RESEARCH ARTICLE

Hospital-associated methicillin-resistant Staphylococcus aureus: A cross-sectional analysis of risk factors in South African tertiary public hospitals

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Abstract

Introduction

Hospital-associated methicillin-resistant S. aureus (HA-MRSA) remains a significant cause of morbidity and mortality worldwide. We conducted a study to determine risk factors for HA-MRSA in order to inform control strategies in South Africa.

Methods

We used surveillance data collected from five tertiary hospitals in Gauteng and Western Cape provinces during 2014 for analysis. A case of HA-MRSA was defined as isolation of MRSA from a blood culture 48 hours after admission and/or if the patient was hospitalised in the six months prior to the current culture. Multivariable logistic regression modelling was used to determine risk factors for HA-MRSA.

Results

Of the 9971 patients with positive blood cultures, 7.7% (772) had S. aureus bacteraemia (SAB). The overall prevalence of MRSA among those with SAB was 30.9% (231/747; 95% confidence interval [CI] 27.6%–34.3%). HA-MRSA infections accounted for 28.3% of patients with SAB (207/731; 95% CI 25.1%–31.7%). Burns (adjusted odds ratio [aOR] 12.7; 95% CI 4.7–34.4), age ≤1 month (aOR 8.7; 95% CI 3.0–24.6), residency at a long-term care facility (aOR 5.2; 95% CI, 1.5–17.4), antibiotic use within two months of the current SAB episode (aOR 5.1; 95% CI 2.8–9.1), hospital stay of 13 days or more (aOR 2.8; 95% CI 1.3–5.6) and mechanical ventilation (aOR 2.2; 95% CI 1.07–4.6), were independent risk factors for HA-MRSA infection.

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Conclusion

The prevalence of MRSA remains high in South African tertiary public hospitals. Several identified risk factors of HA-MRSA infections should be considered when instituting infection and prevention strategies in public-sector hospitals, including intensifying the implementation of antimicrobial stewardship programmes. There is an urgent need to strengthen infection prevention and control in burn wards, neonatal wards, and intensive care units which house mechanically ventilated patients.

Introduction

Nosocomial infections are a significant cause of morbidity, mortality, and excess healthcare costs globally [1]. *Staphylococcus aureus* is the most common human pathogen causing both community- and hospital-associated infections, including pneumonia and bacteraemia [2]. Hospital-associated methicillin-resistant *S. aureus* (HA-MRSA) accounts for a high proportion of hospitalised patients infected with *S. aureus* [3]. In most African countries, including South Africa, HA-MRSA constitutes 20–50% of *S. aureus* infections [3].

Since its emergence in the 1960s and recognition as a nosocomial pathogen, MRSA remains a significant cause of illness among the population today [3]. Compared to infections with methicillin-sensitive *S. aureus* (MSSA), methicillin-resistant *S. aureus* (MRSA) infections are associated with higher morbidity and mortality [4]. A meta-analysis found that the risk of death due to MRSA bacteraemia was two times higher compared to MSSA bacteraemia [5]. MRSA infections also result in longer hospital stays compared to MSSA infections [6]. This increases utilization of hospital resources such as medication and additional staff, resulting in 1.3 to 3 times higher cost of treatment [7,8].

In order to control HA-MRSA infections, it is important to understand the burden of disease and risk factors associated with infection. Identification of risk factors for HA-MRSA is essential as it guides infection control and prevention policies, guidelines and related activities. In South Africa, there are limited reports on HA-MRSA and its associated risk factors. We aimed to describe the epidemiology of HA-MRSA and identify risk factors in comparison to HA-MSSA in five public sector hospitals in South Africa.

Methods

Study design and setting

We conducted a cross-sectional analysis on demographic, laboratory and clinical data collected through GERMS-SA, an active laboratory-based surveillance system for selected pathogens of public health importance. All hospitals taking part in the surveillance program and included in our study were tertiary academic facilities with diagnostic stewardship programs that includes clinical microbiology consultancy on specimen submission practices as one of the components. All patients presenting with clinical signs and symptoms such as temperature >38˚C, increased white cell count, elevated C-reactive protein, erythrocyte sedimentation rate, urea and electrolytes, and lung abnormalities on a chest X-ray, qualify for a blood culture. Five tertiary public-sector hospitals, including Helen Joseph Hospital (HJH), Steve Biko Academic/Tshwane District Hospital (SBH), Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), Groote Schuur Hospital (GSH) and Tygerberg Hospital (TBH) participated in the GERMS-SA surveillance system during 2014. HJH (900 beds), SBH (832 beds) and CMJAH
(900 beds) are in Gauteng Province, and GSH (975 beds) and TBH (1,384 beds) are in the Western Cape Province. These hospitals are affiliated with universities and serve mainly urban populations.

Data collection and laboratory testing

Patient level and laboratory data were obtained from the GERMS-SA electronic database. GERMS-SA surveillance officers interviewed consenting patients who had *S. aureus* bacteraemia (SAB) and captured data using standard case report forms. For patients who refused to give consent, only medical and laboratory records were used to obtain data. Isolates from these patients were submitted to the Antimicrobial Resistance Reference Laboratory at the National Institute for Communicable Diseases for confirmatory identification and antimicrobial susceptibility testing. Isolate identification was done using the Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS) Flex analysis system, version 3.4 (Bruker Daltonics, Germany). Antimicrobial susceptibility testing was done using the automated Microscan Walkaway system (Beckman Coulter Inc.) and minimum inhibitory concentrations were interpreted using Clinical and Laboratory Standard Institute guidelines [9]. Data were entered or imported into the GERMS-SA electronic database. A proportion of SAB cases had no isolates submitted to the surveillance laboratory as they were identified during quarterly audits done by GERMS-SA. Audits were performed to detect missed cases using data from the National Health Laboratory Service Corporate Data Warehouse database, which houses routine laboratory test results for public-sector hospitals in South Africa. For such cases, antimicrobial susceptibility results used in the current study were those obtained from the hospitals’ laboratory reports. We obtained data on total blood cultures performed at sentinel sites from the National Health Laboratory Service Corporate Data Warehouse.

Study population and case definition

A case of SAB was defined as a *S. aureus* positive blood culture isolated between 1st January 2014 and 31st December 2014 from patients admitted to any of the sentinel sites. Where a patient had additional isolates within 21 days of the first positive culture, only the first episode was included. MRSA was defined as non-susceptibility to oxacillin. Hospital-associated infection was defined as collection of a positive blood culture more than 48 hours after admission, or if a patient was hospitalised within a six-month period preceding the positive culture. SAB cases occurring within 48 hours of admission with no prior hospitalisation in the preceding six months were considered community-associated infections, and were not included in our analysis for risk factors.

Data analysis

To calculate positivity rates for *S. aureus*, the number of blood cultures positive for *S. aureus* was divided by the total number of blood cultures performed at hospital laboratories (one culture per patient per day). To determine the proportion of patients with SAB among patients with bloodstream infections (patients with a positive blood culture for any bacterial organisms, de-duplicated in the same manner as SAB cases), the number of SAB cases was divided by the total number of positive cultures. The corresponding 95% confidence intervals (CI) were also calculated for positivity rates and for the proportions. Descriptive statistics were used to describe characteristics of HA-MRSA and HA-MSSA cases. Associations between categorical variables were tested using Chi-square tests. Differences in non-normally distributed continuous variables between two groups were tested using the non-parametric Wilcoxon rank-sum test. Logistic regression was used to determine risk factors for HA-MRSA infection. The
potential risk factors analysed included demographic characteristics, clinical characteristics such as presence of mechanical ventilation and central venous catheters, and underlying conditions such as heart disease, diabetes mellitus, smoking and malignancy. All variables with a p-value of ≤ 0.2 in the univariate analyses were entered into the multivariable model using the manual forward stepwise selection. Multi-collinearity tests were performed before entering variables in the multivariable model to ensure that only non-collinear variables were included. Variables with a p-value of ≤ 0.05 were kept in the model. The final model was tested using the Hosmer-Lemeshow Chi-square goodness-of-fit test. All statistical analyses were performed using STATA statistical software (Version 13; StataCorp LP Texas USA) and a p-value of ≤ 0.05 was considered statistically significant.

Ethics

Ethical approval for this study was obtained from the Faculty of Health Sciences Research Ethics Committee of the University of Pretoria (458/2015). The protocol was also approved by the U.S Centers for Disease Control and Prevention (CDC)’s Human Subjects Research Office. Ethics approval for the GERMS-SA enhanced S. aureus surveillance was granted by the Human Research Ethics Committee (Medical) of the University of Witwatersrand (No: M10464). Permission to use data from the National Health Laboratory Service Corporate Data Warehouse was obtained from the National Health Laboratory Service Research and Academic Committee. Extracted data were anonymised and stored on password protected computers.

Results

Rates of S. aureus

There were 772 SAB cases diagnosed at the five sentinel sites during 2014 (Fig 1). Of these patients, 68.8% (520/756) had hospital-associated infections and 27.9% (211/756) had community-associated infections. Among SAB cases who had oxacillin susceptibility results, the overall prevalence of MRSA was 30.9% (231/747; 95% CI 27.6%– 34.3%). HA-MRSA infections accounted for 28.3% (207/731; 95% CI, 25.1%– 31.7%) of S. aureus bloodstream infections. S. aureus was isolated from 1.4% (876/62069; 95% CI 1.3% - 1.5%) of all blood cultures performed at sentinel sites, with ranges of 1.1%– 1.5% between hospitals (Table 1). Among patients with bloodstream infections, the proportion of SAB was 7.7% (772/9971; 95% CI 7.2%– 8.3%).

Characteristics of patients with HA-MRSA and HA-MSSA infections

There were 313 HA-MSSA cases and 207 HA-MRSA cases. Neonatal cases (≤1 month old) accounted for the highest proportion (56/207 [27.1%]; p < 0.001) of HA-MRSA infections across all hospitals, while none of the patients aged 6–14 years were infected with HA-MRSA (Table 2). Antibiotic use in the previous two months before the current SAB episode was strongly associated with HA-MRSA compared to HA-MSSA infection (62.1% vs 22.5%; p < 0.001). Compared to HA-MSSA cases, a higher proportion of HA-MRSA cases were mechanically ventilated (30.7% vs 14.2%; p < 0.001) and had central venous catheters in place (45.5% vs 38.7%; p = 0.132) at the time of specimen collection, although the latter result was not statistically significant. A significantly higher proportion of HA-MRSA cases were disoriented (15.5% vs 8.5%; p = 0.002), stuporous (26.2% vs 12.3%; p = 0.002) or sedated (4.8% vs 3.3%; p = 0.002) compared to HA-MSSA cases. The total length of hospital stay was also significantly longer among those with HA-MRSA compared to those with HA-MSSA infections (median days: 39 vs 21; p < 0.001). Lastly, a higher proportion of patients with HA-MRSA died
compared to patients with HA-MSSA (38.9% vs 26.6%; p = 0.015). The proportion of cases with HIV and tuberculosis infections, those previously infected/colonised with MRSA, those currently receiving antibiotic treatment, and those with pre-existing conditions was similar between HA-MSSA and HA-MRSA infections.

**Risk factors analysis**

In the univariate analysis, age ≤ 1 month (odds ratio [OR] 10.9; 95% CI 4.5–25.9), admission at hospital D (OR 3.8; 95% CI 1.5–9.1) and hospital E (OR 6.1; 95% CI 2.5–14.6), hospital stay of 5–12 days (OR 4.5; 95% CI 2.7–7.4), hospitals stay of ≥13 days (OR 7.2; 95% CI 4.3–12.0), burns (OR 4.7; 95% CI 2.3–9.4), mechanical ventilation (OR 2.7; 95% CI 1.7–4.1), abdominal surgery (OR 1.9; 95% CI 1.04–3.4), residence in long-term care facilities (LTCFs) (OR 3.4; 95% CI 1.3–8.3), and antibiotic use in the last two months (OR 5.7; 95% CI 3.7–8.4) were significantly associated with HA-MRSA (Table 3). Previous haemodialysis (OR 0.2; 95% CI 0.06–0.5), current haemodialysis (OR 0.1; 95% CI 0.04–0.3), current peritoneal dialysis (OR 0.2; 95% CI 04–0.8), renal disease (OR 0.2; 95% CI 0.07–0.3), having malignancies (OR 0.5; 95% CI

**Table 1. Rates of SAB at five hospitals in Gauteng and Western Cape during 2014.**

| Hospital | Total number of blood cultures | S. aureus positive cultures (%) | Total number of positive cultures | SAB cases (%) |
|----------|-------------------------------|--------------------------------|---------------------------------|---------------|
| A        | 9190                          | 104 (1.1%)                     | 1436                            | 104 (7.2%)    |
| B        | 9696                          | 143 (1.5%)                     | 2267                            | 105 (4.6%)    |
| C        | 13246                         | 191 (1.4%)                     | 1704                            | 155 (9.1%)    |
| D        | 13456                         | 241 (1.8%)                     | 1801                            | 195 (10.8%)   |
| E        | 16481                         | 233 (1.4%)                     | 2763                            | 213 (7.7%)    |
| Total    | 62069                         | 876 (1.4%)                     | 9971                            | 772 (7.7%)    |

SAB, S. aureus bacteraemia.
### Table 2. Characteristics of patients with HA-MRSA and HA-MSSA infections at five hospitals in Gauteng and Western Cape during 2014.

| Characteristics                  | MSSA N = 313 | MRSA N = 207 | p value |
|----------------------------------|--------------|--------------|---------|
| **Age**                          |              |              |         |
| ≤ 1 month                        | 12 (3.8)     | 56 (27.1)    | <0.001  |
| > 1 month—5 years                | 30 (9.6)     | 27 (13.0)    |         |
| 6–14 years                       | 15 (4.8)     | 0 (0)        |         |
| 5–24 years                       | 25 (8.0)     | 9 (4.3)      |         |
| 25–34 years                      | 54 (17.3)    | 14 (6.8)     |         |
| 35–44 years                      | 36 (11.5)    | 13 (6.3)     |         |
| 45–54 years                      | 30 (9.6)     | 20 (9.7)     |         |
| 55–64 years                      | 22 (7.0)     | 13 (6.3)     |         |
| ≥ 65 years                       | 35 (11.2)    | 15 (7.3)     |         |
| Unknown                          | 54 (17.2)    | 40 (19.3)    |         |
| **Sex**                          |              |              |         |
| Female                           | 89 (28.4)    | 63 (30.4)    | 0.651   |
| Male                             | 170 (54.3)   | 104 (50.2)   |         |
| Unknown                          | 54 (17.3)    | 40 (19.3)    |         |
| **Hospital**                     |              |              |         |
| A                                | 33 (10.5)    | 7 (3.4)      | <0.001  |
| B                                | 50 (16.0)    | 21 (10.1)    |         |
| C                                | 80 (25.6)    | 25 (12.1)    |         |
| D                                | 82 (26.2)    | 66 (31.9)    |         |
| E                                | 68 (21.7)    | 88 (42.5)    |         |
| **Source of bacteraemia**        |              |              |         |
| Bacteraemia without focus        | 207 (66.1)   | 145 (70.0)   | 0.009   |
| Lower respiratory tract infection| 23 (7.3)     | 23 (11.1)    |         |
| Cerebral spinal fluid            | 4 (1.3)      | 2 (1.0)      |         |
| Skin/soft tissue infection       | 49 (15.7)    | 32 (15.5)    |         |
| Other                            | 30 (9.6)     | 5 (2.4)      |         |
| **Mental status**                |              |              |         |
| Alert                            | 161/212 (75.9)| 45/84 (53.6)| 0.002   |
| Disoriented                      | 18/212 (8.5) | 13/84 (15.5) |         |
| Stuporous                        | 26/212 (12.3)| 22/84 (26.2)|         |
| Sedated                          | 7/212 (3.3)  | 4/84 (4.8)   |         |
| **Pre-disposing factors**        |              |              |         |
| HIV positive                      | 55/229 (24.0)| 24/116 (20.7)| 0.487   |
| Tuberculosis                     | 13/307 (4.2) | 5/203 (2.5)  | 0.286   |
| Residence at a LTCF               | 7/302 (2.3)  | 15/201 (7.5) | 0.006   |
| Referred from a LTCF/hospital     | 68/306 (22.2)| 60/166 (29.3)| 0.060   |
| Previous MRSA infection/colonisation | 11/303 (3.6)| 8/197 (4.1)  | 0.806   |
| Previous dialysis                 |              |              |         |
| Haemodialysis                     | 28/300 (9.3) | 4/203 (1.9)  | 0.001   |
| Peritoneal                        | 11/300 (3.7) | 3/203 (1.5)  |         |
| Current dialysis                  |              |              |         |
| Haemodialysis                     | 38/312 (12.2)| 4/207 (1.9)  | <0.001  |
| Peritoneal                        | 13/312 (4.2) | 2/207 (0.9)  |         |
| Previous surgery                  | 77/304 (25.3)| 58/202 (28.7)| 0.387   |

(Continued)
HA-MRSA risk factors

In our study, we found a high prevalence of MRSA, and HA-MRSA accounted for approximately a third of *S. aureus* bloodstream infections among patients admitted to tertiary public-sector hospitals in Gauteng and Western Cape. Patients infected with HA-MRSA had poorer outcomes such as higher mortality and longer hospital stays, compared to patients infected with MSSA.

**Discussion**

In our study, we found a high prevalence of MRSA, and HA-MRSA accounted for approximately a third of *S. aureus* bloodstream infections among patients admitted to tertiary public-sector hospitals in Gauteng and Western Cape. Patients infected with HA-MRSA had poorer outcomes such as higher mortality and longer hospital stays, compared to patients infected with MSSA.

### Table 2. (Continued)

| Characteristics       | MSSA N = 313 | MRSA N = 207 | p value |
|-----------------------|--------------|--------------|---------|
| Current surgery       | 69/312 (22.0)| 46/207 (22.2)| 0.962   |
| Central venous catheters<sup>c</sup> | 117/302 (38.7) | 91/200 (45.5) | 0.132   |
| Mechanical ventilation<sup>a</sup> | 43/303 (14.2) | 61/199 (30.7) | <0.001 |
| Pre-existing conditions<sup>d</sup> | 267/312 (85.6) | 187/207 (87.9) | 0.444   |
| Antibiotic use        |              |              |         |
| 24 hrs prior to positive culture | 52/304 (17.1) | 72/201 (35.8) | <0.001 |
| Previous 2 months     | 64/285 (22.5)| 123/198 (62.1)| <0.001 |
| Current treatment     | 275/303 (90.5)| 192/203 (94.6)| 0.092   |
| Length hospital stay (days) |              |              |         |
| Before positive culture (median; IQR) | 5 (0–11) | 12 (9–45) | <0.001 |
| After positive culture (median; IQR) | 11 (5–27) | 19 (7–23) | <0.001 |
| Entire stay (median; IQR) | 21 (10–38) | 39 (19–66) | <0.001 |
| Outcome               |              |              |         |
| Recovered/Discharged | 221/308 (71.8) | 119/198 (60.1) | 0.015   |
| Died                  | 82/308 (26.6) | 77/198 (38.9) |        |
| Refused treatment     | 5/308 (1.6) | 2/198 (1.0) |        |

MSSA, methicillin sensitive *S. aureus*; MRSA, methicillin-resistant *S. aureus*; LTCF, long-term care facility; IQR, interquartile range.

<sup>a</sup> On the day of positive culture
<sup>b</sup> Within a year of the current culture
<sup>c</sup> Within 2 days of the current culture
<sup>d</sup> Pre-existing conditions included chronic obstructive pulmonary diseases, chronic renal disease, cerebrovascular disease (cerebro-vascular accident, cerebral palsy, neuromuscular), heart disease, head injuries (head surgery, ventricular shunts, cochlear implants, cerebrospinal fluid leaks), connective tissue diseases, liver disease, aplastic anaemia, primary immunodeficiency conditions, immunosuppressive treatment, diabetes mellitus, malignancy, organ transplant, surgery, prematurity, protein energy malnutrition, burns, alcohol dependency, smoking, pancreatitis, dementia, obesity and decubitus/pressure ulcers.

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0.2–0.9), head injuries (OR 0.3; 95% CI 0.1–0.8), and being on immunosuppressive treatment (OR 0.3; 95% CI 0.1–0.7) reduced the odds of HA-MRSA infection. However, most of these associations were not significant in the multivariable model.

In the multivariable analysis, burns (aOR 12.7; 95% CI 4.7–34.4) and age ≤1 month (aOR 8.7; 95% CI 3.0–24.6) were the strongest risk factors for HA-MRSA (Table 4). Living in long-term care facilities (LTCFs) (aOR 5.2; 95% CI 1.5–17.4), antibiotic use within two months of the current SAB episode (aOR 5.1; 95% CI 2.8–9.1), hospital stay of ≥13 days before the current SAB episode (aOR 2.8; 95% CI 1.3–5.6) and mechanical ventilation (aOR 2.2; 95% CI 1.07–4.6) were also independent risk factors of HA-MRSA infection. Compared to those aged 65 years and older, patients aged between 25–34 years had 70% reduced odds of HA-MRSA infection in the multivariable model (aOR 0.3; 95% CI 0.08–0.7). The Hosmer-Lemeshow’s goodness-of-fit test indicated that our model fit the data well (p = 0.123).
Table 3. Univariate analysis of risk factors for HA-MRSA infection in comparison to HA-MSSA infection among hospitalised patients in Gauteng and Western Cape during 2014.

| Characteristic                          | OR       | 95% CI     | p value  |
|-----------------------------------------|----------|------------|----------|
| **Age**                                 |          |            |          |
| ≤ 1 month                               | 10.9     | 4.5–25.9   | <0.001   |
| > 1 month—5 years<sup>a</sup>           | 2.1      | 0.9–4.6    | 0.068    |
| 15–24 years                             | 0.8      | 0.3–2.2    | 0.725    |
| 25–34 years                             | 0.6      | 0.2–1.4    | 0.261    |
| 35–44 years                             | 0.8      | 0.3–2.0    | 0.702    |
| 45–54 years                             | 1.6      | 0.6–3.5    | 0.296    |
| 55–64 years                             | 1.4      | 0.5–3.4    | 0.491    |
| ≥ 65 years                              | Ref      |            |          |
| **Sex**                                 |          |            |          |
| Male                                    | 0.9      | 0.5–1.2    | 0.480    |
| **Hospital**                            |          |            |          |
| A                                       | Ref      |            |          |
| B                                       | 2.0      | 0.7–5.1    | 0.164    |
| C                                       | 1.5      | 0.5–3.7    | 0.400    |
| D                                       | 3.8      | 1.5–9.1    | 0.003    |
| E                                       | 6.1      | 2.5–14.6   | <0.001   |
| **LOS before positive culture (days)**  |          |            |          |
| 0–4                                     | Ref      |            |          |
| 5–12                                    | 4.5      | 2.7–7.4    | <0.001   |
| ≥ 13                                    | 7.2      | 4.3–12.0   | <0.001   |
| Renal disease                           | 0.2      | 0.07–0.3   | <0.001   |
| Burns                                   | 4.7      | 2.3–9.4    | <0.001   |
| HIV                                     | 0.8      | 0.4–1.4    | 0.487    |
| Antiretroviral therapy                  | 0.6      | 0.2–1.6    | 0.325    |
| Malignancy                              | 0.5      | 0.2–0.9    | 0.028    |
| Head Injuries                           | 0.3      | 0.1–0.8    | 0.021    |
| Diabetes                                | 0.7      | 0.3–1.1    | 0.153    |
| Mechanical ventilation<sup>b</sup>      | 2.7      | 1.7–4.1    | <0.001   |
| Central venous catheter<sup>c</sup>     | 1.3      | 0.9–1.8    | 0.125    |
| Immunosuppressive treatment             | 0.3      | 0.1–0.7    | 0.002    |
| Mixed infections                        | 1.7      | 0.8–3.4    | 0.126    |
| Abdominal surgery                       | 1.9      | 1.04–3.4   | 0.035    |
| Non-abdominal surgery                   | 0.7      | 0.3–1.1    | 0.144    |
| Resident in LTCF<sup>d</sup>            | 3.4      | 1.3–8.4    | 0.009    |
| Exposed to a crowded place              | 0.5      | 0.2–0.9    | 0.039    |
| Previous antibiotic use<sup>e</sup>     | 5.7      | 3.7–8.4    | <0.001   |
| Current antibiotic treatment            | 1.8      | 0.8–3.7    | 0.096    |
| Previous dialysis<sup>f</sup>           |          |            |          |
| Haemodialysis                           | 0.2      | 0.06–0.5   | 0.002    |
| Peritoneal dialysis                     | 0.4      | 0.1–1.3    | 0.125    |
| Current dialysis                        |          |            |          |
| Haemodialysis                           | 0.1      | 0.04–0.3   | <0.001   |
| Peritoneal dialysis                     | 0.2      | 0.4–0.8    | 0.036    |
| Previous infections<sup>f</sup>         | 0.5      | 0.1–1.5    | 0.246    |

(Continued)
with HA-MSSA. Patients with burns, neonates and who lived at LTCFs were at highest risk of developing HA-MRSA infection, and the duration of hospitalisation, mechanical ventilation, and antibiotic exposure were also significant risk factors, but of lower magnitude.

In our study, the prevalence of MRSA among patients with SAB was lower than previously reported in similar South African studies [6,10]. Although differences in geographic regions where studies were conducted and different patient populations could have resulted in the different MRSA rates, other prevalence and incidence studies conducted in South Africa have found a decline in MRSA [11,12]. Lower MRSA rates are likely due to improved infection prevention strategies, diagnostic stewardship activities, and accurate recording of test results in laboratory information systems. Nonetheless, the rate of MRSA among current hospitals remains high compared to the recently published rate of 24% for South Africa, and indicates that control efforts should be strengthened in order to reduce infections [13].

Similar to previous studies, we found that compared to patients with HA-MSSA infections, a higher proportion of patients with HA-MRSA had longer hospital stays and higher mortality rates [14,15]. These results suggest that MRSA could be pre-disposing patient to poor outcomes, although this is difficult to ascertain due to other co-morbidities and differences in treatment practices. Nonetheless, the adverse role of MRSA in patient outcomes has been

### Table 3. (Continued)

| Characteristic                        | OR  | 95% CI   | p value |
|---------------------------------------|-----|----------|---------|
| Previous MRSA infection/colonisation<sup>a</sup> | 1.1 | 0.4–2.8  | 0.806   |

OR, odds ratio; CI, confidence interval; LOS, length of hospital stay; LTCF, long-term care facility; MRSA, methicillin-resistant S. aureus.

<sup>a</sup> The 6–14 years age group was omitted in the model due to zero outcome observations;
<sup>b</sup> On the day of positive culture;
<sup>c</sup> Within two days of the current culture;
<sup>d</sup> Within a year of the current culture;
<sup>e</sup> Two months prior the current culture.

### Table 4. Multivariable analysis of risk factors for HA-MRSA infection in comparison to HA-MSSA infection among hospitalised patients in Gauteng and Western Cape during 2014.

| Characteristic                               | aOR  | 95% CI   | p value |
|----------------------------------------------|------|----------|---------|
| Burns (< 1 month vs ≥65 years)               | 12.7 | 4.7–34.4 | <0.001  |
| Age (< 1 month vs ≥65 years)                | 8.7  | 3.0–24.6 | <0.001  |
| Resident in LTCF<sup>a</sup>                 | 5.2  | 1.5–17.4 | 0.008   |
| Previous antibiotic use<sup>b</sup>          | 5.1  | 2.8–9.1  | <0.001  |
| LOS before positive culture (≥13 days vs 0–4 days) | 2.8  | 1.3–5.6  | 0.004   |
| Mechanical ventilation<sup>c</sup>          | 2.2  | 1.07–4.6 | 0.031   |
| Age (25–34 years vs ≥65 years)              | 0.3  | 0.08–0.7 | 0.016   |
| Sex (Male)<sup>d</sup>                      | 1.3  | 0.7–2.2  | 0.443   |

Hosmer–Lemeshow goodness-of-fit p value = 0.1231. aOR, adjusted odds ratio; CI, confidence interval; LOS, length of hospital stay.

<sup>a</sup> Within a year of the current culture;
<sup>b</sup> Two months prior the current culture;
<sup>c</sup> On the day of positive culture.
<sup>d</sup> Although sex was not a significant risk factor in the univariate analysis, it was kept in the multivariable model to control for possible confounding.
demonstrated in published meta-analyses showing strong evidence that MRSA bacteraemia is independently associated with death, despite the presence of co-morbidities [4,16]. Thus, it is likely that reduction of MRSA bacteraemia, especially in hospital settings, will result in less adverse events and better outcomes for patients.

Control of MRSA in healthcare settings relies on understanding factors that predispose patients to the acquisition. Risk factors for HA-MRSA acquisition have been well described and include, invasive procedures, long hospital stay, antibiotic exposure and use of medical devices [17–19]. The strongest risk factor for HA-MRSA infection in our setting was having burns. To the best of our knowledge, this is the first multi-centre study that included patients of all ages admitted in a variety of wards to demonstrate this independent association. The majority of studies describing the impact of HA-MRSA on burn patients have limited the study population to only patients with burns and/or burn units [15,20–22].

Previous studies done in two tertiary hospitals in South African provinces found that S. aureus was the major pathogen infecting patients in burn units, and MRSA accounted for 66% of these infections in KwaZulu-Natal Province and 58% in Eastern Cape Province [23,24]. A similar study of patients with bloodstream infections and severe burns conducted in Gauteng found that 35% of these infections were due to MRSA [25]. Taken together, these results demonstrate that patients with burns in public hospitals are an important sub-population with increased risk of HA-MRSA.

Our study showed that neonates represented the highest proportion of patients infected with HA-MRSA. In addition, neonates had eight times the odds of HA-MRSA infection compared to HA-MSSA. These findings are contrary to studies done in Scotland, Belgium and the USA that demonstrated a higher incidence of HA-MRSA infections among adults, and an association of HA-MRSA with older age [26–28]. The World Health Organization (WHO) has reported that there is a higher burden of hospital-associated infections in low- and middle-income countries, and as opposed to adults in high-income countries, neonates are most at risk in low- and middle-income countries, with up to 20 times higher infection rates [1]. Thus, our findings support those of WHO and emphasise the need to control MRSA acquisition in neonates as they contribute the most to the burden of disease and are likely to have unfavourable outcomes.

Residents of LTCFs, which are often older frail patients with underlying conditions, were also identified as a subset of hospitalised individuals independently associated with HA-MRSA. Similar to our study, one laboratory-based study including patients of all ages found that MRSA positivity was strongly associated (aOR 3.53; 95% CI 2.79–4.46) with residents of LTCFs compared to patients in acute care hospitals or other facilities such as military hospitals [28]. LTCFs are known as “MRSA reservoirs” due to high colonisation rates of up to 58% in some instances [29]. Colonisation, coupled with the presence of other illnesses, is important as it increases the risk of MRSA infection both at LTCFs and when patients are hospitalised [30]. Thus, our finding supports the conclusion that LTCFs are important sources of MRSA and residents of these facilities are more likely to be infected with HA-MRSA upon hospitalisation.

In our study, previous antibiotic exposure independently increased the odds of HA-MRSA five-fold compared to HA-MSSA. Previous studies have similarly found that antibiotic exposure is a significant risk factor for HA-MRSA infection [18,19,29]. A main strategy to tackle antimicrobial resistance in healthcare settings is through antimicrobial stewardship programmes. However, South African guidelines for stewardship programmes have only recently been published and not fully implemented in public-sector hospitals [31]. Although limited to two wards, an antibiotic stewardship programme successful in reducing antibiotic prescribing was reported by one of the current hospitals [32], suggesting that widespread implementation of
these interventions is likely to reduce antibiotic consumption and infections with antibiotic resistant organisms [33].

We found that the odds of HA-MRSA infection were twice as likely as HA-MSSA when patients were mechanically ventilated, underlining the importance of the presence of medical devices in hospital acquisition of drug-resistant organisms. In the United States, ventilator-associated pneumonia accounts for 39.1% of pneumonia events [34]. In addition, ventilator-associated pneumonia is the leading device-associated infection in China and Turkey [35,36].

Similar to other studies, we also found that HA-MRSA infection is associated with an overall longer hospital stay [6,7,27], and hospital stay of over two weeks increased the odds of HA-MRSA infection three-fold compared to HA-MSSA. These findings demonstrate a reciprocal relationship between MRSA and hospital stay, where hospital stay increases the risk of MRSA infection and MRSA infection lengthens hospital stay. Reasons for infection among patients with lengthy hospital stays include severe illness, use of medical devices and constant and prolonged exposure to healthcare workers and/or other patients that may be colonised or infected with MRSA.

One of the strengths of our study was the use of enhanced surveillance data that were extensive and of good quality. Additionally, we were able to identify important risk factors for HA-MRSA not described in previous South African studies. However, the risk factors described in our study may not reflect risk factors for patients admitted to non-tertiary public-sector hospitals in South Africa. Due to the small number of patients with burns, neonates and LTCFs residents who were found to be at high risk of HA-MRSA, our analysis lacked the statistical power to find any association with known hospital-related factors specific to these patients. Hospital-related factors such as overcrowding, hand hygiene practices, and the existence of antimicrobial stewardship programmes are important determinants of HA-MRSA that were not collected by the surveillance programmes from which we obtained data. Thus, we could not determine their contribution to HA-MRSA acquisition. This information is critical for prevention of HA-MRSA infection and other hospital-related infections.

Conclusions

The prevalence of MRSA among patients with SAB hospitalised in the five tertiary-level public-sector hospitals in South Africa remains higher than expected. In view of our findings that patients with burns, neonates, those admitted in LTCFs, prolonged hospitalisation, mechanical ventilation, and antibiotic exposure are important risk factors for HA-MRSA infection, control strategies should employ use of “MRSA bundles”. These bundles may include optimum hand hygiene, educating healthcare workers on best practices for handling ventilated patients, isolation and cohorting of infected patients, antimicrobial stewardship programmes, surveillance screening, and decolonisation of high risk patients [37–41]. In order to control HA-MRSA, a holistic approach, which includes a combination of these strategies should be adopted in public-sector hospitals.

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