAI, healthcare-associated infection; * medical, doctors (n=90) and allied health professionals (n=16) combined; † care bundles, a collection of evidence-based, best practice interventions which when applied together result in reduced incidence of a particular condition, e.g. ventilator-associated pneumonia or catheter-associated urinary tract infection.

antibiotics, prompt removal of unnecessary invasive devices, and improved disinfection of shared equipment and the patient environment. Participants believed that additional IC training (for providers, patients and caregivers) would reduce infection transmission. Some requested better dissemination of paediatric HAI surveillance data, with feedback to individual wards. In addition to education, providers felt that stricter enforcement of IC protocols, empowerment to reprimand transgressors and 'naming and shaming' punitive measures would be effective. The development of stronger leadership and designated IC champions in the paediatric wards was also suggested as a potential intervention.

Discussion

Overall knowledge of HAI was poor in all job categories and levels of experience, similar to India¹⁴ and Burkino Faso.¹⁵ Although paediatric HC providers had some awareness of the problem, most were unfamiliar with the definition of HAI. These findings suggests deficiencies in training on HAI both in undergraduate medical and nursing training curricula. In addition, this highlights the lack of targeted 'in-service' training on HAI for paediatric nursing and medical staff.

In contrast with some KAP studies of IC,^{10,11,16} our cohort's knowledge of core topics such as hand hygiene,

routes of infection transmission and environmental cleaning was poor. Of note was the misconception that the hospital environment played the major role in infection transmission. Despite its widespread availability and institutional encouragement to use alcohol hand-rub, nearly half of participants felt it was not an acceptable alternative to soap and water. The critical role of hand hygiene compliance in reducing HAI, as well as the benefits and indications for use of alcohol hand-rub should be emphasized in IC training.

Nurses were significantly more likely to know that HAI surveillance is now mandatory in South Africa, probably owing to their closer participation in the recent National Core Standards facility audits.¹⁸ They were also more likely than medical staff to know that the IC service does not perform active HAI surveillance. The establishment of an IC 'link nurse' programme at our institution has fostered greater collaboration (including HAI data dissemination) between the paediatric ward nurses and the IC nurse practitioners. No such programme exists for paediatric medical staff. Establishment of a similar IC training programme for doctors (including regular dissemination of departmental and ward-level HAI data) would be valuable.

It is encouraging that the demand for further training was high, with a generally positive attitude towards the IC service. However, the reasons for the discrepancy

Table 3 Attitudes and practice regarding healthcare-associated infection (HAI)

Attitude questions (maximum score 8)	Total n=201	Nursing n=95	*Medical n=106	P-value
Mean score (SD)	5 (1.2)	5.2 (1.1)	4.8 (1.2)	0.02
Attitudes [†] (desired response)			Desired responses, n (%)	
1. I received adequate teaching about HAI as a student (agree)	77 (38)	56 (59)	21 (20)	≤0.001
2. I would like to receive more teaching on infection prevention and control (IPC) topics (agree)	187 (93)	91 (96)	96 (91)	0.15
3. Tygerberg Hospital paediatric wards have adequate isolation facilities to reduce potential infection transmission (agree)	76 (38)	53 (56)	23 (22)	≤0.001
4. Prevention of HAI is the responsibility of the infection prevention and control (IPC) staff (disagree)	120 (60)	42 (44)	78 (74)	≤0.001
5. HAI are an expected or inevitable consequence of prolonged hospital stay (disagree)	76 (38)	22 (23)	55 (52)	≤0.001
6. Staff members who do not perform hand hygiene or ignore infection control recommendations should be reprimanded (agree)	178 (89)	86 (91)	92 (87)	0.41
7. The paediatric staff have a positive attitude towards infection prevention and control (IPC) (agree)	145 (72)	87 (92)	58 (55)	≤0.001
8. HAI in the paediatric wards should be reported as adverse events (agree)	152 (76)	61 (64)	91 (86)	≤0.001
Practice questions (maximum score 6)	Total n=201	Nurse n=95	*Medical n=106	P-value
Mean score (SD)	3.2 (1.2)	3.7 (1)	2.7 (1.3)	≤0.001
Practice (desired response)			Desired responses, n (%)	
1. I receive an annual influenza vaccination (agree)	50 (25)	23 (24)	27 (25)	0.84
2. I always wash/disinfect my hands before and after contact with my patient or their environment (agree)	177 (88)	88 (93)	89 (84)	0.06
3. I always recognise and adhere to transmission-based precaution signs (agree)	176 (80)	86 (91)	74 (70)	≤0.001
4. When I am sick, I feel obliged to come to work because we are short-staffed (disagree)	48 (24)	43 (45)	5 (5)	≤0.001
5. I always wear personal protective equipment (masks, gloves, aprons) when dealing with potentially infectious patients (agree)	148 (74)	91 (96)	57 (54)	≤0.001
6. I have performed fit-testing for use of N95 respirators (agree)	39 (28)	20 (21)	37 (35)	0.03

* Medical, doctors (n=90) and allied health professionals (n=16) combined; † attitudes were assessed on a Likert scale (agree strongly, agree, neutral, disagree, disagree strongly) where desired responses included a pooled frequency of either 'agree strongly + agree' or 'disagree + disagree strongly' (as applicable); IPC, infection prevention and control; HAI, healthcare-associated infection

Table 4 Regression models for factors influencing paediatric healthcare provider KAP

Model	Predictor	Regression co-efficient (K, A)	Odds ratio (P)	95% CI	P-value
Knowledge*	Job category (medical)	-1.066	-	-1.56--0.58	≤0.001
Attitudes*	Student status	0.679	-	0.285--1.073	0.001
	Job category (nursing)	0.329	-	0.006--0.653	0.04
Influenza vaccination [†]	Age (older)	-	0.94	0.88--0.99	0.03
Presenteeism [†]	Job category (medical)	-	19.18	6.41--57.36	≤0.001
Respirator fit-testing [†]	Job category (nursing)	-	0.43	0.21--0.88	0.02
Hand hygiene compliance [†]	-	-	-	-	NS
Adherence to TBP signs [†]	Job category (nursing)	-	3.62	1.53--8.56	0.003
PPE usage [†]	Job category (nursing)	-	19.22	6.33--58.36	≤0.001

The following possible predictors were included in a *linear regression model evaluating their association with K and A scores (reporting adjusted co-efficients), and in a logistic regression model[†] evaluating their association with self-reported practices (reporting adjusted odds ratios): job category (nursing vs medical); age; gender; professional vs student status and years of work experience. KAP, knowledge, attitudes, practices; presenteeism, attendance at work when sick; TBP, transmission-based precautions; PPE, personal protective equipment; NS, not significant.

in attitudes to IC between nurses and doctors (92% vs 55% desired response) are unclear. These may include the positive influence of the IC link nurse programme and more regular interactions with the IC nurse practitioner assigned to the paediatric wards. Among doctors, possible contributing factors to the poorer attitude scores may be the commonly-held perceptions that IC

activities are a nursing function only and that HAI are an inevitable part of healthcare, with minimal impact of IC efforts. In addition, nurses may have felt less comfortable in reporting unfavourable attitudes, in comparison with doctors who may be more empowered to give their honest opinions and attitudes, regardless of the perceptions of study investigators.

The high level of support for punitive measures for non-compliance with IC recommendation was surprising, given that this is an uncommon practice in South African healthcare facilities. The development of a patient safety focus and culture is also at an early stage, both institutionally and nationally. Despite this, providers (particularly doctors) endorsed the notion of reporting all HAIs as adverse events, perhaps owing to their greater familiarity with 'morbidity and mortality (M&M)' forums. Incorporation of HAI data and discussions into existing M&M meetings appears a viable option for increasing awareness and dialogue around IC with the medical staff.

Despite high self-reported compliance with IC best practice, observed hand-hygiene compliance during a concurrent audit was only 41% and 50% in paediatric and neonatal wards, respectively (personal communication, Marina Aucamp). Most providers were unaware that contact transmission drives HAI and did not believe alcohol hand-rub was as effective as hand-washing. These misunderstandings should be urgently addressed in conjunction with behavioural interventions to improve hand hygiene compliance.

In keeping with an Indonesian KAP study,¹² nurses self-reported significantly higher compliance rates for practices including hand-hygiene, use of personal protective equipment and adherence to precaution recommendations. The authors of that study hypothesised that better IC knowledge correlated with greater difficulty complying with IC guidelines and more realistic self-appraisal of behaviour. This phenomenon may explain the lower self-reported compliance rates in our doctors, but an alternative explanation is less willingness to comply with IC protocols. Nurses may also have felt greater pressure to report what they perceived to be 'correct practices and behaviours', whereas doctors may have felt more comfortable in admitting non-compliance.

Despite reporting high levels of using personal protective equipment, few participants had presented for N95 respirator fit-testing. This low uptake is surprising, given the known high-level of exposure to tuberculosis (TB) and several-fold increased risk of occupational TB among HC providers,^{24,25} which has also recently been reported for paediatric wards.²⁶

Presenteeism (reporting for work whilst ill) was worryingly prevalent, especially among doctors who overwhelmingly reported feeling obliged to work when sick. Despite their high risk of exposure to influenza and the potential for transmission to patients, few paediatric providers reported receiving annual influenza vaccination, a major missed opportunity at our institution.

Responses to the open-ended questions showed a clear appreciation of the complex factors contributing to HAI. Participants suggested multiple approaches and interventions to reduce HAI, many of which are easily implemented. Infrastructural and staffing challenges are more difficult to address, but remain important factors

to consider when instituting interventions. Participants wanted greater leadership and a change in the institution's patient safety culture. Social learning theory²⁷ proposes that desired behaviours are more likely to be adopted if modelled by a respected senior colleague or manager.²⁸ Our data showed that higher level of experience and medical job category were associated with higher knowledge scores. Efforts to improve IC practice in paediatrics should be led by departmental IC champions and leaders who practise the desired behaviours and attitudes.

The study's major limitation is the use of self-reported rather than observed IC practices that may influence the risk of HAIs. However, independently but concurrently collected data suggest that the participants overestimated their compliance levels. It is also possible that bias was introduced by use of a convenience sample, as staff with an interest in IC (and therefore better IC knowledge, attitudes and practices) may have been more likely to participate. Certain questions (K9 and A4) may have been misinterpreted by some participants, thus affecting the frequency of correct and desired answers. The data collection instrument was not validated and may not be applicable to other paediatric inpatient settings.

Paediatric medical providers had higher knowledge scores, but lower desired attitude and practice scores than nurses. These differences in knowledge levels and prevalent misconceptions should inform revisions to the in-service and undergraduate IC training programmes. Expanded IC teaching should in particular emphasize the use of alcohol-based hand-rub for hand-hygiene, routes of infection transmission and adherence to recommended practices such as annual influenza immunization and not working when ill. Paediatric providers support the reporting of HAI events, stricter enforcement of IC recommendations and the creation of departmental IC champions to lead improvements in patient safety and quality of care for hospitalized children.

Authors' contributions

All authors contributed to study design and critical review of the manuscript. The primary author carried out the data collection, data cleaning and statistical analysis. All authors read and approved the final manuscript.

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Competing interests

The authors have no competing interests to declare.

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Chapter 6

A framework for preventing healthcare-associated infection in neonates and children in South Africa

Dramowski A, Cotton M, Whitelaw A. *A framework for preventing healthcare-associated infection in neonates and children in South Africa. S Afr Med J. (in press)*

Abstract

Healthcare-associated infection (HAI) is a frequent and serious complication affecting 4-8% of hospitalized children and neonates in high-income countries. The burden of HAI in South African (SA) paediatric and neonatal wards is substantial but underappreciated, owing to a lack of HAI surveillance and reporting. Maternal and Child Health and Infection Prevention are priority areas for healthcare quality improvement in the National Core Standards programme. Despite increasing recognition in SA, infection prevention efforts targeting hospitalized children and neonates are hampered by health system, institutional and individual patient factors. To ensure safe healthcare delivery to children, a co-ordinated HAI prevention strategy should promote development of infection prevention norms and policy, education, patient safety advocacy, healthcare infrastructure, surveillance and research. We present a framework for South Africa to develop and expand HAI prevention in hospitalized neonates and children.

Introduction

Healthcare-associated infection (HAI) is the most frequent complication of hospitalization with morbidity, excess mortality and increased healthcare costs.^[1-3] Although the neonatal and paediatric HAI burden is well-described in high-income countries (4-8% prevalence)^[4,5], it is poorly quantified among hospitalized African children and neonates. In a meta-analysis of HAI in low-middle income countries (LMIC), the World Health Organisation (WHO) identified only three studies of neonatal/paediatric HAI from Africa between 1995 and 2008 (none from South Africa [SA]).^[6] Prior and subsequent to the WHO meta-analysis, five publications have established HAI risk factors for African children including malnutrition^[7-9], prolonged hospital stay^[7,10], use of indwelling devices^[9,11], paediatric intensive care unit (PICU) admission^[9], blood

transfusion^[8,9], young age^[7,10], underlying co-morbid diseases, HIV-infection and HIV-exposed, uninfected (HEU) status.^[9]

HAI epidemiology in hospitalised South African children and neonates

The epidemiology of paediatric and neonatal HAI in SA is poorly documented. Literature describing neonatal HAI is extremely limited, reporting HA bloodstream infections (BSI) only; HA-BSI incidence of 4 and 14/1000 patient days was reported from two tertiary hospitals in Cape Town and Johannesburg.^[12,13] Among paediatric inpatients in Cape Town, HA-BSI rates of 1.6/1000 patient days were recorded, with excess mortality attributable to hospital- versus community-acquired BSI (25% vs 16%).^[14] In 1987, prospective surveillance on two paediatric wards at Chris Hani Baragwanath hospital established HAI prevalence of 14.3% with a predominance of gastrointestinal and respiratory tract infections.^[7] At King Edward Hospital's PICU, HAI prevalence of 43% was reported in 1992.^[10] A one-day point prevalence study (PPS) of 2652 adults and children at six Gauteng hospitals established pooled HAI prevalence of 9.7% for bloodstream, urinary tract, respiratory tract and surgical site infections. Children had higher HAI rates overall (16.5%) and greater prevalence of bloodstream and respiratory tract infections.^[15,16] Recent prospective clinical surveillance at Tygerberg Children's hospital paediatric wards and PICU documented HAI prevalence of 24%, with hospital-acquired pneumonia and HA-BSI predominating. HAI incidence density was highest on the PICU (94 vs 22/1000 patient days in wards).^[9] PICU device-associated infection densities were double that reported from PICU's in other LMIC.^[9,17] Two-thirds of all in-patient mortality occurred in association with HAI, with crude mortality 6-fold higher (7.4%) than that among HAI-unaffected hospitalizations. HAI-affected patients also had 3-fold higher rates of hospital readmission within 30 days. HAI events incurred substantial direct costs (R5.6 million) and an excess 2275 hospitalization days, 2365 antimicrobial days and 3575 laboratory investigations in 4 wards over 6 months.^[9]

The changing landscape of HAI prevention in SA

A national healthcare quality improvement programme launched in 2012, introduced annual facility audits to benchmark public and private institutions against 'national core standards (NCS) for healthcare establishments.'^[18] In addition, the Office of Health Standards compliance was established to guide NCS implementation and to act as a national healthcare licensing and

accreditation body. Despite a renewed focus on infection prevention (IP) and HAI surveillance, data on HAI burden and epidemiology in SA is extremely limited. Although the development of IP 'standards' is laudable, much greater resources and technical expertise (in healthcare epidemiology, IP and data management) is required to achieve data-driven improvement in HAI prevention services. Furthermore, implementation of HAI prevention in the SA healthcare context is complex with multiple challenges to IP programmes at health system, institutional and patient level (Table 1).

Table 1. Challenges to HAI prevention in hospitalized children and neonates

Health systems factors	Healthcare environment factors	Patient factors
Competing health priorities	Overcrowding	Malnutrition
High burden of community-acquired infections	High patient to staff ratios	HIV-exposure and -infection
Few resources for IP implementation	Lack of IP provisions and consumables	Prematurity
Lack of HAI surveillance programmes and reporting	Lack of isolation facilities	Chronic diseases
Lack of IP policies	Ageing infrastructure and inappropriate built environment design	High device utilisation rates
Inadequate training in IP for healthcare workers	Inadequate environmental cleaning	High antimicrobial usage
Lack of a co-ordinated research agenda for HAI prevention	Re-use and sharing of devices and equipment	
	Lack of a 'patient safety' focus and institutional culture	

*Adapted from Rothe et al.^[19]; HAI = healthcare-associated infection; IP = infection prevention.

A proposed framework for neonatal and paediatric HAI prevention in SA

Programmes to establish safe and high-quality delivery of healthcare to SA children will require a co-ordinated HAI prevention strategy, informed by local surveillance and research. An important goal is to ensure that limited IP resources (at national, provincial and institutional level) are directed at the most common HAI events and populations at greatest risk. Prevention should employ a holistic, integrated approach incorporating policy development, IP education, patient safety advocacy, infrastructure development, surveillance and research. Table 2. outlines the major components and proposed content of a paediatric/neonatal HAI prevention

framework for SA. Table 3. Lists the key national, provincial and institutional partners for developing and implementing the proposed framework.

Table 2. A framework for HAI prevention in South African child health services

Component	Example of core content
Policies and guidelines	IP norms and standards for outpatient and inpatient settings with a specific focus on paediatric and neonatal populations; guideline documents for paediatric/neonatal wards and clinics e.g. patient isolation recommendations, guidelines on personal protective equipment use, environmental cleaning methods and assessment, antimicrobial restriction policies
Education, training and advocacy for patient safety	A national core curriculum on IP and HAI prevention for undergraduate health science and nursing students (with additional neonatal/paediatric content); minimum topics/frequency of in-service training for all healthcare workers; standard in-hospital instructions for caregivers on basic IPC measures; national and provincial IP champions to lead education, advocacy and research; institutional 'buy-in' from managers and departmental HOD's to prioritise safe care of children; collaboration within existing structures e.g. IP and quality improvement committees
Provisions and infrastructure	Building norms for new and renovated neonatal and paediatric services including consensus on a recommended ratio of single (isolation) to cohort beds e.g. 1:2 and requirement for negative-pressure isolation rooms (with either natural or mechanical ventilation to achieve at least 12 air changes per hour); basic provisions for HAI prevention e.g. soap, water, alcohol handrub, personal protective equipment
Surveillance and research	Develop recommendations for HAI surveillance methods, frequency and targets e.g. HAI burden, spectrum, risk factors, distribution by ward/facility type and associated antimicrobial use; outbreak reporting; addition of HAI to existing morbidity and mortality registers; identification of key research questions for HAI prevention.

HAI = healthcare-associated infection; IP = infection prevention.

Table 3. Key partners for HAI prevention framework development and implementation

Level	Key stakeholders and partners
National	The National Department of Health, Quality Assurance directorate and the Office of Health Standards Compliance (OHSC) South African Society for Paediatric Infectious Diseases (SASPID) South African Paediatric Association (SAPA) Infection Control Society of Southern Africa (ICSSA) and Infection Control Africa Network (ICAN)

	National Institute of Communicable Diseases (NICD; soon to be the National Public Health Institute of South Africa) United South Africa Neonatal Association (USANA) The Neonatal Nurses Association of South Africa (NNASA) The Society of Midwives of South Africa (SOMSA) South African Antibiotic Stewardship Programme (SAASP) “Best Care... Always” campaign (BCA) National Health Laboratory Service (NHLS) and other laboratories MRC Burden of Disease Unit
Provincial	Department of Health’s provincial communicable disease teams Department of Health’s provincial mother and child health (MCH) directorates District Health specialist teams (in obstetrics and paediatrics) University departments of Paediatrics and Child Health, Public Health, Infectious diseases, Microbiology, Virology and Infection Prevention
Institutional	Facility medical and nursing managers Infection Prevention and Control committees Antimicrobial stewardship committees Health and safety teams Quality improvement structures Primary healthcare networks (within existing PMTCT, TB, EPI structures)

HAI = healthcare-associated infection; IP = infection prevention and control; MRC = Medical Research Council; PMTCT = prevention of mother to child transmission of HIV; EPI = expanded programme on immunisation

HAI prevention policies and guidelines

Given their vulnerability to infection and the burden of community-acquired infection in hospitalised neonates and children, explicit recommendations on IP norms and standards are needed. Locally adapted IP guidelines and policies would assist paediatric and neonatal clinical managers to ensure implementation of best practices. One example where HAI prevention guidance is needed is for cleaning and disinfecting the healthcare environment e.g. isolation rooms, incubators, shared equipment. The risk of pathogen transmission and hospital outbreaks following ineffective cleaning of the patient environment is well-recognized.^[20-22] Despite widespread implementation in high-income settings, few SA healthcare facilities have guidelines on environmental cleaning and even fewer perform routine assessment of cleaning adequacy.^[23] A study comparing methods for evaluation of paediatric isolation room terminal

cleaning, identified fluorescent markers as an inexpensive option together with providing immediate visual feedback to cleaning personnel.^[23] Other important topics for inclusion include: staffing norms for IP and paediatric staff; management of patient isolation facilities; hand hygiene and personal protective equipment; HAI surveillance and reporting; outbreak investigation recommendations and reporting; antimicrobial usage and restriction and staff vaccination.

Education, training and advocacy for patient safety

Surveys of SA healthcare workers and data from the first national core standards audit show the need for improved in-service and undergraduate health science training in IP.^[24-27] Development of harmonised IP curricula for all cadres of SA healthcare workers is needed, including recommendations on minimum training duration, core topics and competency evaluation. As risks and routes of infection transmission vary by population, additional content on paediatric and neonatal-specific risks would be needed e.g. infant feeding. In a recent survey of 200 paediatric and neonatal medical, nursing and allied health staff at Tygerberg Children's Hospital, several important misconceptions about infection transmission routes and hand hygiene methods were identified.^[26] Although 48% of participants considered HAI to be inevitable, there was broad support for punitive measures for staff ignoring IC recommendations (89%) and for reporting of HAI episodes as adverse events (76%). Multiple opportunities were identified for improvement including: poor uptake of annual influenza vaccination (25%); low rates of N95 respirator fit-testing (28%) and very high presenteeism among doctors (95%), despite the risk of infection transmission to their patients. Participants wanted greater leadership and shared accountability for IP, acknowledging a weak institutional patient safety culture and climate.^[26] From this single centre study it is clear that there is scope for improved IP education for paediatric and neonatal staff. In addition, identification of named 'infection prevention champions' and IP 'link nurses' in paediatric and neonatal departments who 'model' desired IP attitudes and behaviours, could assist with implementation of best practices and institutional culture change. Basic IP teaching packages and information packs for non-healthcare workers with regular patient contact (volunteers, visitors, and caregivers) should also be developed.

Provisions and infrastructure for infection prevention in paediatric/neonatal facilities

In many high-income countries, paediatric wards are designed with single rooms and en-suite facilities to reduce the risk of infection transmission. Ironically in resource-limited settings where infection burden is highest, few or no patient isolation facilities exist.^[19] The IP indications for patient isolation are also likely to differ across SA. At Tygerberg Children's hospital, where isolation room demand consistently exceeded availability, the main isolation indication was airborne precautions for tuberculosis (52%); 26% of children with TB had drug-resistant disease.^[28] To date, there are no published data on availability of patient isolation facilities or negative pressure ventilation rooms elsewhere in South Africa. In renovating and building new children's hospitals in SA, recommendations for the ratio of single to cohort beds, and numbers of airborne isolation beds (whether naturally or mechanically ventilated negative pressure rooms) must be established. In addition, IP building norms for bed spacing, workflows, provision of handwash basins and sluice rooms and guidance on other engineering and ventilation issues for neonatal and paediatric wards should be developed.

HAI surveillance and research

HAI surveillance is a key component of effective IP programmes, allowing for comparison or 'benchmarking' of HAI rates between healthcare facilities. Despite the 'National Core Standards' requirement for HAI reporting since 2012, few SA healthcare facilities have the resources and expertise to perform comprehensive HAI surveillance.^[29] Furthermore, the lack of consensus on HAI surveillance methodology in SA prevents direct comparison of data across healthcare facilities. The paucity of data on incidence, spectrum and local determinants of HAI also hampers development of appropriate IP interventions. Given these constraints and variable laboratory investigation testing rates, some feasible alternative surveillance options include use of routinely collected datasets (e.g. discharge coding, microbiology results or antibiotic prescriptions for HAI). A combination of laboratory and antimicrobial usage data at Tygerberg Children's hospital, achieved high sensitivity (85%) and positive predictive values (97%) for HAI determination, requiring substantially less time to collect and analyse than clinical surveillance data.^[30]

Additional options to improve HAI surveillance and research in neonatal and paediatric wards include: mandatory coding of HAI on patient discharge, transfer or death; mandatory outbreak

reporting and explicit inclusion of HAI in morbidity and mortality estimates (both institutional and provincial e.g. the Perinatal and Child Healthcare Problem Identification Programmes). It is unlikely that a 'one-size fits all' approach to paediatric HAI surveillance in SA will be successful. However, surveillance, even of only one or two parameters, must begin as soon as possible and be gradually expanded. Undoubtedly, development and maintenance of paediatric HAI surveillance and research networks will be challenging, but the data yielded on disease burden, spectrum, distribution, risk factors and outcome will be invaluable.

Conclusion

The lack of data on neonatal and paediatric HAI in South Africa has contributed to an underappreciation of the burden and impact of these infections by clinicians, healthcare managers, policymakers and the public. From the limited local data available, HAI causes considerable suffering, mortality and increased healthcare cost in all age groups. To ensure safe and high quality healthcare for SA children, a framework for a nationally endorsed HAI prevention strategy is needed. The following should be addressed: IP policy and infrastructure development, healthcare worker education, patient safety advocacy, HAI surveillance and research. Key national, provincial and local stakeholder partners should be actively engaged to develop and implement HAI surveillance and prevention programmes for hospitalized SA children and neonates.

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Chapter 7

Conclusion

The aim of this dissertation was to produce a comprehensive description of the epidemiology and impact of HAI in an African paediatric cohort. Secondary objectives entailed investigating HAI surveillance methods and local determinants for paediatric HAI (including healthcare worker HAI-related knowledge, attitudes and practices, isolation facility utilization and terminal cleaning practices).

We established that HAI burden at Tygerberg Children's Hospital exceeds reported incidence and prevalence rates in high-income settings (3-6 fold) and those published in the limited literature from LMIC countries. The magnitude of HAI was greatest in patients hospitalized on the paediatric intensive care unit (PICU), with rates of device-associated infection far exceeding pooled estimates published from 16 LMIC PICU. In contrast to adult populations where surgical site infections (SSI) predominate, we observed hospital-acquired pneumonia, bloodstream and urinary tract infections as the major HAI types. In a separate study evaluating trends in paediatric bloodstream infections, we documented the burden of HA-BSI and risk factors for mortality and antimicrobial resistance. Furthermore, we demonstrated the impact of improved immunization and HIV management programmes on local BSI epidemiology.

We showed that HAI burden is greatest among infants (<12 months of age), HIV-exposed and HIV-infected children, those with severe malnutrition, underlying co-morbidities (prematurity and chronic diseases) and patients in the PICU. The crude HAI-associated mortality rate (7.4%) was 6-fold higher than inpatient mortality from other causes. HAI events were associated with two-thirds of paediatric inpatient deaths during the study period. Although all HAI types prolonged median hospital stay, hospital-acquired pneumonia (2 days), laboratory-confirmed bloodstream infection [LC-BSI] (9 days) and presumed HAI episodes (6 days) significantly increased hospitalization duration when compared to age- and ward-matched controls.

K. pneumoniae and *S. aureus* were the predominant HAI pathogens isolated from patients with LC-BSI, UTI and SSI events, whereas viruses (particularly respiratory syncytial virus and adenovirus) were the predominant HAP pathogens. For both SSI and HAP events, 10-14% of events were diagnosed on clinical grounds only as no laboratory specimens were collected.

Although many of our cohort's risk factors for HAI are non-modifiable (i.e. HIV infection or exposure, malnutrition, PICU stay, indwelling devices and underlying co-morbidities), they provide a clear understanding of the patient profile to be targeted in HAI prevention strategies. The substantial economic impact of HAI and secondary effects on bed utilization, antimicrobial and laboratory test usage provide impetus to accelerate HAI prevention programmes for African children. The impact of paediatric HAI on consumption of ultra broad-spectrum antibiotics is also alarming (carbapenems comprised 61% of all antimicrobials prescribed for HAI). Urgent intervention is needed to ensure better implementation of infection prevention strategies to assist institutional antimicrobial stewardship efforts.

Given the national mandate to perform HAI surveillance at South African healthcare facilities, we investigated the suitability of three 'alternative' methods using our prospectively collected HAI cohort as the 'reference standard'. We demonstrated that a combination of laboratory and antimicrobial surveillance achieved highest sensitivity and positive predictive value in HAI event detection, and required comparatively little time for data collection and analysis. Although repeated point prevalence surveys had the poorest sensitivity for HAI detection in our study, it remains an option for HAI surveillance at institutions with low laboratory testing rates and/or lack of access to antimicrobial consumption data.

We demonstrated opportunities for improved utilization of paediatric isolation facilities at our institution (including better identification of patients eligible for isolation and a need for improved healthcare worker compliance with transmission-based precautions). The need to supply negative-pressure, airborne isolation facilities on children's wards in TB-endemic settings was also highlighted in this study. We investigated three methods for evaluation of isolation room terminal cleaning, and identified fluorescent markers as a cost-effective and feasible strategy for resource-limited settings, with the additional benefit of allowing visual feedback for cleaning personnel. Finally, we surveyed two-thirds of our paediatric

department's staff regarding their knowledge, attitudes and practices related to HAI, identifying several knowledge gaps and opportunities for improved IP practice.

Based on this first detailed description of HAI epidemiology and impact at Tygerberg Children's Hospital, there is a clear imperative to conduct further implementation science and operational research. Future directions for HAI prevention research could include: quality improvement programmes in the PICU to implement care bundles for device-associated infection; implementation of a new guideline using 'syndromic' criteria for HAP to reduce delays and missed opportunities for patient isolation; an audit of neonatal and paediatric isolation facilities countrywide, including availability of negative-pressure ventilation; ongoing evaluation of HAI surveillance methods (using our combined laboratory-antimicrobial data model) with expansion to other institutions; introduction of fluorescent markers for terminal cleaning evaluation and training of cleaning personnel; and behavioral interventions to improve infection prevention practices among paediatric staff e.g. uptake of influenza vaccination and N95 respirator fit-testing, avoidance of presenteeism and hand hygiene compliance.

The lack of published data on paediatric HAI in Africa has contributed to an underappreciation of the burden and impact of these infections by clinicians, healthcare managers, policymakers and the public. We believe that our research findings substantiate the need for greater resource allocation to HAI surveillance and prevention programmes for African children. Now that the scale and some determinants of this public health problem are quantified (albeit at a single institution), our mandate to accelerate implementation of HAI prevention programmes and ensure the safety of hospitalized African children is clear.

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Appendices

Other publications on infection prevention-related topics (2014-2016)

Books

Dramowski A. Infection Prevention and Control. A guide for healthcare workers in low-resource settings. Bettercare. September 2014.

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Journal articles

1. Morkel G, Bekker A, **Dramowski A** et al. Bloodstream infections and antimicrobial resistance patterns in a South African neonatal intensive care unit. Paediatr Int Child Health. 2014;34(2):108-14.
2. von Delft A, **Dramowski A**, Khosa C, Kotze K, Lederer P, Mosidi T, et al. Why healthcare workers are sick of TB. Int J Infect Dis. 2015;32:147-51.
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Presentations related to PhD research (2014-2016)

International and national conferences

1. Dramowski A and Huskins C. Infection Control Issues in Children's Hospitals. The Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 5-9 September 2014, Washington DC, USA.
2. Dramowski A, Cotton M, Whitelaw A. Healthcare-associated infections in children: a survey of paediatric healthcare providers' knowledge, attitudes and practices. Infection Control Africa Network conference (ICAN), Harare, Zimbabwe, 3-6 November 2014.
3. Dramowski A, Cotton MF, Whitelaw A. Utilization of paediatric isolation facilities in a TB-endemic setting. International Conference of Infection Control and Prevention (ICPIC), Geneva, 16-19 June 2015.
4. Dramowski A. Update of IPC in Paediatrics. Federation of Infectious Disease Societies of Southern Africa (FIDSSA) conference. Drakensberg, 5-8 November 2015.
5. Dramowski A. Infection control and antibiotic stewardship symposium (3 talks). South African Paediatric Association congress, Durban, South Africa, 31 August 2016.
6. Dramowski A, Cotton MF, Whitelaw A. Surveillance of healthcare-associated infection in hospitalized South African children: which method performs best? Infection Control Africa Network conference (ICAN), Johannesburg, South Africa, 25-28 September 2016.
7. Dramowski A. Healthcare-associated infection in hospitalized children and neonates. Infection Control Africa Network conference (ICAN), Johannesburg, South Africa, 25-28 September 2016.

Local presentations

1. Paediatric PhD club (February 2014)
2. 58th Stellenbosch University Annual Academic Day (August 2014)
3. Microbiology PhD club (September 2014)
4. Centre for Infectious Diseases journal club (October 2014)
5. Department of Paediatric Surgery (October 2014)
6. Paediatric PhD club (May 2015)
7. 59th Stellenbosch University Annual Academic Day (August 2015)
8. Microbiology Journal club (August 2015)
9. 60th Stellenbosch University Annual Academic Day (August 2016)

Student supervision of infection prevention-related topics (2014-2016)

Postgraduate students

Graduated:

1. Dr Gerald Morkel (MMed Paeds): Bloodstream infections and antimicrobial resistance patterns in a South African neonatal intensive care unit
2. Ms Lydia Mudzikati (MClinEpi): Neonatal septicaemia: Prevalence and antimicrobial susceptibility patterns of common pathogens at Princess Marina Hospital, Botswana
3. Ms Rufaro Munemo (MSc ClinEpi): Risk Factors and Outcomes of Neonatal Bacteremia due to Extended Spectrum β -Lactamase Producing Enterobacteriaceae at Princess Marina Hospital
4. Dr Chandre Geldenhuys (MMed Paeds): Central line-associated bloodstream infections in neonates

Current:

5. Sr Arina Jenkins: Implementation of a central line-associated bloodstream infection prevention programme in public sector neonatal intensive care unit
6. Dr Lerato Sikhosana (MMed Path Medical Virology): Seroprevalence of measles, rubella, varicella-zoster, hepatitis A and hepatitis B virus antibodies in first year medical students in the Western Cape, South Africa.

Undergraduate students

Graduated:

1. Helene-Mari van der Westhuizen (MBChB VI): When students become patients: TB disease among undergraduate health science students
2. Helene-Mari van der Westhuizen, Koot Kotze and Heena Narotam (MBChB V): Knowledge, attitudes and practices of health science students regarding TB-IPC
3. Jonas Bovijn (MBChB V): Medical interns and occupational hazards: an infection prevention and control opportunity

Current:

4. Courtney Olivier (MBChB V): Investigating the burden of hospital-acquired infection at four district hospitals' paediatric and neonatal wards (current).

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List of abbreviations

ACC	aerobic colony count
AMR	antimicrobial resistance
ART	antiretroviral therapy
ASA	American Society of Anaesthesiologists
ATP	adenosine triphosphate
BC	blood culture
BSI	bloodstream infection
CA	community-acquired
CAUTI	catheter-associated urinary tract infection
CDC	Centers for Disease Control
CI	confidence interval
CLABSI	central line-associated bloodstream infection
CoNS	coagulase-negative staphylococci
CPAP	continuous positive airway pressure
CRAB	carbapenem-resistant <i>Acinetobacter baumannii</i>
DNA	deoxyribonucleic acid
DS	drug-susceptible
DR	drug-resistant
ESBL	extended spectrum β -lactamase (ESBL)-producing
HAI	healthcare-associated infection
HAP	hospital-acquired pneumonia
HIV	human immunodeficiency virus
IP	infection prevention
IPC	infection prevention and control
IQR	interquartile range
IT	information technology
KAP	knowledge, attitudes and practice
LCBSI	laboratory-confirmed bloodstream infection
LMIC	low-middle income countries
MDR	multidrug-resistant
MDR PA	multidrug-resistant <i>Pseudomonas aeruginosa</i>
<i>M.tb</i>	<i>Mycobacterium tuberculosis</i>

MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
NHSN	National Healthcare Safety Network
OR	odds ratio
PCV	pneumococcal conjugate vaccine
PICU	paediatric intensive care unit
PPE	personal protective equipment
PPS	point prevalence survey
PMTCT	prevention of mother to child transmission of HIV
RLU	relative light unit
SIR	standardized infection ratio
SSI	surgical site infection
SD	standard deviation
TB	tuberculosis
TCH	Tygerberg Childrens' Hospital
USD	United States Dollars
UTI	urinary tract infection
UV	ultraviolet
VAP	ventilator-associated pneumonia
WAZ	weight-for-age z-score