GERMS-SA LABORATORY-BASED SURVEILLANCE FOR ANTIMICROBIAL-RESISTANT BACTERIAL AND FUNGAL BLOODSTREAM INFECTIONS, 2016

Nelesh Govender, Olga Perovic

Centre for Healthcare-Associated Infections, Antimicrobial Resistance and Mycoses, NICD

Introduction

The Centre for Healthcare-Associated Infections, Antimicrobial Resistance and Mycoses (CHARM) at the National Institute for Communicable Diseases (NICD) uses the GERMS-SA laboratory-based surveillance platform to conduct intermittent surveys for antimicrobial-resistant bacterial and fungal bloodstream infections. The primary objective is to describe the epidemiology of key bloodstream infections, including antimicrobial resistance trends. The GERMS-SA platform facilitates a more detailed epidemiological description of laboratory-confirmed cases through enhanced sentinel surveillance. This report summarises preliminary results of national or sentinel surveys conducted in 2016 for *Staphylococcus aureus* and carbapenem-resistant Enterobacteriaceae (CRE) bacteraemia and candidaemia (compared to the preceding year's results where applicable).

Enhanced sentinel surveillance for *Staphylococcus aureus* bacteraemia in Gauteng and Western Cape provinces

The epidemiology of *S. aureus* bacteraemia has been poorly described in low- and middle-income countries (LMICs) compared to high-income countries (HICs).[1,2] Historically, methicillin-resistant *S. aureus* (MRSA) isolates that are resistant to β-lactam antibiotics were confined to healthcare facilities. However, in the mid-1990s, the emergence of community-associated MRSA (CA-MRSA) strains, which cause infections among patients with no previous exposure to the healthcare environment, resulted in a considerable shift to CA-MRSA-associated disease in HICs in North America, Asia, Europe and Australia, but less so in LMICs. These strains may be distinguished by molecular characterization of the staphylococcal cassette chromosome *mec* (SCC*mec*) with HA-MRSA strains typically carrying a large SCC*mec* type I-III and CA-MRSA strains carrying the smaller SCC*mec* elements IV-V. The aim of this project was therefore to determine the prevalence of antimicrobial resistance and molecular epidemiology of *S. aureus* bacteraemia at enhanced surveillance sentinel sites in two provinces for guideline/ policy formulation and antimicrobial stewardship activities.

Methods

NICD-CHARM initiated laboratory-based enhanced surveillance for *S. aureus* bacteraemia in September 2012 in Gauteng and Western Cape provinces. The results for the period 1 January 2015 through to 31 December 2016 are reported here. A case was defined as an individual diagnosed with culture-confirmed *S. aureus* bacteraemia at any sentinel site. A new episode was defined if an individual had a positive culture >21 days after the first culture. Quarterly audits of the NHLS Corporate Data Warehouse (CDW) were

conducted to confirm completeness of reporting. At sentinel public-sector hospitals, nurse surveillance officers collected clinical data from admitted case patients by interview or chart review. Corresponding bloodstream isolates were submitted to CHARM for confirmation of identification using a matrix-assisted laser desorption/ionization time of flight instrument (MALDI Biotyper System, Bruker Diagnostics, Bremen, Germany). Antimicrobial susceptibility testing was performed using commercially-available microbroth dilution panels MIC Panel Type 33 (MicroScan, Beckman Coulter, USA). Minimum inhibitory concentrations were interpreted using Clinical and Laboratory Standards Institute (CLSI) M100-S27 breakpoints.

Results

In 2016, 955 cases of *S. aureus* bacteraemia were detected (Table 1). The majority of cases were detected from sentinel sites in Johannesburg and Pretoria (560; 59%). 586 (61%) patients were male. Adults aged ≥18 years accounted for 548 (57%) cases. *Staphylococcus aureus* isolates were available for 78% (746/955) of case patients. The proportion of MRSA cases decreased from 32% (242/748) in 2015 to 25% (188/746) in 2016 (p=0.002) (Figure 1). SCC*mec* typing was performed for 187 *mec*A-positive *S. aureus* isolates in 2016. There was a predominance of type III SCC*mec* in Gauteng (73/187; 39%) and type IV in the Western Cape (38/187; 20%) (Figure 2). Among 746 viable *S. aureus* isolates, 200 (73%) were non-susceptible to clindamycin. All isolates were susceptible to vancomycin and daptomycin in 2016. A total of 731 (95%) isolates were susceptible to mupirocin (Table 2 and Figure 2). Among 955 patients, 273 (29%) died.

Table 1. Numbers and percentages of cases of *Staphylococcus aureus* bacteraemia reported to GERMS-SA sentinel sites by province, South Africa, 2015 (n=927) and 2016 (n=955) (including audit cases).

Province	2015		2016		Total	
	n	%	n	%	n	%
Gauteng	516	56	560	59	1076	57
Western Cape	395	44	395	41	806	43
Total	**927**	**100**	**955**	**100**	**1882**	**100**

Table 2. Numbers and percentages (parentheses) of viable *Staphylococcus aureus* isolates susceptible to various antimicrobial agents, 2016, n=746.

Province	Oxacillin	Clindamycin	Vancomycin	Mupirocin	Daptomycin
	n=746	n=746	n=746	n=746	n=743
Gauteng	305 (75)	292 (72)	406 (100)	401 (99)	406 (100)
Western Cape	253 (74)	254 (75)	340 (100)	330 (97)	337 (100)
Total	**558 (75)**	**546 (73)**	**746 (100)**	**731 (98)**	**743 (100)**

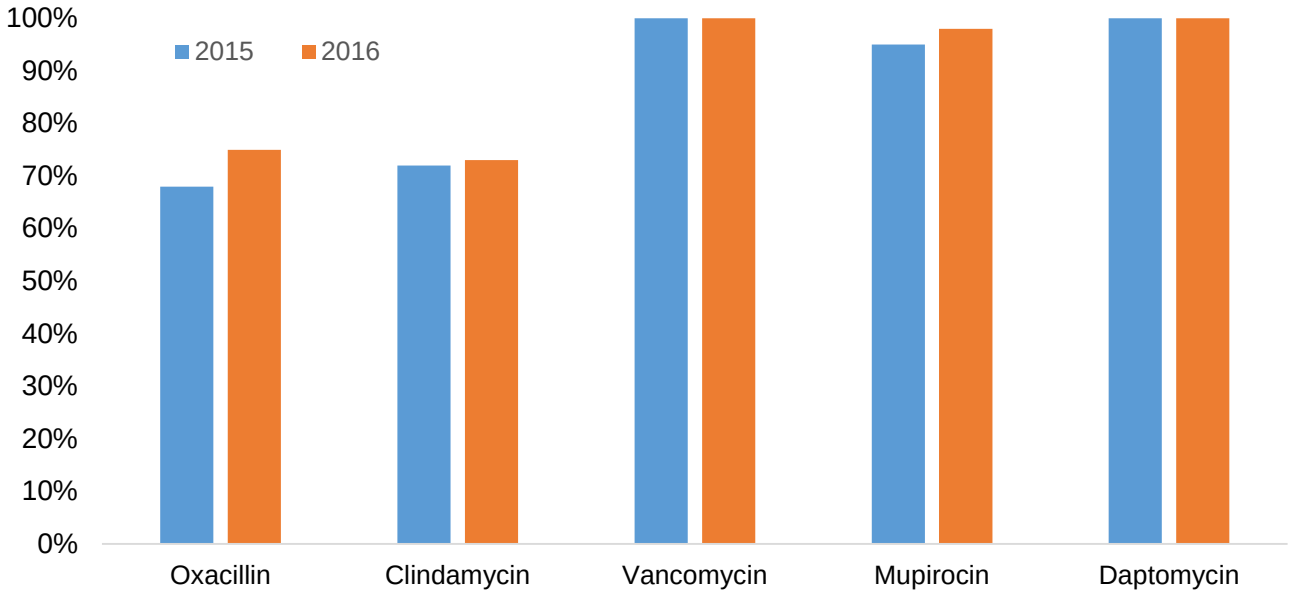

Figure 1. Proportion of cases of laboratory-confirmed *Staphylococcus aureus* bacteraemia with isolates susceptible to various anti-microbial agents reported to GERMS-SA in Gauteng Province, 2015 and 2016, n=1494.

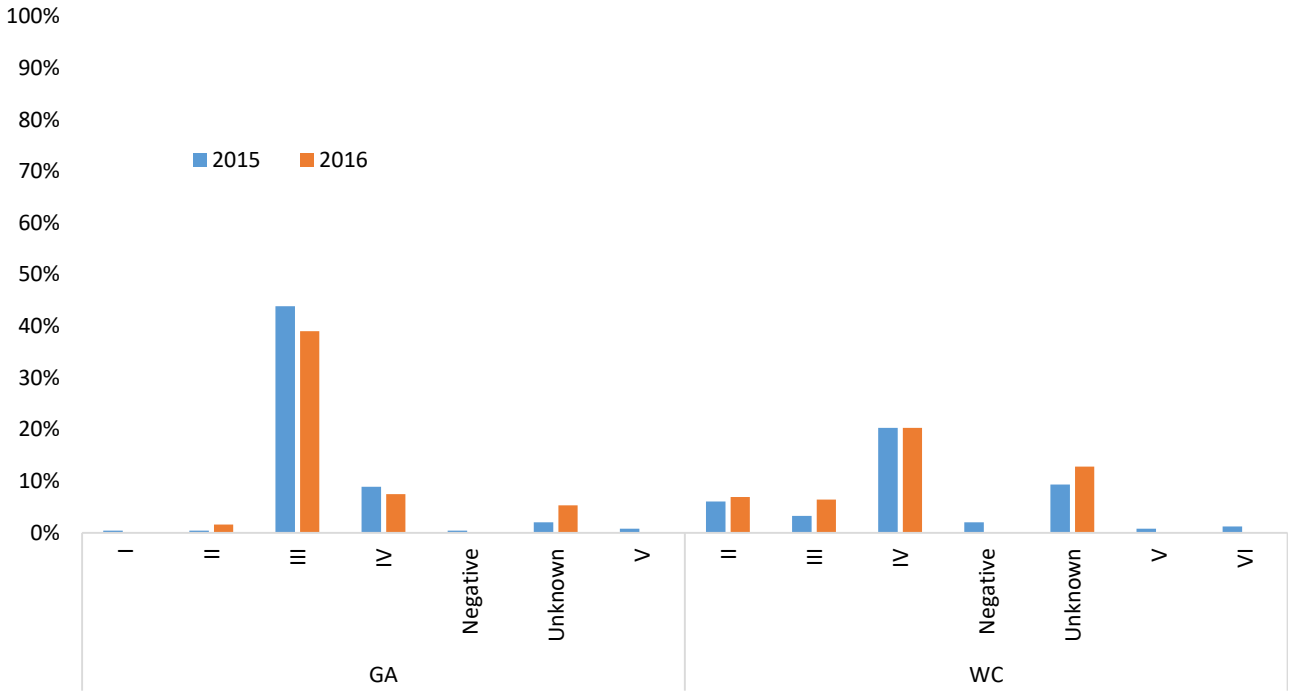

Figure 2. Staphylococcal cassette chromosome *mec* (SCC*mec*) distribution for laboratory-confirmed cases of *Staphylococcus aureus* bacteraemia reported to GERMS-SA by province, 2015 and 2016, n=433. GA = Gauteng Province; WC = Western Cape Province.

Discussion

There was a significant decrease in the proportion of cases of MRSA bacteraemia in 2016 compared to 2015. Overall, SCC*mec* type III predominated and was more common in Gauteng while type IV was dominant in the Western Cape. A similar proportion of isolates was resistant to clindamycin and oxacillin. As expected, no vancomycin or daptomycin non-susceptible isolates were identified. Other than a reduction in MRSA cases, there was no change in the susceptibility pattern of bloodstream *S. aureus* isolates over the reporting period.

References

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Enhanced sentinel surveillance for Carbapenem-resistant Enterobacteriaceae (CRE) bacteraemia in four provinces

The past few decades have seen the rapid emergence and spread of antimicrobial resistance with clinicians having to rely on the carbapenem class of antibiotics to treat resistant bacterial infections.[1] However, carbapenem resistance is increasingly being reported. The mechanism of resistance to carbapenems in the Enterobacteriaceae is complex and mediated by several different mechanisms such as over-production of ampC enzymes, extended-spectrum β-lactamases (ESBLs), carbapenemases, efflux pumps and loss of porin channels.[2-4] There are two main subsets of carbapenemase-producing Enterobacteriaceae (CPEs), producing either non-metallo-enzymes including *Klebsiella pneumoniae* carbapenemases (KPC), Guiana extended-spectrum β-lactamases (GES), and oxacillinase-type carbapenemases (OXA-48) and their derivatives; or metallo-β-lactamases (MBLs) including imipenemases (IMP), Verona integrated metallo-beta-lactamases (VIM) and New Delhi metallo-beta-lactamase (NDM-1/2). Genes encoding these enzymes can be detected using molecular methods. Infections caused by CPEs are associated with increased patient morbidity and mortality owing to limited treatment options rather than the expression of specific virulence characteristics.[5,6] There is potential for widespread transmission of carbapenem resistance owing to easily-transmissible resistance genes.[5,6] CPE are thus a high-priority group of pathogens (versus other mechanisms of resistance). The aim of this project was therefore to estimate the burden of laboratory-confirmed CRE bacteraemia at sentinel sites in South Africa and to describe the epidemiological characteristics to support development of guidelines for antimicrobial use.

Methods

NICD-CHARM initiated laboratory-based enhanced surveillance for CRE bacteraemia on 1 July 2015 at 12 sentinel public-sector hospitals in four South African provinces. The results for the period 1 July 2015 through 31 December 2016 are reported here. A case was defined as an individual diagnosed with bacteraemia at a surveillance site with Enterobacteriaceae isolates resistant to any of the carbapenems (ertapenem, imipenem, meropenem and/or doripenem) at a diagnostic laboratory based on the disk diffusion method, Etest, automated systems (Vitek 2 or MicroScan) or modified Hodge test (MHT). *Enterobacter* species showing borderline resistance to ertapenem but susceptibility to other carbapenems were excluded. A new episode was defined if an individual had a positive culture >21 days after the first culture. Quarterly audits of the NHLS CDW were conducted to confirm completeness of reporting. At sentinel hospitals, nurse surveillance officers collected clinical data from admitted case patients by interview or chart review.

Corresponding bloodstream isolates were submitted to the Centre for confirmation of identification using the MALDI Biotyper System. Antimicrobial susceptibility testing was performed using commercially-available microbroth dilution panels MIC Panel Type 44 (MicroScan). Minimum inhibitory concentrations were interpreted using CLSI M100-S27 breakpoints. Molecular tests were performed for confirmation of CPE genes. After DNA extraction by using a crude boiling method at 95°C for 25 minutes for cell lysis, the supernatant was harvested and screened for *bla*$_{NDM}$, *bla*$_{KPC}$, *bla*$_{OXA-48}$ and its variants (OXA-162, 163, 244 245, 247, 181, 204, 232), *bla*$_{GES}$ (GES-1-9, 11), *bla*$_{IMP}$ (IMP-9, 16, 18, 22, 25) and *bla*$_{VIM}$ (VIM-1-36) using a multiplex real-time polymerase chain reaction (PCR) (LightCycler 480 II, Roche Applied Science, LightCycler 480 Probes Master kit and the individual LightMix Modular kits (Roche Diagnostics, IN, USA).

Results

There were 440 cases of CRE bacteraemia (as detected by a diagnostic laboratory) reported to GERMS-SA from July 2015 through to December 2016 (Table 3). Half (n=220) were male and the majority (233; 53%) were adults aged 16-55 years. The majority of cases were detected from sentinel sites in Gauteng (298; 68%) followed by KwaZulu-Natal (105; 24%) (Table 3). CRE isolates were available for 67% (294/440) of patients and submitted to NICD for antimicrobial susceptibility testing (Table 4). *Klebsiella pneumoniae* was the commonest organism (217; 74% of cases) followed by *Enterobacter cloacae* (28; 10%), *Serratia* (19; 7%) and *Escherichia coli* (17; 6%) (Figure 3). Most cases occurred in adult medical wards (Figure 4). Among all isolates, 87% (256) were non-susceptible to ertapenem, 57% (168) non-susceptible to imipenem and 58% (171) non-susceptible to meropenem and doripenem (Figure 5). Carbapenemase genes were confirmed in 81% (238/294) of isolates including NDM (109/238; 45%) and OXA-48 or variants (111/238; 47%) (Figure 6). 23 (8%) isolates were susceptible to ertapenem with an MIC ≤ 0.5 mg/L but were OXA-48 positive. Over the surveillance period, there was a shift towards CRE mediated by OXA-48 & variants (Figure 6). Among viable isolates, 76% were susceptible to tigecycline (Table 4). Of all patients with CRE bacteraemia, 158 (36%) died.

Table 3. Numbers of cases of carbapenem-resistant Enterobacteriaceae (CRE) bacteraemia reported to GERMS-SA by province, July 2015 to December 2016, n=440 (including audit cases).

Province	2015		2016		Total	
	n	%	n	%	n	%
Free State	1	1	3	1	4	1
Gauteng	80	68	218	67	298	68
KwaZulu-Natal	32	27	73	23	105	24
Western Cape	4	4	29	9	33	7
Total	**117**	**100**	**323**	**100**	**440**	**100**

Table 4. Numbers and percentages of carbapenem-resistant Enterobacteriaceae (CRE) bloodstream isolates reported to GERMS-SA susceptible to antimicrobial agents by province, 2015-2016, n=294.

Province	Antimicrobial agents							
	Tigecycline		Ceftazidime		Ciprofloxacin		Doripenem	
	S	%	S	%	S	%	S	%
Free State	2	100	0	0	0	0	1	50
Gauteng	149	75	21	11	25	13	112	56
KwaZulu-Natal	60	76	1	1	6	8	4	5
Western Cape	12	80	0	0	2	13	7	47
Total	**223**	**76**	**22**	**7**	**33**	**11**	**124**	**42**

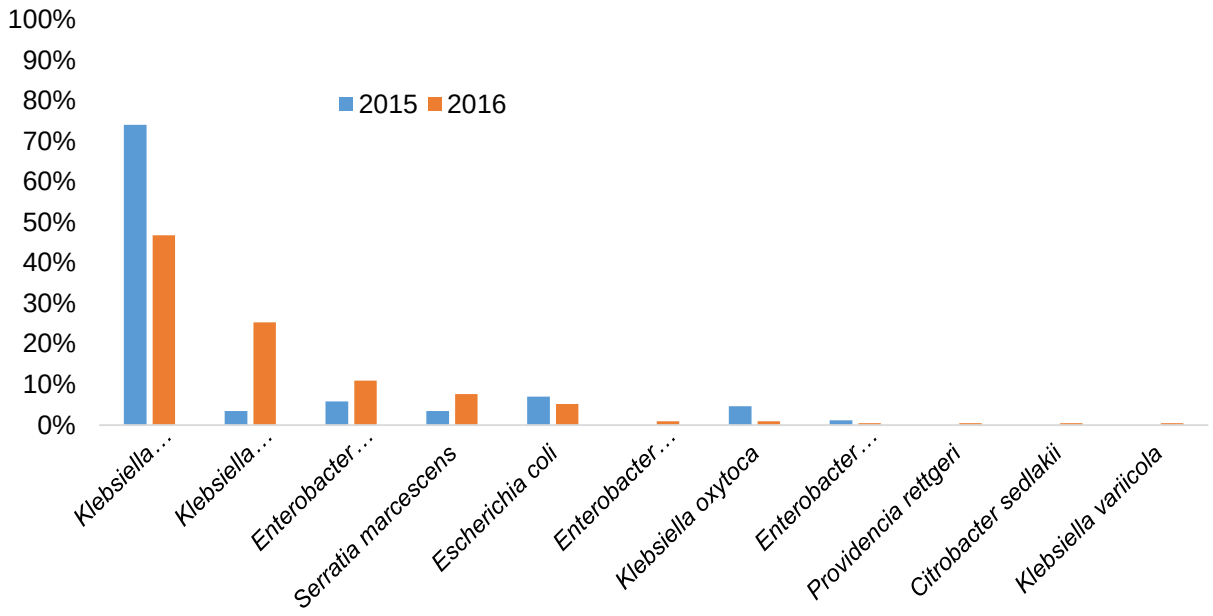

Figure 3. Species distribution of Enterobacteriaciae submitted for carbapenem-resistant Enterobacteriaceae (CRE) bacteraemia surveillance to GERMS-SA, n=294.

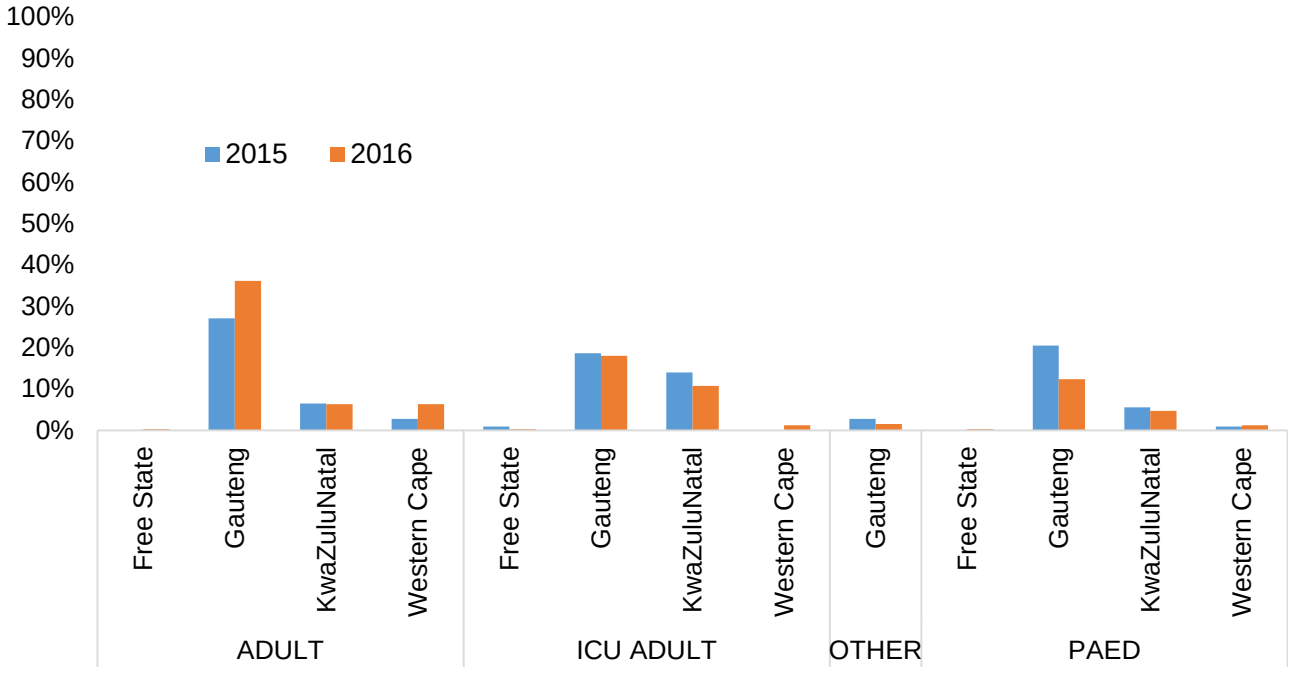

Figure 4. Distribution of cases of carbapenem-resistant Enterobacteriaceae (CRE) bacteraemia by hospital ward type, n=440.

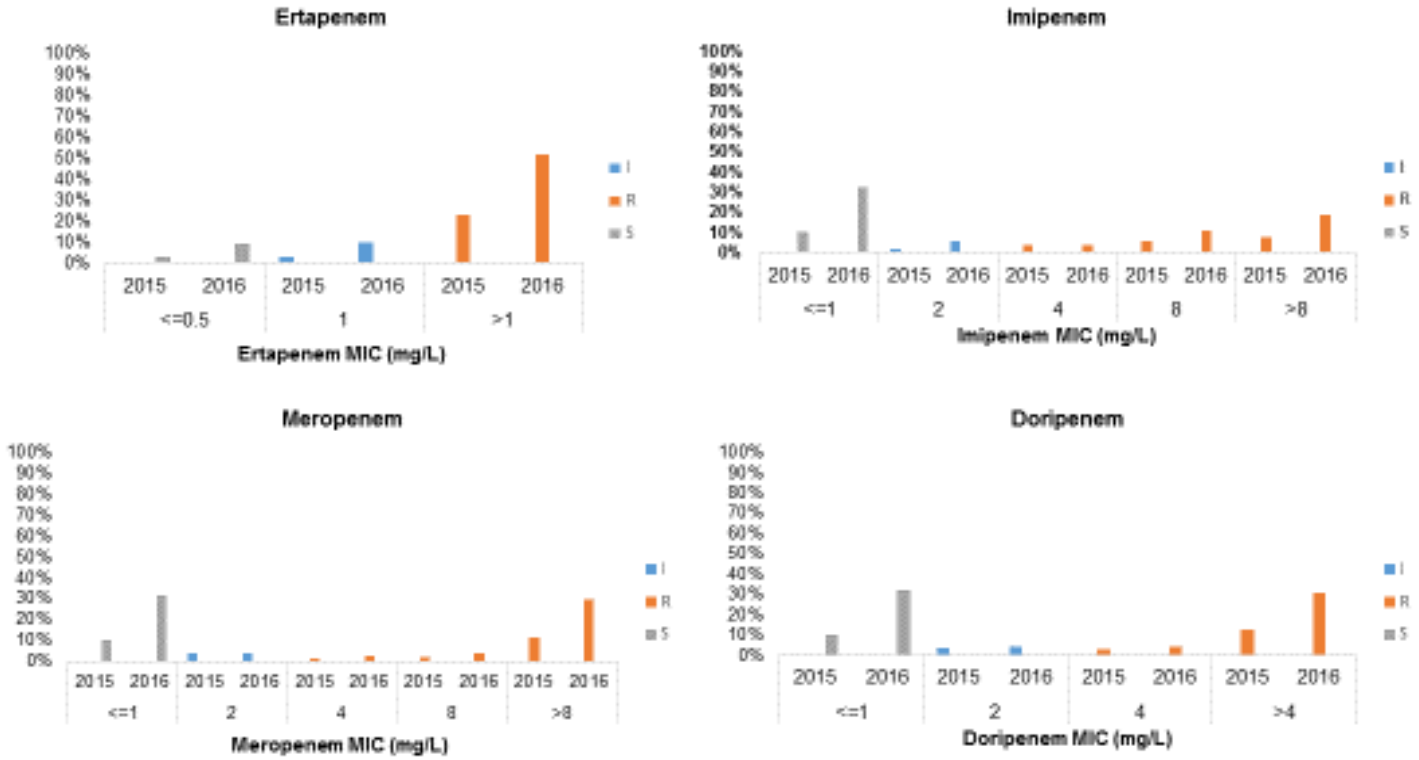

Figure 5. Antimicrobial susceptibility results for Enterobacteriaceae bloodstream isolates, n=294. I=intermediate; R=resistant; S=susceptible

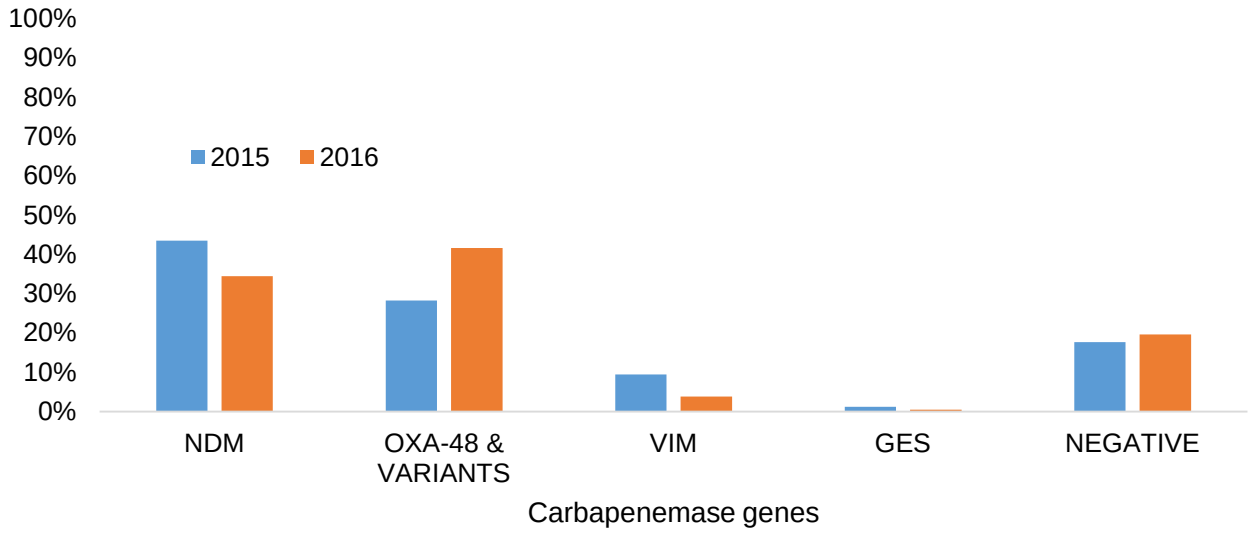

Figure 6. Carbapenemase gene detection in 238 (81%) of 294 Enterobacteriaceae bloodstream isolates.

Discussion

The number of CRE bacteraemia cases detected over the surveillance period is relatively small but these highly-resistant organisms have an impact on the public-sector health system in terms of patient outcomes and healthcare costs. Most cases were detected in Gauteng and KwaZulu-Natal. A shift to CPE mediated by OXA-48 & variants was noted even though these enzymes are not easily detected in the laboratory. In addition, the OXA genes are located on a very efficient transposon with the potential for point mutations.

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National and enhanced sentinel surveillance for candidaemia

In 2009 and 2010, the first national surveillance for candidaemia was conducted which described the species distribution and baseline antifungal susceptibility profiles of the most common *Candida* species in the public and private sectors.[1] In that survey, *Candida albicans* was the most common species isolated from 906 cases in the public sector followed by *C. parapsilosis, C. glabrata, C. tropicalis, C. krusei* and other *Candida* species. In contrast, *C. parapsilosis* was the dominant species among private-sector cases, accounting for 53% of all reported cases. In 2014, the initial emergence of *Candida auris* in South Africa was described.[2] Five years on from the first survey, national surveillance with the aim of describing changes to the epidemiology of candidaemia was re-initiated. In addition, enhanced surveillance at all GERMS sentinel hospitals and for the first time, at three private facilities in Johannesburg and Pretoria to determine the clinical epidemiology of disease, was set up.

Methods

NICD-CHARM conducted national laboratory-based surveillance for candidaemia from 1 January through 31 December 2016. A case was defined as a person diagnosed with candidaemia at any public- or private-sector laboratory in South Africa by culture of any *Candida* species from blood. A new episode was arbitrarily defined if a person had a positive culture >30 days after the first culture. Quarterly audits of the NHLS CDW were conducted to ensure completeness of reporting. Similar audits were not performed in the private sector. At sentinel public- or private-sector hospitals, nurse surveillance officers collected clinical data from admitted case patients by interview or chart review. Corresponding bloodstream isolates were submitted to the Centre for confirmation of species-level identification using the MALDI Biotyper System (Bruker) or sequencing of the internal transcribed spacer region of the multi-copy fungal ribosomal gene. Antifungal susceptibility testing

was performed for anidulafungin, fluconazole and voriconazole using commercially-available microbroth dilution panels containing Alamar Blue (Thermo Fisher Scientific, Cleveland, Ohio, USA) and for amphotericin B using the Etest method (bioMérieux, Marcy l'Etoile, France). Minimum inhibitory concentrations were interpreted using CLSI M27-S4 species-specific breakpoints.

Results

In 2016, 1760 cases of candidaemia were detected, 1127 (64%) of which were diagnosed in Gauteng Province. Of all cases, 473 (27%) were reported from the private sector. The age of cases was significantly lower in the public vs. the private sector (median, 3 years [IQR, 7 months to 46 years] vs. median, 56 years [IQR, 37 to 68 years]; p<0.001). Where sex was known, 54% (939/1732) of patients were male. Clinical case report forms were completed for 979 (55%) patients, including 75 cases at 3 private facilities in Gauteng Province. The overall crude case-fatality ratio was high (408/964; 42%) and varied significantly by species (*C. albicans*, 49%; *C. parapsilosis*, 35%; *C. glabrata*, 48%; *C. tropicalis*, 33% and *C. auris*, 48%; p=0.02) and age category (infants <1 year, 36%; children 1-17 years, 27%; adults 18-44 years, 50%; adults 45-64 years, 54% and adults ≥65 years, 69%; p<0.001). HIV infection was not an independent risk factor for candidaemia; however, 23% (127/542) of patients were HIV-infected, all but 3 in the public sector. A significantly higher proportion of patients was admitted to an intensive care unit in the private vs. public sector (68/74 [92%] vs. 633/875 [72%]; p<0.001). At least one viable isolate was identified to species level for 1408 (80%) cases of candidaemia. Overall, *C. parapsilosis* was the commonest species followed by *C. albicans;* the species distribution differed significantly by sector (p<0.001) (Table 5; Figure 7). Of particular concern, *C. auris* accounted for 9% (126/1372) of cases and was the second commonest species in the private sector and the fourth commonest in the public sector. All *Candida* isolates had an amphotericin B minimum inhibitory concentration (MIC) ≤2 µg/ml (apart from 4 *C. krusei*, 2 *C. parapsilosis* and 1 *C. albicans* isolate). Susceptibility results for five commonest *Candida* species, including *C. auris*, and three antifungal agents are summarised in Table 6. Anidulafungin MICs are presented as a proxy for susceptibility to the echinocandin class.

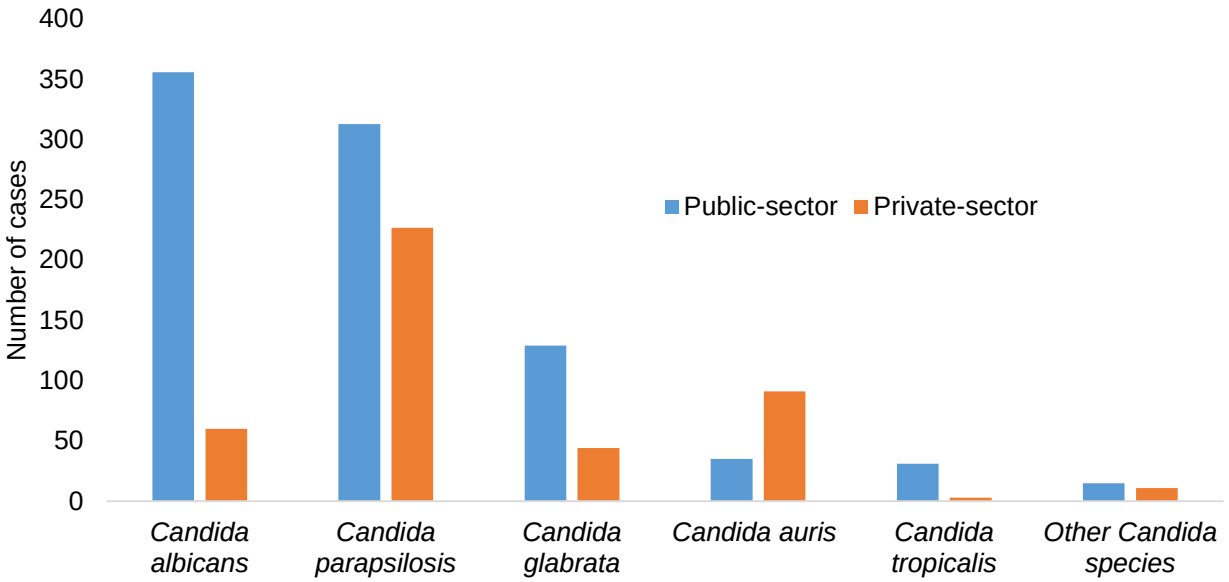

Figure 7. Species distribution of cases of candidaemia with a viable bloodstream isolate by health sector, South Africa, 2016, n=1366.

Table 5. *Candida* species distribution for cases of candidaemia with a viable bloodstream isolates by health sector and province, South Africa, 2016, n=1366.

Species	n (%):									
	EC	FS	GA	KZ	LP	MP	NC	NW	WC	Overall
Public-sector facilities										
Candida albicans	21 (46)	34 (37)	165 (33)	49 (42)	12 (55)	7 (70)	7 (54)	5 (38)	56 (46)	356 (38)
Candida parapsilosis	8 (17)	47 (51)	188 (38)	37 (32)	1 (5)	0 (0)	4 (31)	4 (31)	24 (20)	313 (34)
Candida auris	0 (0)	0 (0)	32 (6)	0 (0)	2 (9)	0 (0)	0 (0)	0 (0)	1 (1)	35 (4)
Candida glabrata	11 (24)	7 (7)	56 (11)	15 (13)	4 (18)	2 (20)	2 (15)	3 (23)	29 (24)	129 (14)
Candida tropicalis	3 (7)	0 (0)	11 (2)	10 (9)	0 (0)	0 (0)	0 (0)	1 (8)	6 (5)	31 (3)
Other *Candida* species	3 (7)	4 (4)	42 (9)	6 (5)	3 (14)	1 (10)	0 (0)	0 (0)	7 (6)	15 (2)
Sub-total	46	92	494	117	22	10	13	13	123	930
Private-sector facilities										
Candida albicans	0 (0)	0 (0)	48 (13)	2 (22)	1 (100)	3 (19)	0 (0)	2 (33)	4 (13)	60 (14)
Candida parapsilosis	0 (0)	0 (0)	192 (52)	5 (56)	0 (0)	9 (56)	0 (0)	1 (17)	20 (61)	227 (52)
Candida auris	0 (0)	1 (100)	83 (22)	2 (22)	0 (0)	4 (25)	0 (0)	0 (0)	1 (3)	91 (21)
Candida glabrata	2 (100)	0 (0)	35 (10)	0 (0)	0 (0)	0 (0)	0 (0)	3 (50)	4 (12)	44 (10)
Candida tropicalis	0 (0)	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)
Other *Candida* species	0 (0)	0 (0)	7 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (12)	11 (3)
Sub-total	2	1	368	9	1	16	0	6	33	436
Total	**48**	**93**	**862**	**126**	**23**	**26**	**13**	**19**	**156**	**1366**

EC: Eastern Cape, FS: Free State, GA: Gauteng, KZ: KwaZulu-Natal, LP: Limpopo, MP: Mpumalanga, NC: Northern Cape, NW: North West

Table 6. Numbers and percentages of *Candida* bloodstream isolates (five commonest species only) susceptible[a] to fluconazole, voriconazole and anidulafungin by health sector, South Africa, 2016, n=1288.

Antifungal agent	Number (%) of isolates susceptible to:				
	C. albicans	*C. parapsilosis*	*C. glabrata*	*C. tropicalis*	*C. auris*
Public-sector facilities	n=354	n=316	n=130	n=31	n=33
Fluconazole	345 (97)	101 (32)	0 (0)	30 (97)	No breakpoints or ECV[b]
Voriconazole	349 (99)	170 (54)	No breakpoints	27 (87)	No breakpoints or ECV[c]
Anidulafungin	354 (100)	316 (100)	128 (98)	30 (97)	No breakpoints or ECV[d]
Private-sector facilities	n=60	n=227	n=44	n=3	n=90
Fluconazole	60 (100)	31 (14)	0 (0)	3 (100)	No breakpoints or ECV[b]
Voriconazole	60 (100)	68 (30)	No breakpoints	3 (100)	No breakpoints or ECV[c]
Anidulafungin	60 (100)	227 (100)	43 (98)	3 (100)	No breakpoints or ECV[d]

[a]Based on CLSI M27-S4 species-specific breakpoints for susceptibility; [b]98% of isolates with an MIC ≥8 mg/L; [c]44% of isolates with an MIC ≥1 mg/L; [d]3 isolates with an MIC ≥1 mg/L; ECV: epidemiologic cut-off value

Discussion

The epidemiology of culture-confirmed candidaemia has changed since a national survey was last conducted in 2009 and 2010, with the emergence of *C. auris* as a major pathogen. There continue to be differences in epidemiology between the public and private sector, with some variation by province. In 2016, candidaemia was diagnosed far more commonly among young children, predominantly neonates, in the public sector and among older adults in the private sector. Overall, more than a third of patients with candidaemia, many of whom were critically ill, died in hospital. A large majority of bloodstream *C. parapsilosis* isolates were resistant to fluconazole. *Candida auris*, an emerging pathogen, is also fluconazole resistant, with very few exceptions. Azole-resistant strains of *C. parapsilosis* and *C. auris* now dominate in the private sector, particularly in Gauteng Province. Fluconazole prophylaxis should thus be discouraged in this setting, even in high-incidence hospital units. Knowledge of local hospital or hospital unit epidemiology should guide empiric treatment choices. Conventional amphotericin B remains the empiric antifungal agent of choice for candidaemia in the public sector because of the high prevalence of azole-resistant *C. parapsilosis* isolates. Caspofungin, micafungin or anidulafungin are also good choices for empiric treatment in all settings where these agents are available.

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Acknowledgements

- NICD CHARM: Amanda Shilubane, Ashika Singh-Moodley, Boniwe Makwakwa, Cheryl Hamman, Crystal Viljoen, Ernest Tsotetsi, Gloria Molaba, Mbali Dube, Mabatho Mhlanga, Manqoba Rodney Shandu, Mpho Thankjekwayo, Naseema Bulbulia, Phelly Matlapeng, Rosah Mabokachaba, Rubeina Badat, Ruth Mohlabeng, Sanelisiwe Nkabinde, Serisha Naicker, Thokozile Zulu, Tsidiso Maphanga, Sydney Mogokotleng, Wilhelminah Strasheim, Erika van Schalkwyk, Liliwe Shuping, Husna Ismail, Ruth Mpembe, Marshagne Smith.
- NICD DPHSR: Vanessa Quan, Penny Crowther, Neo Legare.
- GERMS site investigators: John Black, Shareef Abrahams, Vanessa Pearce (EC); Masego Moncho (FS); Alan Karstaedt, Caroline Maluleka, Charl Verwey, Charles Feldman, David Moore, Gary Reubenson, Jeannette Wadula, Jeremy Nel, Maphoshane Nchabeleng, Nazlee Samodien, Nicolette du Plessis, Nontombi Mbelle, Nontuthuko Maningi, Norma Bosman, Theunis Avenant, Trusha Nana, Vindana Chibabhai (GA); Adhil Maharj, Fathima Naby, Halima Dawood, Khine Swe Swe Han, Koleka Mlisana, Lisha Sookan, Nomonde Dlamini, Praksha Ramjathan, Prasha Mahabeer, Romola Naidoo, Sumayya Haffejee, Surendra Sirkar (KZN); Ken Hamese, Ngoaka Sibiya, Ruth Lekalakala (LP); Greta Hoyland (MP); Pieter Jooste (NC); Ebrahim Variava, Erna du Plessis (NW); Andrew Whitelaw, Colleen Bamford, Kessendri Reddy (WC); Adrian Brink, Craig Corcoran, Ebrahim Hoosien, Elizabeth Prentice, Inge Zietsman, Maria Botha, Peter Smith, Terry Marshall, Xoliswa Poswa (AMPATH); Chetna Govind, Juanita Smit, Keshree Pillay, Sharona Seetharam, Victoria Howell (LANCET); Catherine Samuel, Marthinus Senekal, Andries Dreyer, Khatija Ahmed, Louis Marcus, Warren Lowman (Vermaak/ PathCare); Angeliki Messina, Dena van den Bergh, Karin Swart, Caroline Maslo (Netcare).