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FOREWORD

Gonorrhoea is a major public health concern worldwide. The causative bacterium, *Neisseria gonorrhoeae*, has a remarkable capacity to acquire resistance to antimicrobials. An analysis of *N. gonorrhoeae* antimicrobial susceptibility profiles and trends for Gauteng Province over the past eight years has revealed that high-prevalence resistance to penicillin, tetracycline and ciprofloxacin obviates the use of these agents in empiric therapy guidelines for syndromic management.

This issue also contains the GERMS-SA report for 2015. This report contains summaries of national surveillance data by disease including data collected from the enhanced surveillance sites that cover all nine of South Africa's provinces. This will be the last GERMS-SA Annual Report in this format. Going forward, the GERMS-SA laboratory-based surveillance data will be incorporated into the Communicable Diseases Surveillance Bulletin under the respective NICD Centre activities.

The antimicrobial resistance surveillance conducted at the NICD aims to determine the extent of resistance amongst the most important disease causing pathogens in South Africa. Data presented in this issue show the extent of antimicrobial resistance by pathogen for 2015.

Lastly, this issue does not contain diseases incidence statistics for diseases under surveillance because the format for presenting these statistics is currently being revised. The next issue will showcase the new format which will include incidence statistics for all notifiable medical conditions (NMCs) in South Africa and will include comparative retrospective statistics for the preceding five years. It should also be noted that the scope of the Communicable Diseases Surveillance Bulletin has been revised to ensure that this publication serves as a vehicle for the critical analysis of current and retrospective disease incidence and public health information in South Africa.

All participating laboratories and contributors are thanked for their inputs, especially Penny Crowther-Gibson and Vanessa Quan who co-edited the GERMS-SA report.

Basil Brooke, Editor

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NEISSERIA GONORRHOEAE ANTIMICROBIAL RESISTANCE SURVEILLANCE IN GAUTENG PROVINCE, SOUTH AFRICA

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Introduction

Gonorrhoea is a sexually transmitted disease caused by the bacterium *Neisseria gonorrhoeae*. Although many infected persons are asymptomatic, gonorrhoea is a major public health concern worldwide. The infection has a short incubation period lasting a few days, as well as a high transmission efficiency, and leads to a fivefold increase in HIV transmission and complications such as pelvic inflammatory disease and infertility which compound the global health burden.[1] The WHO 2012 prevalence data for curable sexually transmitted infections revealed that the estimated global prevalence of gonorrhoea among women aged 15-49 years was 0.8% (95% uncertainty interval 0.6-1.0%) ; and among 15-49 year old males 0.6% (0.4-0.9%).[2] These estimates corresponded to 78 million (53-110 million) new cases of gonorrhoea.

Neisseria gonorrhoeae, an obligate human pathogen, has displayed an alarming propensity to acquire resistance, through genetic mechanisms (both chromosomal and plasmid-mediated), to all sequential first-line antimicrobial agents used over the years.[3] Penicillin was first used in the 1940s and tetracycline from the 1950s - 1980s, but high-level plasmid-mediated resistances to both agents were being described by the 1980s. Quinolones were introduced in the early 1980s but resistance emerged in the Asia-Pacific region and then spread globally.[4] Antimicrobial resistance does not appear to confer a fitness cost as resistant strains predominate globally following withdrawal of the antimicrobial in question from clinical use.[4]

Extended-spectrum cephalosporins (ESCs) are considered to be the last antimicrobial class suitable for widespread single-dose, single-agent treatment. Cefixime is the only oral ESC that meets the criteria for the effective treatment of pharyngeal gonorrhoea with a > 95% cure rate. In Japan in the 1990s, use of a variety of oral ESCs with suboptimal efficacies in inadequate dosing regimens led to ultimate treatment failure with cefixime.[5] By 2010, clinically confirmed treatment failures had been described in Europe and North America.[6]

The WHO Global Gonococcal Antimicrobial Surveillance Program (GASP) was relaunched in 2009 to monitor the trends of antimicrobial resistance in *N. gonorrhoeae* and improve knowledge on potential resistance mechanisms through laboratory testing.[1] South Africa is a participating country, and the Sexually Transmitted Infections (STI) laboratory of the Centre for HIV and STIs (CHIVSTI) of the NICD is a regional institution for the GASP network in WHO-Africa.

Data showing the distribution of STI syndromes among males and females attending primary healthcare facilities (PHCs) in South Africa reveal that Male Urethritis Syndrome (MUS) and Vaginal Discharge Syndrome comprise the bulk of STI presentations.[7] Periodic aetiological surveillance of STI syndromes is essential to update and validate the existing syndromic management guidelines. The Centre for HIV and STIs has co-ordinated microbiological surveillance in patients

presenting to sentinel PHCs since 2005. Results indicate that *N. gonorrhoea* is the predominant cause of MUS (70-80%) and is present in 10-15% of symptomatic VDS cases.[8] Antimicrobial susceptibility testing of *N. gonorrhoeae* isolates forms an integral part of this aetiological surveillance. Resistance surveys have been conducted annually in Gauteng since 2007, and periodically in other provinces.

Resistance patterns and trends to various antimicrobials in *N. gonorrhoeae* isolates from STI surveillance in Gauteng Province over an eight-year period spanning 2008 to 2015 are described here.

Methods

Neisseria gonorrhoeae was cultured from swab specimens of genital discharge (endocervical and urethral) in consenting adult patients. From 2007-2014, national microbiological surveillance activities were undertaken by the provincial Department of Health. This required the systematic recruitment of consecutive consenting adult patients (both male and female) presenting with genital discharge to each sentinel PHC. In 2015, STI surveillance was incorporated into the NICD GERMS-SA surveillance platform. Surveillance activities involved sampling of approximately 150-200 males presenting with urethritis for the isolation of at least 100 viable gonococcal isolates per site.

Specimens were either directly inoculated onto specialised agar and the culture plates were placed in candle jars for transfer to the NICD STI laboratory, or swabs were placed in Amies™ transport media and transported on ice for culture in the reference laboratory. At the laboratory, gonococcal isolates were tested for susceptibility to antimicrobials by E-test™ (cefixime, ceftriaxone, ciprofloxacin) or agar dilution (penicillin, tetracycline, azithromycin) according to established standard operating protocols. Minimum inhibitory concentrations (MICs) were interpreted according to criteria recommended by the Clinical Laboratory Standards Institute (CLSI)[9], or for azithromycin susceptibility, according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints.[10] For purposes of quality assurance a panel of control strains of *N. gonorrhoeae* with known MICs to each antimicrobial was included in every batch of clinical isolates tested.

Data analysis: Analysis of susceptibility trends was performed using Stata™ version 14 for *Neisseria gonorrhoeae* isolates obtained from annual Gauteng surveillance at a single sentinel site between 2008 and 2015. The relative prevalence of susceptibility and resistance was determined for those antimicrobials to which resistance is well-established. Chi-square tests were used to determine whether the difference in high-level resistance prevalence between calendar years reached statistical significance.

For antimicrobials currently recommended for use, MIC50 (minimum concentration needed to inhibit 50% of isolates); MIC90 (minimum concentration needed to inhibit 90% of isolates); and maximum MICs were determined by year. The K-sample test was used to test for equality of medians (MIC50) across calendar years, while linear regression and likelihood-ratio tests were used to test for MIC trends.

Results

Resistance profiles of N. gonorrhoeae to antimicrobials tested by calendar year: Neisseria gonorrhoeae isolates for E-test MIC were available for every consecutive year from 2008-2015 (Table 1). Fewer isolates were tested using agar dilution, and data are available from 2011-2015 (Table 1). Agar dilution MIC testing was not performed in the 2014 calendar year.

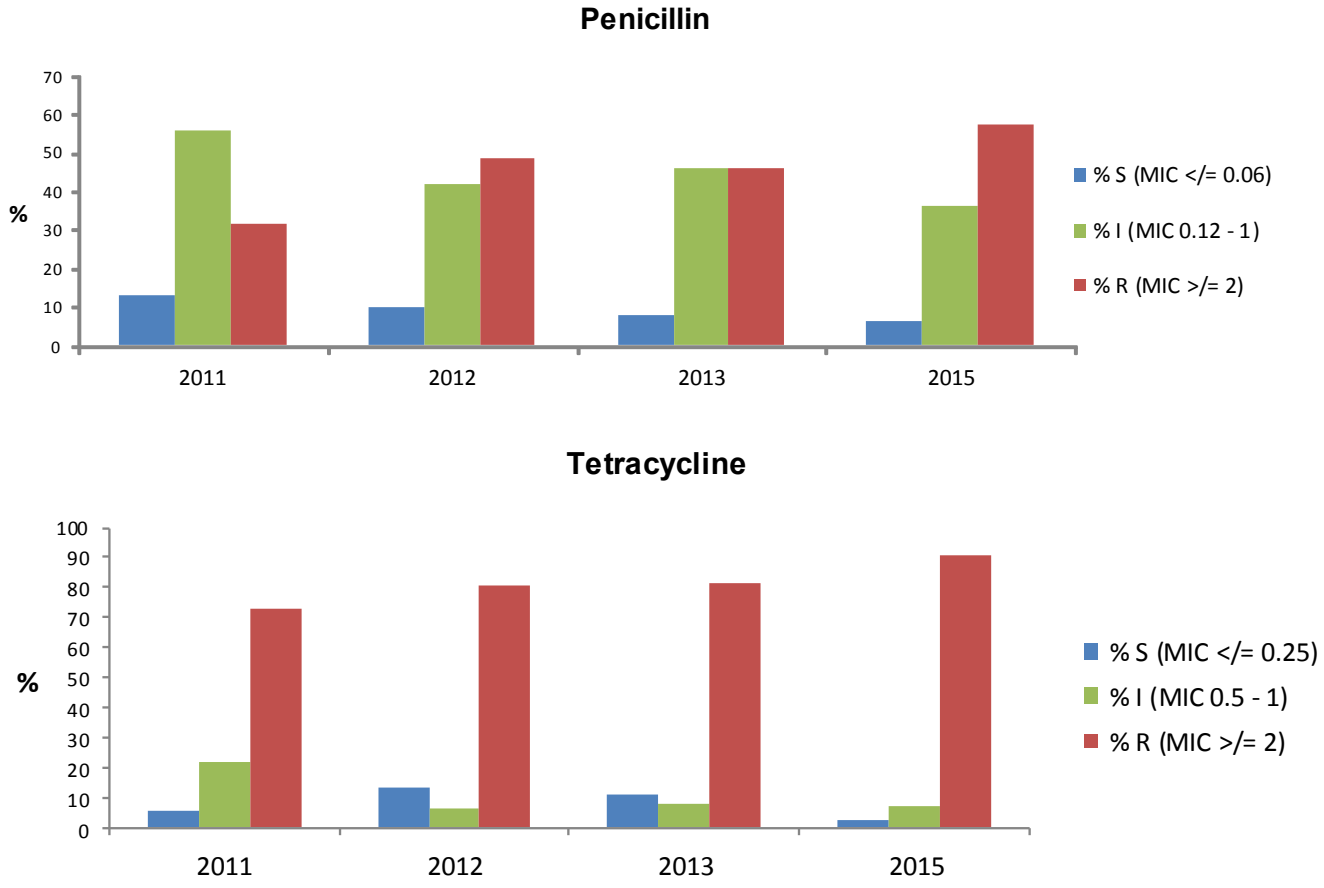
Table 1: Numbers of *Neisseria gonorrhoeae* isolates used for antimicrobial susceptibility testing (AST) by calendar year for the period 2008 to 2015, Gauteng, South Africa.

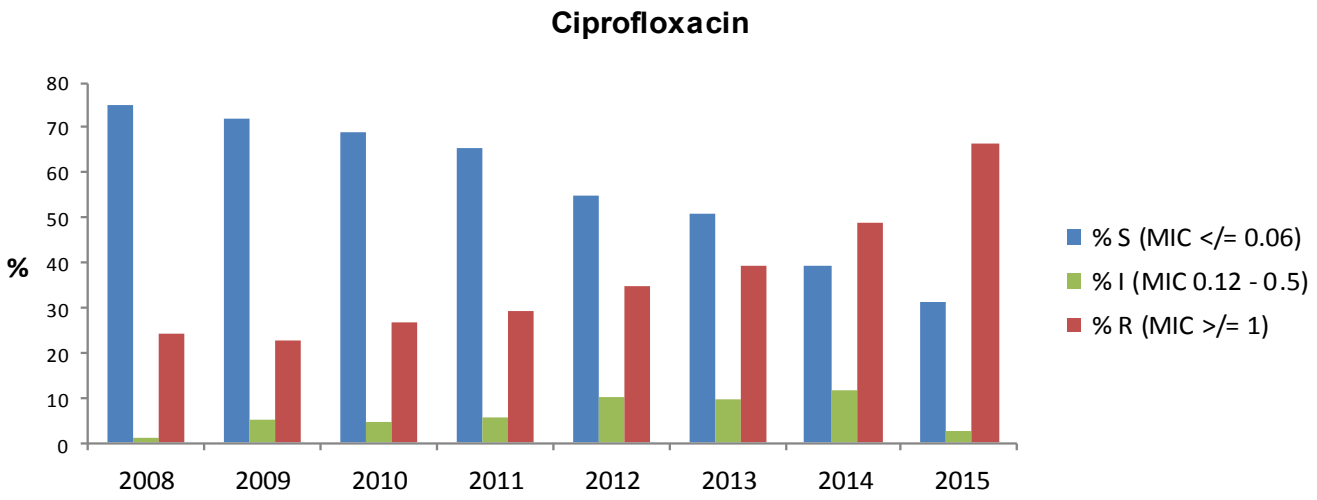
Year	Antimicrobials & AST Method Cefixime (CXM), Ceftriaxone (CTR), Ciprofloxacin (CIP) E-test MIC	Azithromycin (AZT), Penicillin (PEN), Tetracycline (TET) Agar dilution MIC
2008	328 (CTR & CIP only)	
2009	324	
2010	316	
2011	282	70
2012	294	31
2013	228	78
2014	205	
2015	135 (CXM & CTR only)	125 (TET; PEN; CIP; AZT)

MIC = minimum inhibitory concentration

During the periods under review, there was a general increase in the prevalence of *N. gonorrhoeae* resistance to penicillin, tetracycline and ciprofloxacin (Figure 1). Between 2011 and 2015, the prevalence of high-level resistance rose from 31% to 57% for penicillin (p=0.009) and from 73% to 91% for tetracycline (p=0.009). Between 2008 and 2015, the prevalence of high-level resistance to ciprofloxacin rose exponentially from 24% to 67% (p <0.001).

Figure 1: Antimicrobials to which resistance was established by calendar year, Gauteng, South Africa.





S = Susceptible; I = Intermediately-resistant; R = resistant; MIC = minimum inhibitory concentration

The Clinical Laboratory Standards Institute defines decreased susceptibility to extended-spectrum cephalosporins (DS ESC) as a MIC ≥ 0.5 µg/ml[7]; whereas EUCAST uses a cut-off that is one double-dilution lower at ≥ 0.25 µg/ml.[7] More than 99% of isolates were especially sensitive to ESCs (Table 2). Decreased susceptibility to cefixime was not observed using CLSI interpretive criteria, whereas it was seen in one isolate from 2013 (0.4%) using EUCAST cut-offs. Two isolates from 2009 exhibited decreased susceptibility to ceftriaxone using EUCAST criteria (0.6%) and one of these (0.3%) also showed reduced ceftriaxone susceptibility according to CLSI breakpoints (Table 3). Unfortunately, these two isolates were not available for further analysis.

Trend analysis revealed an MIC creep for cefixime, i.e. a significant increase in MIC50 and MIC90, notably in 2015 (Table 2).

Table 2: Minimum inhibitory concentration (MIC) trend analyses for cefixime, Gauteng, South Africa, 2008-2015.

Year	No of isolates	MIC_{50}	MIC_{90}	Maximum MIC	% with MIC = 0.125	% with MIC = 0.25	% with MIC >/= 0.5
2009	324	<0.016	0.016	0.064	0.00	0	0.0
2010	316	<0.016	<0.016	0.016	0.00	0	0.0
2011	282	<0.016	<0.016	0.016	0.00	0	0.0
2012	294	<0.016	<0.016	0.016	0.00	0	0.0
2013	228	<0.016	0.016	0.25	0.00	0.4 (1)	0.0
2014	205	<0.016	0.016	0.047	0.00	0	0.0
2015	125	0.016	0.032	0.064	0.00	0	0.0

p-value for equality of medians across years < 0.001

Table 3: Minimum inhibitory concentration (MIC) trend analyses for ceftriaxone, Gauteng, South Africa, 2008-2015

Year	No of isolates	MIC_{50}	MIC_{90}	Maximum MIC	% with MIC = 0.125	% with MIC =0.25	% with MIC >/= 0.5
2008	328	0.002	0.004	0.008	0	0	0
2009	324	0.003	0.006	0.38	0	0.3 (1)	0.3 (1)
2010	316	0.002	0.006	0.032	0	0	0
2011	282	0.003	0.004	0.012	0	0	0
2012	294	0.003	0.004	0.016	0	0	0
2013	197	0.003	0.006	0.064	0	0	0
2014	205	0.004	0.008	0.016	0	0	0
2015	135	0.003	0.006	0.023	0	0	0

The Clinical Laboratory Standards Institute has not established interpretive criteria for azithromycin. EUCAST defines resistance as MIC > 0.5 µg/ml, based on an epidemiological cut-off of 1 µg/ml for wild-type *N. gonorrhoeae* isolates.[10] The US Gonococcal Isolate Surveillance Project (GISP) uses a breakpoint of $\geq$ 2 µg/ml to define elevated MICs to azithromycin and increased likelihood of treatment failure.[6]

Elevated azithromycin MICs were observed in 2013 and 2015: in 10/78 isolates (13%) and 5/125 isolates (4%), respectively, according to EUCAST criteria (Table 4). Further analysis, including repeat agar-dilution MIC testing, will be undertaken to determine reproducibility of these results and whether these isolates represent a single clone. Isolates with MIC $\geq$ 2 µg/ml, and defined as having reduced susceptibility based on the GISP surveillance case definition, were detected only in 2013 (2/78; (3%)).

Table 4: Minimum inhibitory concentration (MIC) trend analyses for azithromycin, Gauteng, South Africa, 2011-2015

Year	No. of isolates	MIC_{50}	MIC_{90}	Maximum MIC	% with MIC </= 0.25	% with MIC > 0.5	% with MIC >/= 2
2011	70	0.128	0.25	0.5	93	0.0	0.0
2012	31	0.128	0.5	0.5	87	0.0	0.0
2013	78	0.25	1	4	72	13 (10)	3 (2)
2015	125	0.25	0.5	1	89	4 (5)	0.0

p-value for equality of medians across years < 0.001

Discussion

These data reveal that penicillin and tetracycline are unlikely to be included in any future genital discharge treatment algorithms in South Africa. In South African isolates, high-level penicillin resistance was found to be plasmid-mediated i.e. a novel beta-lactamase producing "Johannesburg" plasmid was identified and these penicillinase-producing isolates were discovered to be clonally related.[11] Similarly, two types of tetracycline resistant *N. gonorrhoeae* (TRNG) plasmids have been

detected and they confer high-level resistance to the drug.[12]

Escalating ciprofloxacin resistance was seen in Johannesburg and Cape Town when data from 2004 and 2007 were compared.[13] In Johannesburg, there was a 2.9-fold increase in resistance prevalence from 11% to 32%; and in Cape Town a 3.8-fold increase from 7% to 27%. The World Health Organization recommends a change of empirical treatment for gonorrhoea when the resistance threshold reaches 5%.[14] The South African syndromic management guidelines were therefore formally revised in 2008 to replace ciprofloxacin and incorporate cefixime as first-line therapy for gonorrhoea.[15]

The primary resistance determinant to extended-spectrum cephalosporins (ESCs) is a specific alteration in the *penA*gene encoding penicillin binding protein 2 (PBP2). This occurs through acquisition and recombination into its genome of foreign gene sequences from commensal *Neisseria* species residing in the oropharynx. This transformation gives rise to a mosaic *penA* gene encoding a mosaic PBP2 with reduced target affinity for ESCs: the MICs of cefixime are increased proportionately more than those of ceftriaxone.[16] In South Africa, in 2012, the first two cases of DS ESC associated with cefixime treatment failure were described in two patients presenting with persistent urethral discharge.[17] Genetic characterization of the two isolates using *N. gonorrhoeae* multi-antigen sequence typing (NG-MAST) and multi-locus sequence typing (MLST), revealed identical sequence types which represent a multi-drug resistant clone characterized by DS ESC and global spread. Both patients were in the men-who-have-sex-with-men (MSM) risk group. There are two factors that could lead to the spread of resistance in this key population: high risk sexual behaviour and participation in international sexual networks, and the presence of pharyngeal gonorrhoea, which is typically asymptomatic. Gonococci residing in the pharynx are at a survival advantage due to differential concentrations of antimicrobials at this site, and the opportunity for DNA exchange with oropharyngeal commensal *Neisseria* species. An additional two cases of DS to cefixime were identified in MSM residing in Cape Town and East London, respectively (D. Lewis, unpublished data).

In 2009, the world's first confirmed extensively-drug resistant (XDR) *N. gonorrhoeae* infection was reported from Japan.[18] The gonococcal strain, isolated from the pharynx of a female sex worker (FSW), displayed high-level resistance to both cefixime (MIC = 8) and ceftriaxone (MIC = 2-4). It was also resistant to several other classes of antimicrobials, including fluoroquinolones, macrolides and tetracycline. Following these reports and in accordance with WHO recommendations, there was a national change in recommended first-line therapy for gonorrhoea from oral cefixime to injectable ceftriaxone (250mg single-dose) in 2014 in South Africa. Additional dual therapy with oral azithromycin (1g stat) was recommended.[19] This was a pro-active and pre-emptive approach, endorsed by the WHO, to limit the emergence of XDR *N. gonorrhoeae* worldwide, particularly in areas where there is a general lack of surveillance in key populations, such as MSM and FSW.[20]

Although clinical effectiveness of azithromycin for urethral and endocervical infections has been estimated to be >95%,[21] it is recommended only in dual therapy due to the ease of resistance development to macrolide monotherapy. Resistance has been described even with use of higher dose (2g) azithromycin monotherapy,[22] and this dose is associated with increased gastro-intestinal side-effects.

Failure of dual ceftriaxone-azithromycin therapy has recently been described, with persistence of pharyngeal gonorrhoea in a heterosexual man treated for urogenital symptoms.[23] The patient was infected with an XDR strain, which had acquired multiple resistance mechanisms to both ceftriaxone and azithromycin. Molecular epidemiology identified the isolate as MLST ST1901 and a new NG-MAST ST 12133, which belongs to a genogroup that is associated with extensive drug-resistance and is spreading in Japan.

This surveillance report describes resistance trends to various antimicrobials used in past and current gonorrhoea treatment regimens. It is limited by a lack of corresponding demographic and clinical data, including behavioural characteristics of patients presenting with genital discharge. Future analyses incorporating this information could be used to better understand transmission dynamics and inform control efforts. Additional analyses are planned using data from other provinces to study national trends in gonococcal antimicrobial resistance.

The ease with which *N. gonorrhoeae* develops drug resistance means that antimicrobial stewardship strategies are urgently needed. These should include rational, standardized and regulated prescription practice for genital discharge syndrome, as well as research and development initiatives for novel antimicrobials with unique mechanisms of action and their incorporation into appropriate therapeutic regimens.

There is a need for accurate rapid diagnostics that would facilitate screening for asymptomatic and extra-genital infection in high-risk and key population groups. Additionally, allocation of resources is required for enhanced local surveillance strategies. These would include theimplementation of activities designed to increase detection of treatment failure cases and extragenital (pharyngeal) infections at healthcare level, as well as sustained antimicrobial surveys (including test -of-cure using culture) in key populations.

Conclusions

Neisseria gonorrhoeae antimicrobial susceptibility profiles and trends for Gauteng over a period of eight years reveal that high-prevalence resistance to penicillin, tetracycline and ciprofloxacin obviates the use of these agents in empiric therapy guidelines for syndromic management.

The prevalence of resistance to ESCs is < 1%, validating continued use of ceftriaxone in dual therapy for gonorrhoea. However, it is essential that ESC and azithromycin susceptibility trends for representative numbers of isolates are monitored to detect emerging resistance timeously.

Key Points

- Antimicrobial resistance in *Neisseria gonorrhoeae* is increasing worldwide
- Extensively-drug resistant (XDR) strains are characterised by high extended-spectrum cephalosporin MICs
- Dual therapy with injectable ceftriaxone and azithromycin may curtail emergence of XDR strains
- Enhanced national and regional culture-based surveillance is essential to detect emerging resistance, particularly in key populations

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GROUP FOR ENTERIC, RESPIRATORY AND MENINGEAL DISEASE SURVEILLANCE FOR SOUTH AFRICA (GERMS-SA) REPORT FOR 2015

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The GERMS-SA Annual Report 2015 is also available from:
http://www.nicd.ac.za/assets/files/2015%20GERMS-SA%20AR.pdf

Introduction

This report summarises the findings from national laboratory-based surveillance, including clinical data from the 36 enhanced surveillance (ESS) hospital sites in all 9 provinces, for 2015.

Challenges with staffing at National Health Laboratory Service (NHLS) diagnostic laboratories have impacted on the numbers of isolates sent to National Institute for Communicable Diseases (NICD) reference laboratories. The annual percentage of viable isolates received continues to fall. The GERMS-SA surveillance system monitors the impact of programmes, like the Expanded Programme on Immunisations and the Comprehensive Care, Management and Treatment Programme for HIV/ AIDS, on the South African population.

Funding for GERMS-SA has been fully absorbed by the NICD through the South African Department of Health.

The GERMS-SA platform has been expanded to include clinic surveillance of drug resistance in TB and HIV, as well as STI surveillance. These reports can be found in the NICD Surveillance Bulletin.[1] This will be the last GERMS-SA Annual Report in this format. Going forward, the GERMS-SA laboratory-based surveillance data will also be incorporated into the NICD Surveillance Bulletin under the respective Centre activities.

Methods

In 2015, diseases under surveillance included:

1. Opportunistic infections associated with HIV, e.g. cryptococcosis, invasive non-typhoidal Salmonella enterica (NTS) disease, invasive pneumococcal disease (IPD) and rifampicin-resistant Mycobacterium tuberculosis
2. Epidemic-prone diseases, e.g. Neisseria meningitidis, Salmonella enterica serotype Typhi,

Shigella species, Vibrio cholerae and diarrhoeagenic Escherichia coli
3. Vaccine-preventable diseases, e.g. Haemophilus influenzae type b (Hib) and Streptococcus pneumonia
4. Hospital infections, e.g. Staphylococcus aureus, Pseudomonas aeruginosa and Candida species

The methods utilised by the GERMS-SA surveillance programme have been previously described in detail.2
In brief, approximately 222 South African clinical microbiology laboratories participated in the surveillance programme in 2015.

The population under surveillance in 2015 was estimated at 54.9 million (Table 1). Diagnostic laboratories reported case patients to the National Institute for Communicable Diseases (NICD) using laboratory case report forms according to standard case definitions. If available, isolates from case patients were submitted on Dorset transport media to the NICD for further phenotypic and genotypic characterisation. From 1 July 2008 to 31 December 2013, surveillance methodology for the cryptococcal project was changed, so that only enhanced surveillance sites (ESS) (29 hospitals in 9 provinces), NHLS laboratories in KZN, and laboratories in the private, mining and military sectors were required to directly report case patients to NICD. In 2014 and 2015, no laboratories were required to directly report case patients or send isolates to the NICD. For these cases of cryptococcosis, data were obtained directly from the NHLS Corporate Data Warehouse (CDW) which stores information from Disa*Lab and TrakCare laboratory information systems. Cryptococcal isolates obtained from patients at ESS continued to be characterised by phenotypic and genotypic tests through 2013, but were not available in 2014 or 2015. From July 2010 through August 2012, 7 sentinel sites reported cases of S. aureus bacteraemia to GERMS-SA. From September 2012 through 2013, laboratory-based bacteraemic S. aureus surveillance continued at 3 Gauteng sites only, and in 2014 and 2015, 2 additional sites in the Western Cape were included. From January 2012, 7 sentinel sites in Gauteng and Western Cape provinces reported cases of candidaemia to GERMS-SA, increasing to 12 sites in 2013. Candidaemia surveillance changed to 18 new sites in the remaining seven provinces in 2014, with an additional 2 in 2015. Enhanced surveillance was not conducted on any of the enteric pathogens in 2014 and 2015. At ESS, surveillance officers completed clinical case report forms electronically using the Mobenzi application on mobile phones for patients with seven laboratory-confirmed diseases (cryptococcosis [for January through March only, except at 4 cryptococcal screening sites], candidaemia, invasive pneumococcal disease, invasive meningococcal disease, invasive Haemophilus influenzae disease, bacteraemic S. aureus disease [at 5 sites] and rifampicin-resistant tuberculosis [at 7 sites]), by case patient interview or hospital medical record review, to obtain additional clinical details, including antimicrobial use, vaccination history, HIV status, and patient outcome. Case patients were followed up only for the duration of the hospital admission. Data management was centralised at the NICD. Laboratory, clinical and demographic data from case patients were recorded on a Microsoft Access database. A surveillance audit was performed for NHLS laboratories in all provinces using the NHLS CDW. For all diseases under surveillance, except cryptococcosis, the audit was designed to obtain basic demographic and laboratory data from additional case patients with laboratory-confirmed disease not already reported to GERMS-SA by participating laboratories. For cryptococcosis, the audit was designed to obtain data from cases that were no longer reported by NHLS laboratories. Data from case patients, detected by audit, were included on the surveillance database, and have been included in this

report. However, the NHLS changing over from the DISA*lab to TrakCare Lab has proved difficult for our auditing purposes and all case numbers may not be reflected. Incidence was calculated using mid-year population estimates for 2014 and 2015 from Statistics South Africa (Table 1).3 Incidence in the HIV-infected and AIDS populations was calculated for 2014 and 2015 using estimated population denominators from the Actuarial Society of South Africa (ASSA) 2008 model (Table 1), assuming that the HIV/AIDS prevalence amongst cases with known status was similar to those with unknown status.4 All reported incidence is expressed as cases per 100,000 population unless otherwise stated. Reported p-values were calculated using the Mantel-Haenszel chi-squared test and p values <0.05 were considered significant throughout. Ethics approval for the on-going activities of the surveillance programme was obtained from the Human Research Ethics Committee (Medical), University of Witwatersrand (clearance number M08-11-17) and from relevant University and Provincial Ethics Committees for other enhanced surveillance sites. Surveillance activities were funded by the NICD/NHLS.

Table 1: Population denominators used to calculate incidence rates, South Africa, 2014 and 2015.

Province	General population*		HIV-infected population**		AIDS population**	
	2014	2015	2014	2015	2014	2015
Eastern Cape	6,786,880	**6,916,185**	777,096	**796,634**	75,325	**80,652**
Free State	2,786,757	**2,817,941**	363,254	**366,895**	39,323	**41,238**
Gauteng	12,914,817	**13,200,349**	1,229,076	**1,229,068**	146,240	**152,552**
KwaZulu-Natal	10,694,434	**10,919,077**	1,654,551	**1,680,200**	177,961	**187,299**
Limpopo	5,630,464	**5,726,792**	449,748	**461,927**	43,143	**46,526**
Mpumalanga	4,229,323	**4,283,888**	511,625	**520,480**	52,712	**55,965**
Northern Cape	1,166,680	**1,185,628**	81,550	**82,723**	8,896	**9,432**
North West	3,676,274	**3,706,962**	446,737	**451,339**	49,611	**51,915**
Western Cape	6,116,324	**6,200,098**	287,163	**289,915**	32,721	**34,743**
South Africa	54,001,953	**54,956,920**	5,880,382	**5,967,061**	629,183	**665,502**

Data source: *Statistics South Africa; **Actuarial Society of South Africa (ASSA2008).

Operational Report

Site visits

In 2015, NICD staff members visited 34 sites to do feedback, training and trouble-shooting at laboratories, hospitals and clinics linked to GERMS surveillance (Table 2). Feedback is important to maintain or improve surveillance participation.

Coordination of meetings

Surveillance officer meeting, 28-29 May 2015: All surveillance officers from all provinces attended the meeting in Johannesburg. We concentrated on antimicrobial resistance as Carbapenem-Resistant Enterobacteriaceae surveillance was starting, fed back on the routine lab surveillance projects, did counselling and debriefing of surveillance staff as well as how surveillance officers can help educate patients on their diseases, and the usual re-training on specific challenges in quality as well as electronic data capture problems.

Surveillance officer meeting, 19-20 November 2015: Surveillance staff attended this surveillance officer and data clerk meeting in Cape Town. Discussions and

training on all projects were useful and we went through the changes for the 2016 case report forms. Once again data quality was emphasised. It was an opportunity for staff who do not usually present to have a chance to learn these skills. The data team also trained on data cleaning.

GERMS-SA NICD Annual Surveillance Review, 27-28 October 2015: A number of clinicians, laboratorians, and Provincial and District DOH members attended the meeting at NICD. It focused on NICD Centre surveillance feedback (mostly through the GERMS platform – laboratory and clinic surveillance) and included some of the Severe Acute Respiratory Infections (SARI) results.

GERMS-SA Western Cape PI Meeting, 20 November 2015: There was less participation than usual from the WC at our Annual Surveillance Review, due to prior commitments, so a mini Principal Investigators' meeting was held in the WC. We covered the most important projects that are done through GERMS in the WC - mostly respiratory diseases and meningitis including cryptococcal meningitis. Expansion into other sentinel sites was discussed.

Surveillance audit

A total of 16,244 surveillance cases were detected by GERMS-SA in 2015. Excluding the cases of cryptococcosis (n=6,174), which are all detected by audit as isolates, are no longer required to be sent to the NICD, and cases of rifampicin-resistant TB (n=943), for which no audits are performed, 25% (2,254/9,127) of cases were not reported to the NICD by the clinical microbiology laboratories, but were detected by audit of the NHLS Corporate Data Warehouse (Table 3). GERMS-SA constantly strives to reduce the number of cases detected on audit by raising awareness of the surveillance programme; this is important because GERMS-SA is unable to perform additional microbiological characterisation of isolates detected only through audit.

Enhanced surveillance site performance indicators

Surveillance organisms have changed in 2015, making it less comparable to previous years. Enhanced surveillance was not conducted on any of the enteric pathogens. The proportion of completed CRFs in 2015 was similar to that in 2014; the addition of pathogens that cause more severe illness (candidaemia and *S. aureus*) make it more difficult to follow-up patients (Table 4 and 5): 93% (2,889/3,107) of cases had a case report form (CRF) completed (target = 90%). The interview rate continues to improve over the years [2,465 (85%) of the CRFs were completed by patient interview (target = 70%)]. Since 2007, enhanced surveillance site operational reports (ESSOR) have been provided to the site coordinators, laboratory staff and surveillance officers to enable the site team to regularly review site performance, in comparison with set targets. The main objective of these reports is to provide information regarding the overall functioning of the surveillance site by providing indicators of laboratory participation (submission of isolates) and indicators of surveillance officer performance (completion of CRFs). By reviewing these indicators, problems with data collection can be targeted and recommendations are provided to improve the site performance. In 2015, these reports were provided quarterly.

Enhanced surveillance site quality monitoring

In 2015, surveillance officers (SOs) were audited in terms of quality of work. CRFs from a fixed time period were randomly selected for each surveillance officer so that there were 7 CRFs (one for each organism) to audit per SO. The medical record files were drawn and the GERMS-coordinating staff filled in a modified clean CRF from the original source data and compared their CRF with the original SO CRF. A scoring system was set up and, although the scores varied widely amongst SOs, many of the errors were ones of omission and overlooking information rather than entry of incorrect data.

Table 2: GERMS-SA surveillance site visits between 1 January and 31 December 2015.

Date	Province*	Laboratory (NHLS or private)	Hospital/ Clinic
20 January	MP	NHLS Nelspruit	Surrounding clinics
16 February	GA	NHLS Helen Joseph	Helen Joseph Hospital
7-9 March	KZ	NHLS Northdale	Surrounding clinics
27 March	FS	-	Pelonomi Hospital
20-21 April	WC	NHLS George	MDR TB facility, George
24 April	GA	NHLS Chris Hani Baragwanath	Chris Hani Baragwanath Hospital
13 May	NW	-	Jouberton clinic
19 May	NW	NHLS Klerksdorp/ Tshepong	Klerksdorp / Tshepong Hospital & Jouberton clinic
20 May	GA	NHLS Helen Joseph	Helen Joseph Hospital
17-18 June	EC	-	Gqebera clinic
22-25 June	MP	-	Hluvukani clinic
13 July	GA	NHLS Helen Joseph	Helen Joseph Hospital
13-15 July	EC	NHLS Port Elizabeth	Port Elizabeth
17 July	MP	NHLS Nelspruit	Rob Ferreira Hospital & Nelspruit clinics
21 July	GA	NHLS Chris Hani Baragwanath	Chris Hani Baragwanath Hospital
22 July	GA	NHLS Helen Joseph	Helen Joseph Hospital
30 July	GA	NHLS Helen Joseph	Helen Joseph Hospital
5 August	GA	NHLS Helen Joseph	Helen Joseph Hospital
5-7 August	LP	NHLS Polokwane	Polokwane/ Mankweng Hospital
12-14 August	LP	NHLS Polokwane	Polokwane Hospital & surrounding clinics
19-20 August	FS	NHLS Universitas	Universitas/ Pelonomi Hospital
20 August	GA	NHLS Dr George Mukhari	Dr George Mukhari Hospital
31 August	GA	NHLS Helen Joseph	Helen Joseph Hospital
2-3 September	KZ	NHLS Addington	Addington Hospital
4 September	KZ	NHLS King Edward VIII	King Edward VIII Hospital
4 September	KZ	NHLS RK Khan	RK Khan Hospital
4 September	KZ	NHLS Inkosi Albert Luthuli	Inkosi Albert Luthuli Hospital
10-11 September	NC	NHLS Kimberley	Kimberley Hospital
17-18 September	KZ	-	Durban & Pietermaritzburg clinics
21 September	LP	NHLS Polokwane	Polokwane/ Mankweng Hospital & surrounding clinics
12 October	NW	-	Jouberton clinic
21 October	GA	-	Chiawelo clinic
4-5 November	EC	-	Gqebera & Zwide clinics
18 November	WC	NHLS Tygerberg	Tygerberg Hospital
26 November	GA	NHLS Charlotte Maxeke Johannesburg Academic	-
8 December	GA	NHLS Charlotte Maxeke Johannesburg Academic	-
11 December	GA	NHLS Chris Hani Baragwanath	-

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

Table 3: Cases detected by surveillance audit by province, South Africa, 2015.

Surveillance case		Percentage of cases detected by audit* n_1/n_2 (%)	Number of cases detected by audit									
			EC	FS	GA	KZ	LP	MP	NC	NW	WC	SA
Invasive	Cryptococcosis**	6,174/6,174 (100%)	783	259	1527	1745	393	523	50	468	426	6,174
	Candidaemia	75/432 (17%)	16	18	3	11	5	12	2	8	N/A	75
	Salmonella Typhi	3/61 (5%)	1	0	1	1	0	0	0	0	0	3
	Non-typhoidal salmonellosis†	214/730 (29%)	16	3	115	38	14	6	1	4	17	214
	Shigellosis	15/41 (37%)	1	0	11	1	0	0	1	0	1	15
	Meningococcal disease	24/156 (15%)	4	0	8	9	0	0	0	1	2	24
	Haemophilus influenzae disease	110/322 (34%)	12	2	46	18	4	6	0	2	20	110
	Pneumococcal disease	731/2,640 (28%)	64	38	290	164	24	40	6	68	37	731
	Staphylococcus aureus disease (BC only)	169/930 (18%)	N/A	N/A	124	N/A	N/A	N/A	N/A	N/A	45	169
	Pseudomonas aeruginosa (BC only)	180/560 (32%)	N/A	6	114	34	N/A	N/A	N/A	N/A	26	180
Non-invasive	*Salmonella* Typhi	3/15 (20%)	1	0	0	0	0	1	0	0	1	3
	Non-typhoidal salmonellosis†	380/1,778 (21%)	61	4	99	86	37	42	7	9	35	380
	Shigellosis	350/1,462 (26%)	48	5	58	81	12	13	2	13	118	350
	Cholera††	0/0 (N/A)	0	0	0	0	0	0	0	0	0	0
	Rifampicin-resistant tuberculosis***	0/943 N/A)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total		**2,254/9,127 (25%)**	**224**	**76**	**869**	**443**	**96**	**120**	**19**	**105**	**302**	**2,254**

*Percentage of cases detected by audit = number of cases detected on audit (n_1)/total number of cases detected by GERMS-SA (n_2) x 100; **All cryptococcal cases are detected on audit and no isolates are received, therefore this organism is excluded from the total; ***Audits are not performed on TB cases, therefore this organism is excluded from the total; †Excluding *Salmonella enterica* serotype Paratyphi; ††Only *Vibrio cholerae* O1; EC: Eastern Cape; FS: Free State; GA: Gauteng; KZ: KwaZulu-Natal; LP: Limpopo; MP: Mpumalanga; NC: Northern Cape; NW: North West; WC: Western Cape; SA: South Africa; BC: Blood culture.

Table 4: Enhanced surveillance site performance indicators, 2015.

Enhanced surveillance site	Case patients, n	Completed case report forms*, n (%)**		Case report forms completed by interview, n (%)***	
Addington [1]	44	40	(91)	34	(85)
Bertha Gxowa [3]	7	6	(86)	0	(0)
Bongani Regional [3]	12	12	(100)	1	(8)
Charlotte Maxeke Johannesburg Academic [2]	390	383	(98)	370	(97)
Chris Hani Baragwanath/ Zola-Jabulani District [4]	332	282	(85)	225	(80)
Dr George Mukhari [1]	185	167	(90)	151	(90)
Edendale/ Greys'/ Northdale [1,4]	173	168	(97)	167	(99)
Groote Schuur/ Red Cross [2]	356	338	(95)	317	(94)
Helen Joseph/ Rahima Moosa Mother & Child [2]	357	325	(91)	257	(79)
Kimberley [1,4]	37	32	(86)	31	(97)
King Edward VIII [1]	90	87	(97)	64	(74)
Klerksdorp/ Tshepong [1,4]	96	90	(94)	59	(66)
Mankweng/ Polokwane/ Seshego [1,4]	57	43	(75)	38	(88)
Natalspruit [3]	31	30	(97)	17	(57)
Nelson Mandela Academic/ Umtata General [1,4,5]	50	24	(48)	21	(88)
Parys [3]	1	1	(100)	0	(0)
Pelonomi/ Universitas [1]	127	119	(94)	89	(75)
Pholosong [3]	9	9	(100)	3	(33)
Port Elizabeth/ Dora Nginza/ Livingstone [1,6]	99	95	(96)	65	(68)
RK Khan [1]	67	66	(99)	58	(88)
Rob Ferreira/ Themba [1,4]	79	75	(95)	70	(93)
Steve Biko Pretoria Academic/ Tshwane District [2]	184	178	(97)	174	(98)
Tambo Memorial [3]	14	13	(93)	4	(31)
Tygerberg [2]	310	306	(99)	250	(82)
Total†	**3,107**	**2,889**	**(93)**	**2,465**	**(85)**

Note - The percentage (in brackets) in each cell was calculated using the numerator from that cell and the corresponding denominator from the cell to the left; Cryptococcal surveillance was only enhanced for the first quarter of 2015; *Low case report form completion rates at certain sites are due to challenges in completing CRFs for certain pathogens; **Target = 90%; ***Target = 70%; [1]Sites doing candidaemia surveillance; [2]Sites doing *S. aureus* enhanced surveillance (bacteraemia only); [3]Sites doing only cryptococcal surveillance (ended on 31 August 2015); [4]Sites doing rifampicin-resistant TB surveillance; data not shown; [5]Surveillance ended at these sites on 30 June 2015; [6]Surveillance started at these sites on 1 July 2015. †Data excludes rifampicin-resistant TB surveillance.

SURVEILLANCE REPORTS

Enhanced surveillance site project

In 2015, of 16,244 surveillance case patients detected by GERMS-SA, 4,393 (27%) were diagnosed at enhanced surveillance sites. Of case patients with recorded HIV status, 62% (1,810/2,903) were HIV-infected (Table 5). The proportion of case patients with confirmed HIV infection varied by surveillance disease. Unsurprisingly, a very high proportion of patients with AIDS-defining infections like cryptococcosis (97%) and

rifampicin-resistant TB (75%) were HIV-infected. HIV infection amongst patients with invasive pneumococcal disease, for which HIV is a known risk factor, was 69%, and 42% of patients with invasive meningococcal disease and 27% with *Staphylococcus aureus* bacteraemia were HIV-infected.

Table 5: Numbers and percentages* of patients, diagnosed with laboratory-confirmed invasive disease at GERMS-SA enhanced surveillance sites, with confirmed HIV-1 infection**, South Africa, 2015.

Pathogen	Case patients, n	Case patients with completed case report forms, n (%)*		Case patients with known HIV status, n (%)		Case patients with confirmed HIV infection, n (%)**	
Cryptococcus species†	562	488	(87)	412	(84)	398	(97)
Candida species	432	398	(92)	255	(64)	67	(26)
Neisseria meningitidis	60	59	(98)	48	(81)	20	(42)
Streptococcus pneumoniae	967	895	(93)	692	(77)	478	(69)
Haemophilus influenzae	156	145	(93)	97	(69)	44	(45)
Staphylococcus aureus	930	904	(97)	508	(56)	137	(27)
Rifampicin-resistant TB	1,286	943	(73)	891	(95)	666	(75)
Total	**4,393**	**3,832**	**(87)**	**2,903**	**(76)**	**1,810**	**(62)**

*The percentage (in brackets) in each cell was calculated using the numerator from that cell and the corresponding denominator from the cell to the left. **HIV infection was confirmed by an age-appropriate laboratory test and recorded by surveillance officers at enhanced surveillance sites. †For cryptococcal disease, case report forms were completed for the first quarter of 2015 at all GERMS enhanced surveillance sites and until the end of August at 4 enhanced surveillance sites linked to the Gauteng screen and treat evaluation.

Cryptococcus species

Results

During 2015, 6,174 case patients with laboratory-confirmed incident cryptococcal disease (including meningitis, fungaemia and disseminated disease but excluding cryptococcal antigenaemia) were reported (Table 6). A total of 4,295 cases of cryptococcal antigenaemia (with no concurrent laboratory evidence of cryptococcal meningitis or fungaemia) were detected in 2015 (Table 7). These cases are excluded from the rest of the report. A direct comparison with 2014 data has been omitted from this report owing to an incomplete audit of the NHLS Corporate Data Warehouse (CDW) for this period. The highest incidence was recorded among patients aged 35-39 years (Figure 1). Two hundred children younger than 15 years had laboratory-confirmed cryptococcosis; 98 (49%) were younger than 5 years of age. Where sex was known, 55% (3,365/6,086) of patients were male. Most patients (93%) with incident symptomatic disease (n=6,174) were diagnosed with meningitis (laboratory tests on cerebrospinal fluid positive for *Cryptococcus* species); 4% were diagnosed with fungaemia (Table 7). One hundred and seventy two patients were diagnosed by culture of urine, sputum, pleural fluid and other specimen types. In 2015, corresponding isolates were not submitted to NICD. Clinical case data were collected

from patients at ESS for the first quarter of the year. Completed case report forms were available for 87% (488/562) of patients (Table 4). Of 412 patients with known HIV status, 398 (97%) were HIV-infected (Table 5). Of 390 HIV-infected patients with known antiretroviral treatment (ART) status, 206 (53%) were on ART at the time of diagnosis of cryptococcal disease or had previously received ART. Among 312 HIV-infected patients who had a CD4+ T-lymphocyte (CD4) count test result recorded close to the time of diagnosis, 286 (92%) had a CD4 count <200 cells/µl. The median CD4 count was 39 cells/µl (interquartile range, 16 – 92). The in-hospital case-fatality ratio for patients at ESS with a first episode of cryptococcal disease was 35% (168/477).

Discussion

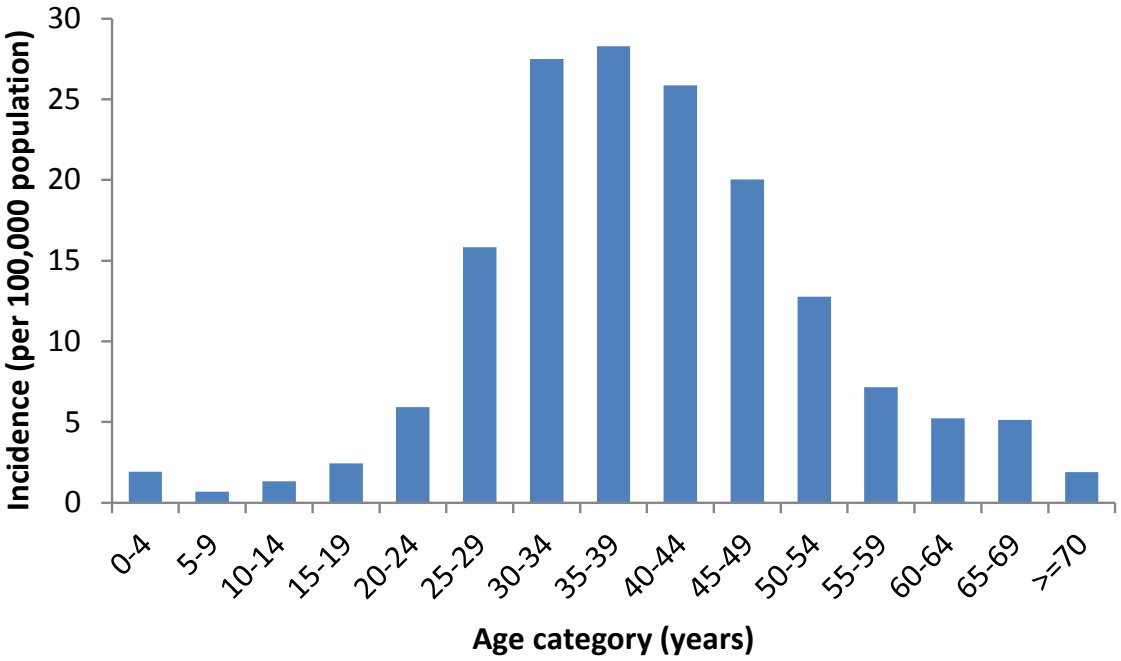
The most notable finding in this year's report is the large number of cases of cryptococcal antigenaemia detected at microbiology/ clinical pathology laboratories through provider requests. Many of these patients with antigenaemia and advanced HIV disease may have been asymptomatic. This follows inclusion of a cryptococcal antigen (CrAg) screen-and-treat intervention in the 2015 national consolidated guidelines for management of HIV. Further improvements in case finding are expected when reflex laboratory CrAg screening is implemented at all NHLS CD4 laboratories in 2016. When these cases of cryptococcal antigenaemia are excluded, the epidemiology of symptomatic cryptococcal disease has remained largely unchanged compared to previous reports. It is difficult to comment on the overall and provincial incidence compared to previous years because of recently-detected inconsistencies in NHLS CDW reporting. This is currently being addressed.

Table 6: Numbers of cases and incidence of cryptococcal disease detected by GERMS-SA by province, South Africa, 2015, n=6,174.

Province	2015	
	n*	Incidence**
Eastern Cape	783	98
Free State	259	71
Gauteng	1527	124
KwaZulu-Natal	1745	104
Limpopo	393	85
Mpumalanga	523	100
Northern Cape	50	60
North West	468	104
Western Cape	426	147
South Africa	**6,174**	**103**

*These case numbers exclude patients who had blood specimens submitted to an NHLS microbiology laboratory for early detection of cryptococcal disease and who tested positive for cryptococcal antigenaemia (n=4,295).
**Incidence was calculated using HIV-infected population denominators determined by the Actuarial Society of South Africa (ASSA-2008) model and is expressed as cases per 100,000 population (refer to Table 1).

Figure 1: Incidence* of laboratory-confirmed cryptococcal disease reported to GERMS-SA by age category, South Africa, 2015, n=6,174 (age unknown for 610 cases).



*Incidence was calculated using population denominators from Statistics South Africa and has been expressed as cases per 100,000 persons in the general population; Note: due to the large number of cases with unknown age, incidence is under-estimated.

Table 7: Numbers and percentages of cases of cryptococcal disease reported to GERMS-SA by specimen type, South Africa, 2015, n=10,469.

Site of specimen	2015	
	n	(%)
Cerebrospinal fluid	5,758	(55)
Blood culture	244	(2)
Blood (for CrAg test*)	4,295	(41)
Other	172	(2)
Total	**10,469**	**(100)**

*CrAg: cryptococcal antigen

Candida species

Results

In 2014 and 2015, 864 cases of candidaemia were detected from 22 ESS (all public-sector hospitals) in 8 provinces (Table 8). The vast majority of cases occurred among children aged 0-4 years and 39% (172/435) of all cases occurred among neonates (≤28 days of age) (Figure 2). Where sex was known, 49% (419/852) of patients were male. Clinical case report forms were completed for 790 (91%) patients. The overall crude case-fatality ratio was high (290/771; 38%) and varied

significantly by species (*Candida albicans*, 48%; *Candida parapsilosis*, 24%; *Candida glabrata*, 58%; *Candida tropicalis*, 35%; and *Candida krusei*, 18%; p<0.001) and age category (infants <1 year, 28%; children 1-17 years, 30%; adults 18-44 years, 58%; adults 45-64 years, 65% and adults ≥65 years, 71%; p<0.001). HIV infection is not an independent risk factor for candidaemia. However, 24% (134/549) of patients were HIV-infected. Almost a quarter of patients (175/790; 22%) had a recorded predisposing factor for candidaemia including abdominal surgery (121; 15%), diabetes mellitus (26; 3%), non-abdominal surgery (14; 2%) and burns (5; 1%). Thirty seven per cent (283/767) had a central venous catheter *in situ* at the time of or before diagnosis. At least one viable isolate was identified to species level for 659 (76%) cases of candidaemia. Overall, *Candida albicans* was the most common species followed by *Candida parapsilosis* (Table 9). While *Candida krusei* was the third most common species, the vast majority of these cases were diagnosed at a hospital in Gauteng where two large outbreaks occurred. All *Candida* isolates had an amphotericin B minimum inhibitory concentration (MIC) ≤ 1 µg/ml (apart from 6 *C. krusei* isolates and 1 *Candida glabrata* isolate). Susceptibility results for five common *Candida* species and three antifungal agents are summarised in Table 10. Anidulafungin MICs are presented as a proxy for susceptibility to the echinocandin class.

Discussion

Most cases of candidaemia diagnosed at 22 public-sector hospitals in 8 provinces were diagnosed among young children, predominantly neonates. More than a third of patients died in hospital. Large outbreaks of candidaemia caused by *C. krusei* occurred in a neonatal intensive care unit at a single Gauteng hospital (Britz E, *et al*. Unpublished data). More than half of bloodstream *C. parapsilosis* isolates were resistant to fluconazole. Fluconazole prophylaxis would therefore be discouraged, even in high-incidence units. Knowledge of local hospital or hospital unit epidemiology should guide empiric treatment choices. Conventional amphotericin B remains the empiric drug 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.

Table 8: Numbers of cases of candidaemia detected by GERMS-SA by enhanced surveillance site, 2014 and 2015, n=864.

Enhanced surveillance site	Province	2014	2015
Addington	KZ	7	10
Dora Nginza	EC	0	10
Dr George Mukhari	GA	114	122
Edendale	KZ	43	28
Greys'	KZ	38	26
Kimberley	NC	10	7
King Edward VIII	KZ	32	43
Livingstone	EC	0	12
Mankweng	LP	9	6
Nelson Mandela Academic/ Mthatha Provincial	EC	13	9
Northdale	KZ	2	4
Pelonomi	FS	29	32
Polokwane	LP	5	7
Port Elizabeth Provincial	EC	0	5
RK Khan	KZ	5	14
Rob Ferreira	MP	19	12
Themba	MP	4	8
Tshepong/ Klerksdorp	NW	30	14
Universitas	FS	72	63
Total		**432**	**432**

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

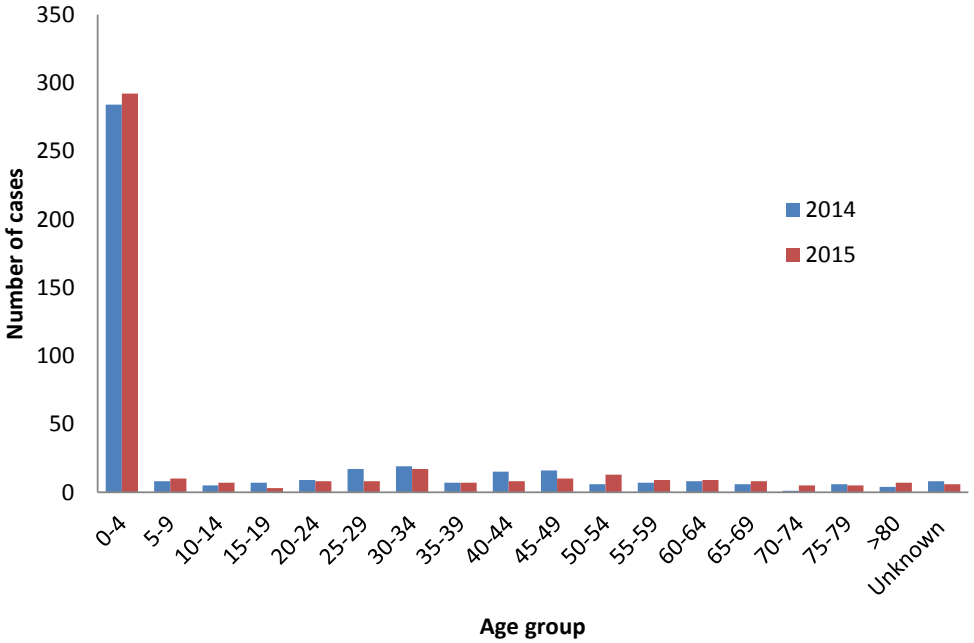


Figure 2: Numbers of cases of laboratory-confirmed candidaemia reported to GERMS-SA by age category, 2014-2015, n=864 (age unknown for 14 cases).

Table 9: *Candida* species distribution for cases of candidaemia with a viable bloodstream isolate by province, South Africa, 2014 and 2015, n=659.

Species	n (%)								
	EC	FS	GA*	KZ	LP	MP	NC	NW	Overall
Candida albicans	11 (46)	65 (42)	74 (34)	85 (44)	7 (58)	17 (71)	4 (29)	11 (50)	274 (42)
Candida parapsilosis	8 (33)	62 (41)	18 (8)	63 (32)	2 (17)	3 (13)	6 (43)	8 (37)	170 (26)
Candida glabrata	4 (17)	13 (8)	24 (11)	24 (12)	2 (17)	2 (8)	1 (7)	2 (9)	72 (11)
Candida tropicalis	1 (4)	4 (3)	4 (2)	11 (6)	0 (0)	2 (8)	1 (7)	0 (0)	23 (3)
Candida krusei	0 (0)	4 (3)	93 (43)	7 (4)	1 (8)	0 (0)	0 (0)	0 (0)	105 (16)
Other *Candida* species	0 (0)	4 (3)	5 (2)	3 (2)	0 (0)	0 (0)	2 (14)	1 (5)	15 (2)
Total	**24**	**152**	**218**	**193**	**12**	**24**	**14**	**22**	**659**

*All cases from Dr George Mukhari hospital – outbreak of *Candida krusei* in 2014 and 2015; EC: Eastern Cape, FS: Free State, GA: Gauteng, KZ: KwaZulu-Natal, LP: Limpopo, MP: Mpumalanga, NC: Northern Cape, NW: North West

Table 10: Numbers and percentages of *Candida* bloodstream isolates (five commonest species only) susceptible* to fluconazole, voriconazole and anidulafungin by broth microdilution testing, 2014 and 2015, n=644.

Antifungal agent	Number (%) of isolates susceptible				
	C. albicans	*C. parapsilosis*	*C. glabrata*	*C. tropicalis*	*C. krusei*
Fluconazole	273/274 (99)	78†/170 (46)	N/A**	23/23 (100)	N/A
Voriconazole	273/274 (99)	128†/170 (75)	N/A	23/23 (100)	105/105 (100)
Anidulafungin	274/274 (100)	170/170 (100)	72/72 (100)	23/23 (100)	105/105 (100)

*Based on CLSI M27-S4 species-specific breakpoints for susceptibility; †Isolates with MICs in the intermediate, susceptible dose-dependent or resistant categories confirmed by Etest; **Only 3 isolates with MIC ≥64 µg/ml (resistant)

Neisseria meningitidis

Results

In 2015, a total of 156 cases of laboratory-confirmed meningococcal disease were identified by the surveillance system during the year - 135 reported cases and 21 additional cases on audit (Table 11). The overall disease incidence was slightly lower than 2014 (0.28 vs 0.36 cases per 100,000 population), with the highest rates reported in the Western Cape (0.66/100,000) and Eastern Cape (0.39/100,000). The number of cases reported was greatest during the winter and spring months (Figure 3). Of all cases reported, cerebrospinal fluid (CSF) was the most common specimen (112/156, 72%) yielding meningococci (Table 12). The number of cases diagnosed on blood culture was not significantly different in 2015 compared to 2014 (p=0.3). The most predominant serogroup in South Africa in 2015 was serogroup B (49/127, 39%) (Table 13). This differed from 2014 as serogroup W was the most common in that year (61/156, 39%). In Gauteng, the incidence of meningococcal disease was estimated at 0.35/100,000, and most of that disease was due to serogroup W (15/35, 43%). This contrasted to the

Western Cape where serogroup B was the most common meningococcal serogroup (23/39, 59%). Risk of disease was greatest amongst children less than five years of age. Age- and serogroup-specific incidence rates show that infants were at greatest risk of disease from the two most common serogroups (Figure 4). Of the viable isolates tested for antimicrobial resistance, 9% (7/80) of isolates had penicillin minimum inhibitory concentrations (MICs) >0.06µg/ml and would be considered non-susceptible. This is lower than that seen in 2014 (11/85, 13%, p=0.09).

Only 60/156 (38%) of cases were reported from enhanced sites with additional clinical information. Cases were admitted for a median of 10 (interquartile range [IQR]: 7-14) days. Similar proportions of patients with meningitis (7/48, 15%) and bacteraemia (1/7, 14%) died (p=0.98). Cases predominantly died on the day of admission, median of 0 (IQR: 0-0.5) days. Only 9 cases reported underlying medical conditions, none of which included complement deficiency. Of the 48 patients who had known HIV status, 20 (42%) were HIV-infected (16 of whom were 25-44 years of age) and 9 (45%) were using antiretroviral therapy.

Discussion

Incidence of meningococcal disease remained low in 2015 with serogroup B disease as the predominant serogroup. Changes in meningococcal disease incidence in provinces may reflect changes in ability to confirm disease in the laboratory and changes in reporting to the surveillance network, or may reflect true changes in incidence. The prevalence of non-susceptibility to penicillin decreased compared to 2014 and penicillin is still being recommended, at present, as the drug of choice for therapy for confirmed meningococcal disease. Case-fatality ratios were high in all syndromes and most cases died on the day of admission. Most patients were young with no reported underlying conditions.

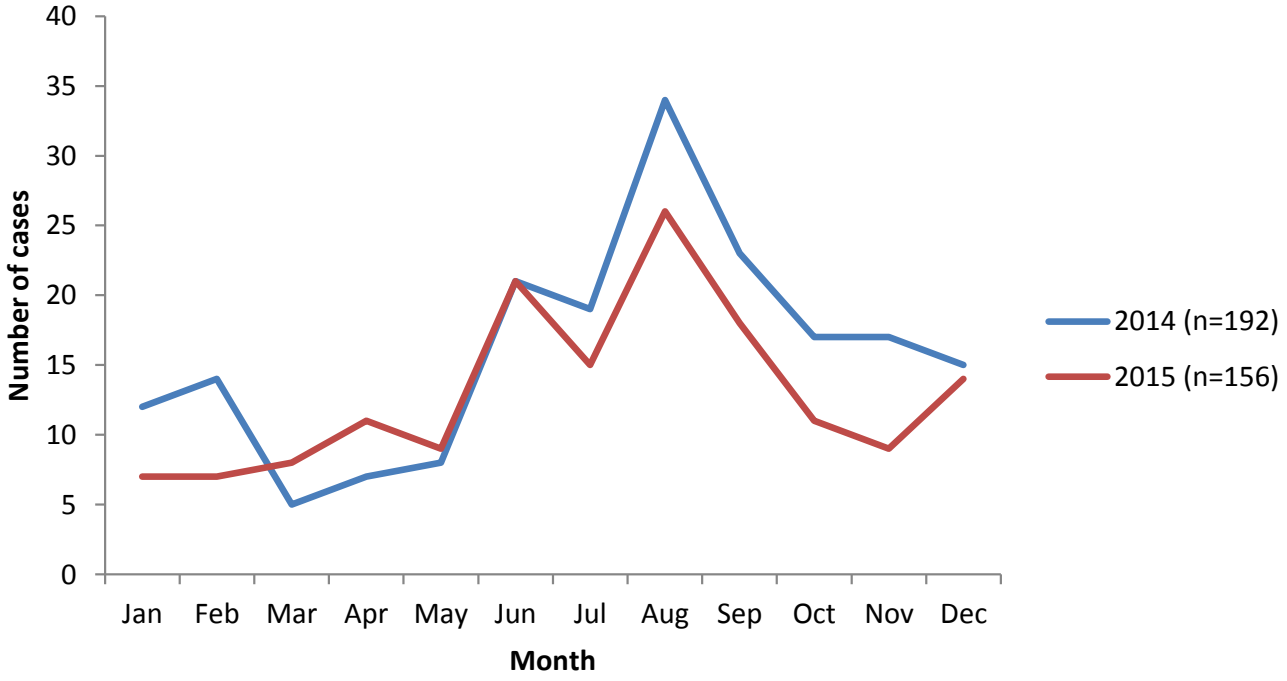


Figure 3: Numbers of laboratory-confirmed, invasive, meningococcal cases reported to GERMS-SA, by month and year, South Africa, 2014-2015, n=348.

Table 11: Numbers of cases and incidence rates of meningococcal disease reported to GERMS-SA by province, South Africa, 2014 and 2015, n=348 (including audit cases).

Province	2014		2015	
	n	Incidence rate*	n	Incidence rate*
Eastern Cape	36	0.53	27	0.39
Free State	5	0.18	9	0.32
Gauteng	56	0.43	46	0.35
KwaZulu-Natal	25	0.23	23	0.21
Limpopo	0	0.00	1	0.02
Mpumalanga	2	0.05	3	0.07
Northern Cape	0	0.00	2	0.17
North West	2	0.05	4	0.11
Western Cape	66	1.08	41	0.66
South Africa	**192**	**0.36**	**156**	**0.28**

*Incidence rates were calculated based on population denominators provided by Statistics South Africa, and are expressed as cases per 100,000 population.

Table 12: Numbers and percentages of cases of meningococcal disease reported to GERMS-SA by specimen type, South Africa, 2014 and 2015, n=348.

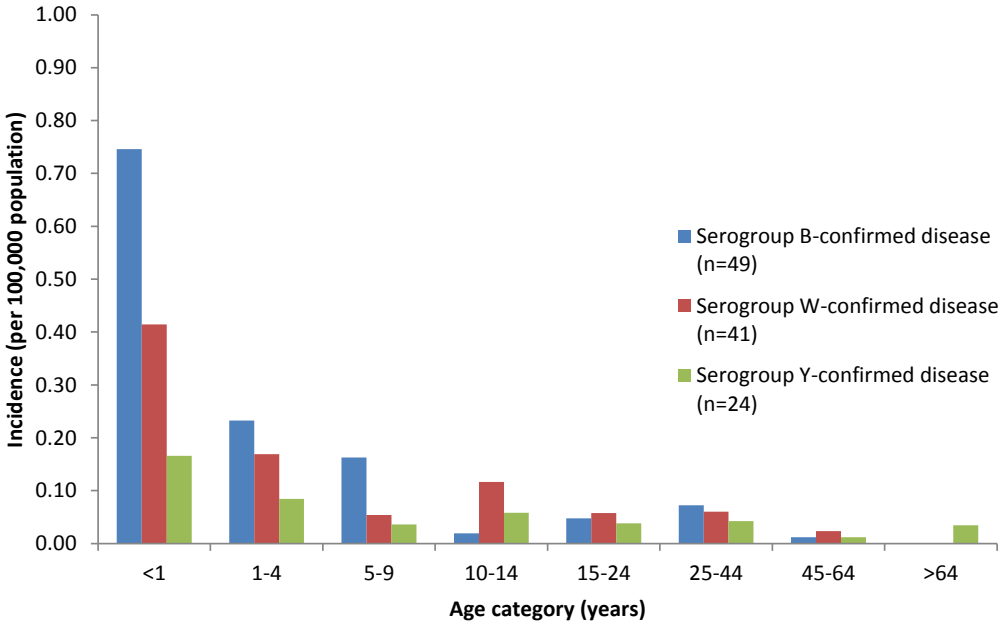
Site of specimen	2014		2015	
	n	%	n	%
CSF	144	75	112	72
Blood	47	24	44	28
Other	1	0.5	0	0
Total	**192**		**156**	

Table 13: Numbers of cases of invasive meningococcal disease reported to GERMS-SA by serogroup and province, South Africa, 2015, n=156*.

Province	Serogroup								
	Serogroup not available	A	B	C	W	X	Y	NG**	Total
Eastern Cape	5	0	7	3	5	0	6	1	27
Free State	1	0	4	0	2	0	2	0	9
Gauteng	11	0	11	3	15	0	6	0	46
KwaZulu-Natal	9	0	3	1	9	0	1	0	23
Limpopo	0	0	0	0	0	0	1	0	1
Mpumalanga	0	0	0	0	1	0	2	0	3
Northern Cape	0	0	0	1	0	1	0	0	2
North West	1	0	1	1	1	0	0	0	4
Western Cape	2	0	23	2	8	0	6	0	41
South Africa	**29**	**0**	**49**	**11**	**41**	**1**	**24**	**1**	**156**

*127 (81%) with viable isolates or specimens available for serogrouping; ** NG: Non-groupable

Figure 4: Age-specific incidence rates* for laboratory-confirmed, invasive, meningococcal cases by serogroup B, W and Y**, South Africa, 2015, n=156 (age unknown for n=4; specimens or viable isolates unavailable for serogrouping n=29).



*Incidence rates were calculated based on population denominators provided by Statistics South Africa, and are expressed as cases per 100,000 population.
**Other serogroups: serogroup C, n=11; serogroup X, n=1; non-groupable, n=1

Haemophilus influenzae

Results

A total number of 322 *Haemophilus influenzae* invasive cases were available for analysis in 2015: 218 reported cases and an additional 104 cases identified during the national audit. Of these total cases, 200 (62%) had isolates or specimens available for serotyping and 35/200 (18%) were confirmed as serotype b (Table 14). Serotype b isolates were more likely to be isolated from CSF than non-typeable *H. influenzae* (14/35, 40% vs. 14/132, 11%, p<0.001) (Table 15). In 2015, a total of 17 cases of *H. influenzae* serotype b (Hib) were reported amongst children <5 years (Figure 5). Serotype b is no longer the commonest serotype of *H. influenzae* causing disease amongst children <5 years (Figure 6); 28/56 (50%) of cases in infants and 14/16 (88%) of cases in neonates were due to non-typeable disease. Rates of Hib disease as recorded by our surveillance network amongst infants <1 year of age decreased from 2010 to 2015 (p<0.001, chi-squared test for trend) (Figure 7). Twenty-seven percent (6/22) of serotype b strains were non-susceptible to ampicillin (MIC>1mg/L) while 11% (9/85) of non-typeable strains were non-susceptible (p=0.04).

Only 156/322 (48%) of cases were reported from enhanced sites, 145 (93%) of which had additional clinical information. Cases were admitted for a median of 10 (IQR: 3-18) days and cases who died usually did so soon after admission, median of 1 (IQR: 0-6) day. A total of 54/145 cases (37%) reported underlying medical conditions (including chronic liver, lung, cardiac or renal disease, stroke, diabetes mellitus, immunosuppressive therapy, cancer) in all age groups. In children <5 years (n=75), 21 (28%) had premature births (gestational age <37 weeks) and of those with data, 33/60 (55%) were malnourished. Of the 97 patients who had known HIV

status, 44 (45%) were HIV infected (14 [32%] of whom were 25-44 years of age) and 25/41 (61%) were using antiretroviral therapy. In all children <15 years of age (n=89) with invasive *Haemophilus influenzae*, only 52 (58%) children older than 6 weeks of age had known vaccination status and of these children only 62% had received the appropriate number of Hib vaccine doses for age at time of admission. Only 65 (73%) children aged <15 years had a known serotype and 12 (18%) had serotype b disease, 11 (92%) of whom had known vaccination histories. Children with serotype b disease who had received 2 or more doses of Hib vaccine (n=6) were assessed to be possible vaccine failures. Five of these apparent failures had underlying medical conditions.

Discussion

There is an ongoing reduction in Hib rates in children <1 year and to a lesser extent in the 1-4 year old age group over the last 5 years. Non-typeable disease in children <5 years has fluctuated over the last few years. A high proportion of Hib cases were non-susceptible to ampicillin. Low rates of vaccination were observed in children admitted with invasive *H. influenzae* disease and clinicians should ensure that children with missed vaccines receive catch-up doses. A number of vaccine failures were observed and even though these were in high risk children, it is important for clinical and laboratory staff to continue reporting all cases of *H. influenzae.*

Table 14: Numbers of cases of invasive *Haemophilus influenzae* disease reported to GERMS-SA by serotype and province, South Africa, 2015, n=322*.

Province	Serotype								
	Serotype not available	a	b	c	d	e	f	Non-typeable	Total
Eastern Cape	13	0	2	0	0	0	0	12	27
Free State	3	0	2	1	0	0	1	2	9
Gauteng	50	3	10	1	1	2	4	40	111
KwaZulu-Natal	19	1	3	0	0	0	3	11	37
Limpopo	4	1	1	0	0	0	0	2	8
Mpumalanga	7	0	0	0	0	0	0	2	9
Northern Cape	1	0	0	0	0	0	0	0	1
North West	2	0	1	0	0	0	0	0	3
Western Cape	23	9	16	0	0	1	5	63	117
South Africa	**122**	**14**	**35**	**2**	**1**	**3**	**13**	**132**	**322**

*200 (62%) with specimens or viable isolates available for serotyping.

Table 15: Numbers and percentages of cases of invasive *Haemophilus influenzae* disease reported to GERMS-SA by specimen type, South Africa, 2015, n=322.

Site of specimen	No serotype available		Serotype b		Serotypes a, c, d, e, f		Non-typeable	
	n	(%)	n	(%)	n	(%)	n	(%)
CSF	27	(22)	14	(40)	14	(42)	14	(11)
Blood	61	(50)	20	(57)	18	(55)	89	(67)
Other	34	(28)	1	(3)	1	(3)	29	(22)
Total	**122**		**35**		**33**		**132**	

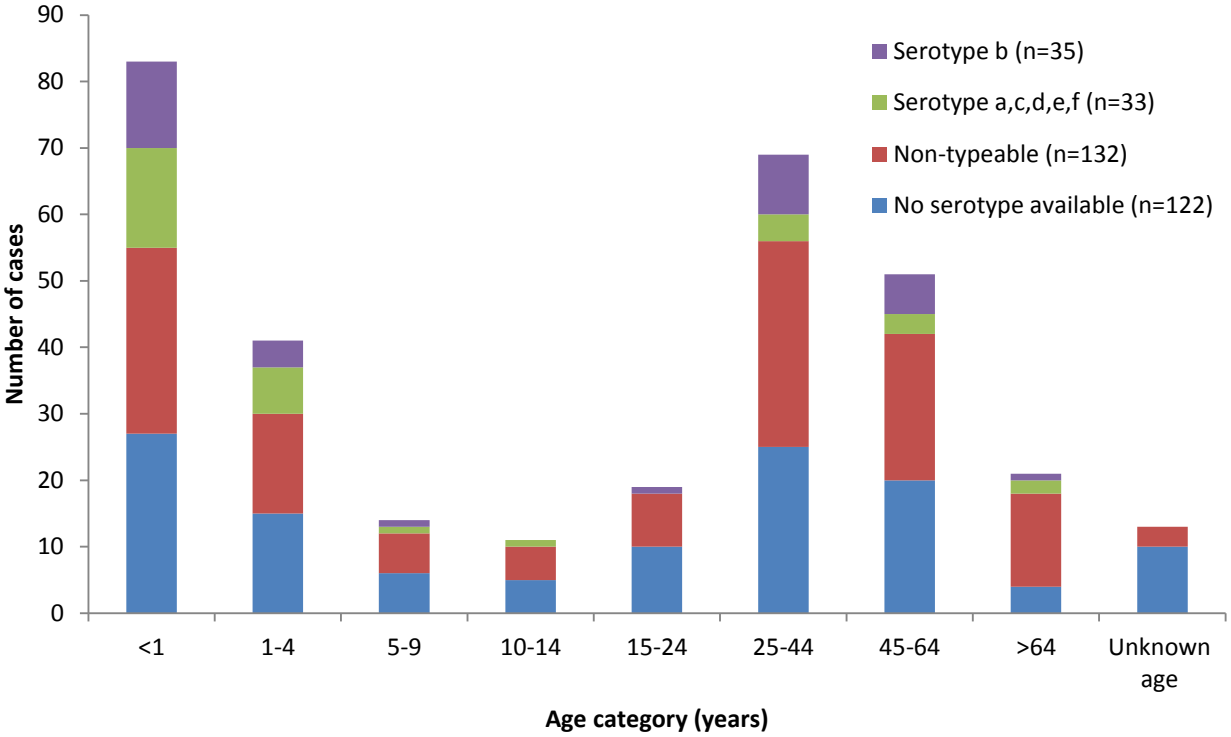
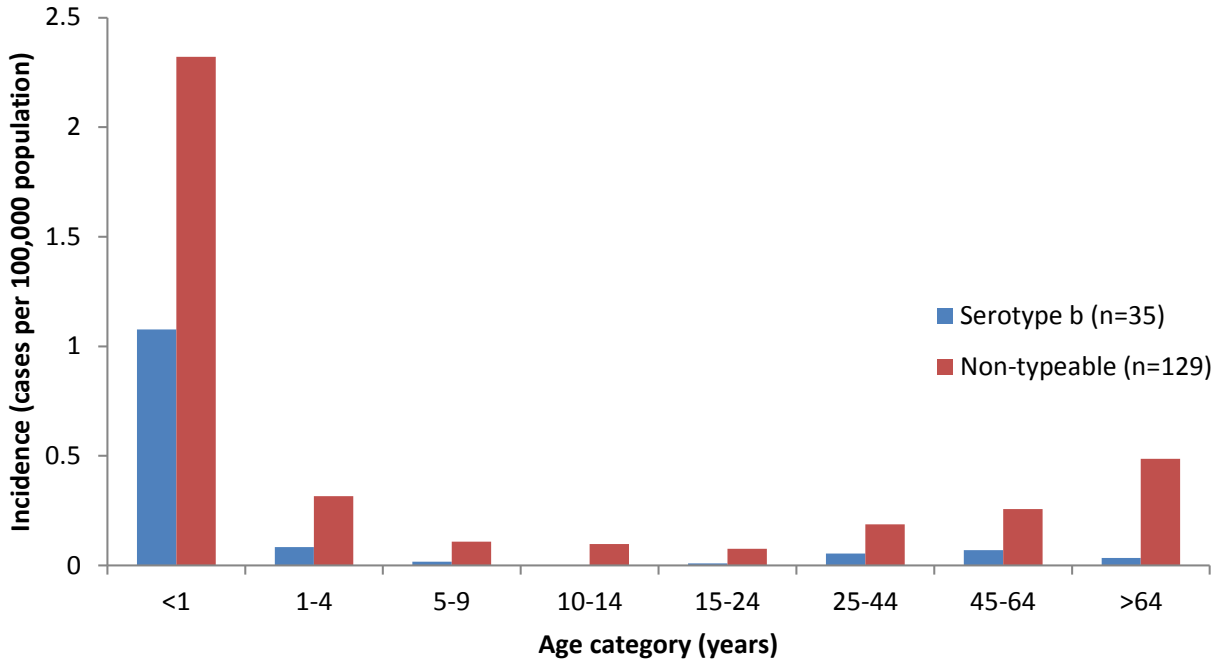


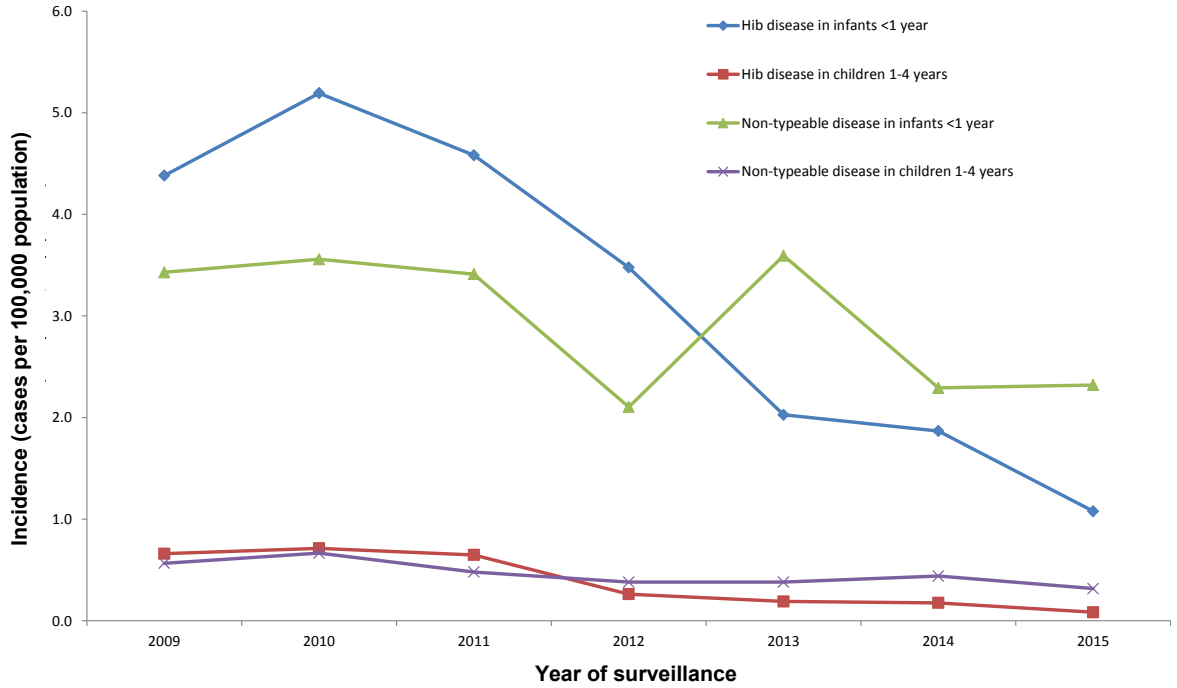
Figure 5: Numbers of laboratory-confirmed, invasive, *Haemophilus influenzae* cases, reported to GERMS-SA, by serotype and age group, South Africa, 2015, n=322 (age unknown for n=13; specimens or viable isolates unavailable for serotyping for n=122).

Figure 6: Age-specific incidence rates* for laboratory-confirmed, invasive *Haemophilus influenzae* disease, reported to GERMS-SA, by serotype b and non-typeable, South Africa, 2015, n=322 (age unknown for n=13; specimens or viable isolates unavailable for serotyping for n=122; other serotypes from cases with known age, n=33).



*Incidence rates were calculated based on population denominators provided by Statistics South Africa, and are expressed as cases per 100,000 population.

Figure 7: Incidence rates* of laboratory-confirmed, *Haemophilus influenzae* serotype b disease, reported to GERMS-SA, in children <5 years old, South Africa, 2009-2015.



*Incidence rates were calculated based on population denominators provided by Statistics South Africa, and are expressed as cases per 100,000 population.

Streptococcus pneumoniae

Results

The 7-valent polysaccharide-protein conjugate pneumococcal vaccine (PCV-7) was introduced into the Expanded Programme on Immunisations (EPI) in South Africa from 1 April 2009 and replaced by PCV-13 from May/June 2011. Incidence of reported invasive pneumococcal disease (IPD) varied widely by province (Table 16). The highest risk of disease in South Africa remained in infants <1 year of age, although disease decreased significantly from 2009 ($p<0.001$ chi-squared test for trend) (Figure 8). The majority of episodes (53%) reported to GERMS-SA were diagnosed from positive blood culture specimens (Table 17). Prevalence of non-susceptible strains ranged from 15% to 41% in different provinces (Table 18). Penicillin non-susceptible isolates were most common amongst children 5-14 years of age (Figure 9). Ceftriaxone non-susceptibility was detected amongst 4% (69/1,699) of all IPD cases; a slight reduction from 2014 (6%, 97/1,751). Amongst isolates from CSF specimens, 3% (14/523) were non-susceptible to ceftriaxone. The number of cases reported amongst children less than 5 years of age due to common serotypes for the period 2009-2015 is shown in Figure 10 with significant reductions in vaccine serotypes. Non-vaccine serotypes showed increases, with serotype 8 and 12F being the most common non-vaccine serotypes in 2015. The percentage of disease in 2015 amongst children less than 5 years of age due to PCV-7 and newer valency vaccine formulations are shown in Table 19. The number of isolates available for serotyping in this age group has decreased since from 75% in 2009: (1,009/1,337 [75%] in 2009; 649/909 [71%] in 2010; 464/695 [67%] in 2011; 353/509 [69%] in 2012; 322/498 [65%] in 2013; 300/464 [64%] in 2014 and 216/381 [57%] in 2015).

Only 967/2,640 (37%) of cases were reported from enhanced sites, of which 895 (93%) had additional

clinical information. Cases were admitted for a median of 7 (IQR: 2-14) days and cases who died usually did so after a few days of admission, median of 2 (IQR: 1-5) days. A total of 352/895 (39%) cases reported underlying medical conditions (including chronic liver, lung, cardiac or renal disease, stroke, diabetes mellitus, immunosuppressive therapy, cancer, sickle cell disease) in all age groups. In older individuals (≥5 years), where 41% (315/761) had underlying conditions, the most common (144/761, 19%) were chronic medical conditions (including chronic liver, lung, cardiac or renal disease, stroke and diabetes mellitus). In children <5 years of age, underlying medical conditions were less common (31/172, 18%), but 25% (43/172) had preceding prematurity and, of those with data, 43% (66/155) had malnutrition. Of the 692 patients who had known HIV status, 478 (69%) were HIV-infected (295/478 [62%] of whom were 25-44 years of age) and 231/460 (50%) were using antiretroviral therapy. In children <5 years of age (n=174), only 116 (67%) children older than 6 weeks of age had known vaccination status and of these children only 77% had received the appropriate number of PCV vaccine doses for age at time of admission. Only 134 (77%) children aged <5 years had a known serotype and 22 (16%) had vaccine serotype disease, 12 (55%) of whom had known vaccination histories. Children with vaccine serotype disease who had received 2 or more doses of PCV vaccine (n=6) were assessed to be possible vaccine failures. Three of these apparent failures had underlying medical conditions.

Discussion

Differences in IPD incidence by province have been documented for several years, and are partly due to differences in specimen-taking practices and laboratory reporting. However real differences in disease incidence cannot be excluded. The decreases in incidence of disease in children <5 years of age after the introduction of PCV have been substantial, although an increase in non-vaccine serotypes has been noted since 2012. We urge clinicians to continue taking relevant specimens when pneumococcal disease is suspected and laboratorians to send all pneumococci isolated from normally sterile site specimens so that the ongoing trends in serotypes can be monitored. It is also vital that children with missed vaccine doses receive appropriate catch-up doses.

Table 16: Numbers of cases and incidence rates of invasive pneumococcal disease reported to GERMS-SA by province, South Africa, 2014 and 2015, n=5,372.

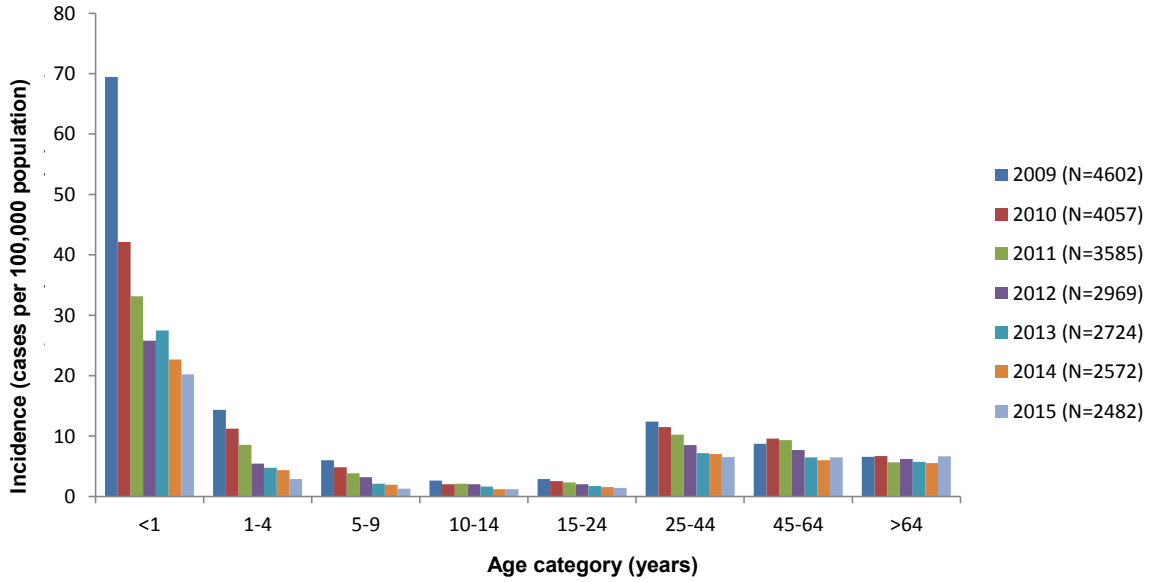
Province	2014		2015	
	n	Incidence rate*	n	Incidence rate*
Eastern Cape	228	3.36	233	3.37
Free State	188	6.75	138	4.90
Gauteng	961	7.44	943	7.14
KwaZulu-Natal	497	4.65	353	3.23
Limpopo	41	0.73	107	1.87
Mpumalanga	133	3.14	85	1.98
Northern Cape	42	3.60	28	2.36
North West	111	3.02	120	3.24
Western Cape	531	8.68	633	10.21
South Africa	**2,732**	**5.06**	**2,640**	**4.80**

*Incidence rates were calculated based on population denominators provided by Statistics South Africa, and are expressed as cases per 100,000 population.

Table 17: Numbers and percentages of cases of invasive pneumococcal disease reported to GERMS-SA by specimen type, South Africa, 2014 and 2015, n=5,372.

Site of specimen	2014		2015	
	n	%	n	%
CSF	1,059	(38)	981	(37)
Blood	1,439	(53)	1,396	(53)
Other	234	(9)	263	(10)
Total	**2,732**		**2,640**	

Figure 8: Age-specific incidence rates* for laboratory-confirmed, invasive pneumococcal disease, reported to GERMS -SA, South Africa, 2009 through 2015.



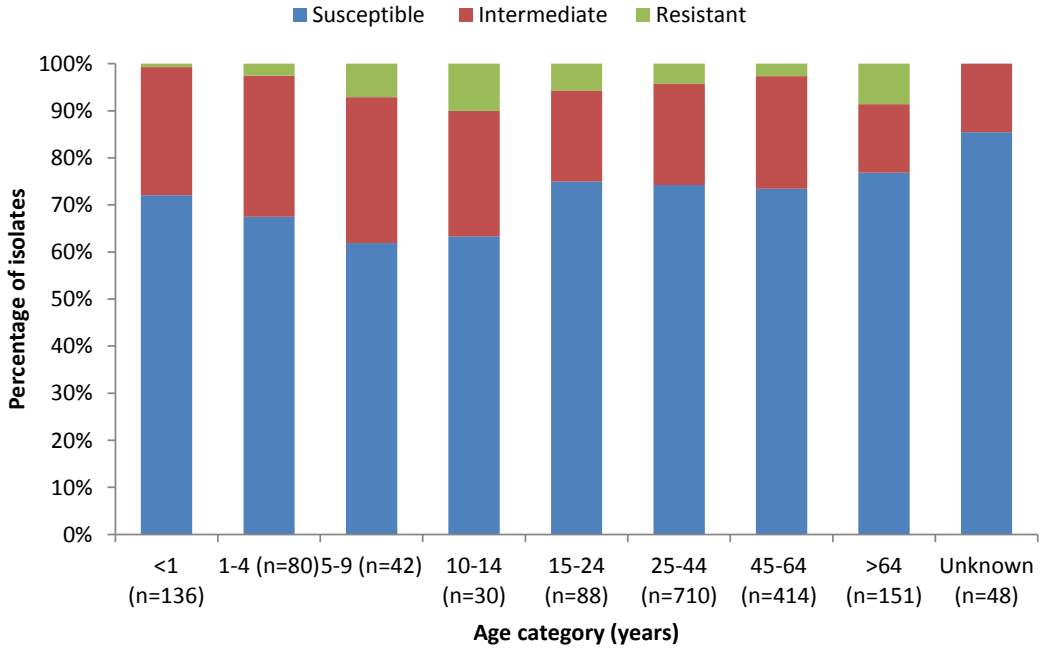
2009: N=4,765, age unknown for n=163; 2010: N=4,199, age unknown for n=142; 2011: N=3,804, age unknown for n=219; 2012: N=3,222, age unknown for n=253; 2013: N=2,866, age unknown for n=142; 2014: N=2,734, age unknown for n=162; 2015: N=2,640, age unknown for n=158. *Incidence rates were calculated based on population denominators provided by Statistics South Africa, and are expressed as cases per 100,000 population.

Table 18: Numbers and percentages of penicillin susceptible and non-susceptible isolates from invasive pneumococcal disease cases reported to GERMS-SA by province, South Africa, 2015, n=2,640.

Province	Isolate not available	Susceptible*		Intermediate*		Resistant*	
	n	n	(%)	n	(%)	n	(%)
Eastern Cape	96	110	(80)	23	(17)	4	(3)
Free State	50	75	(85)	13	(15)	0	(0)
Gauteng	347	424	(71)	141	(24)	31	(5)
KwaZulu-Natal	188	97	(59)	58	(35)	10	(6)
Limpopo	43	47	(73)	17	(27)	0	(0)
Mpumalanga	45	34	(85)	6	(15)	0	(0)
Northern Cape	7	16	(76)	5	(24)	0	(0)
North West	76	31	(70)	10	(23)	3	(7)
Western Cape	89	417	(77)	107	(20)	20	(3)
South Africa	**941**	**1,251**	**(74)**	**380**	**(47)**	**68**	**(4)**

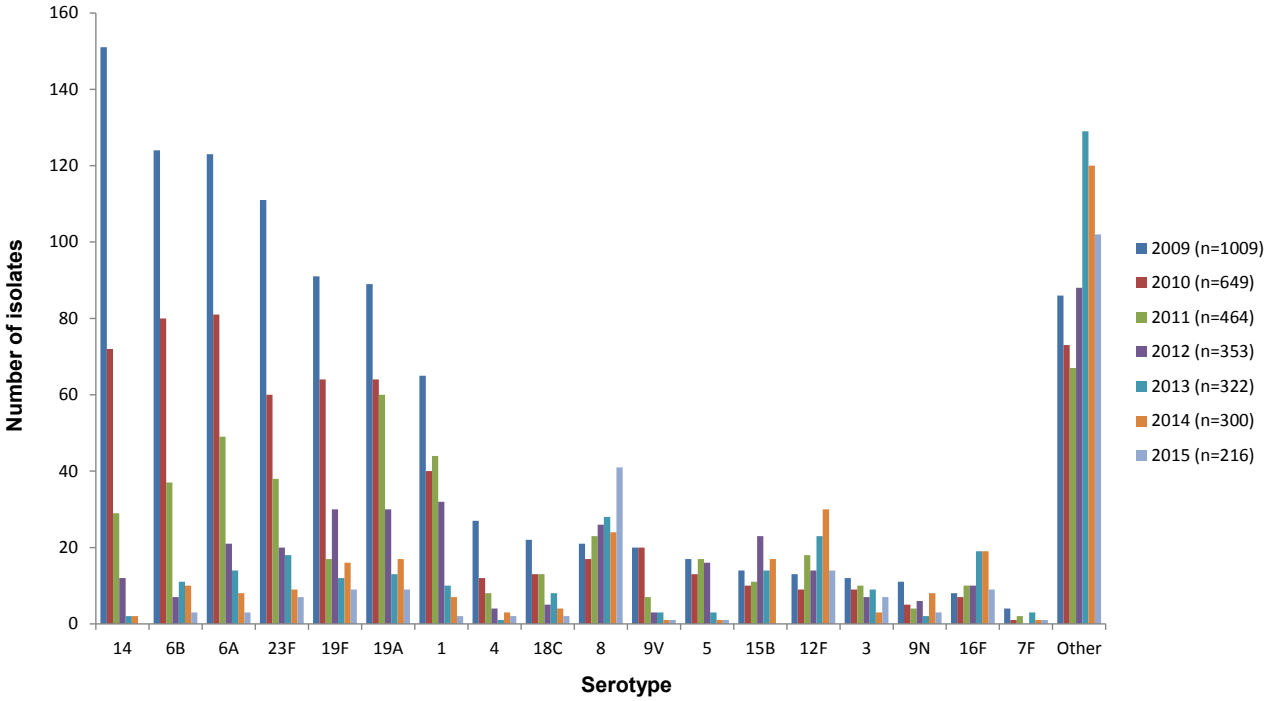
*2015 CLSI breakpoints for penicillin (oral penicillin V) were used: susceptible, ≤0.06mg/L; intermediately resistant, 0.12-1mg/L; resistant, ≥2mg/L.

Figure 9: Numbers and percentages of laboratory-confirmed, invasive pneumococcal disease isolates, reported to GERMS-SA, by age group and penicillin susceptibility, South Africa, 2015, n=2,640 (n=1,699 with viable isolates).



2015 CLSI breakpoints for penicillin (oral penicillin V) were used: susceptible, ≤0.06mg/L; intermediately resistant, 0.12-1mg/L; resistant, ≥2mg/L.

Figure 10: Pneumococcal serotypes, in descending order, causing laboratory-confirmed, invasive pneumococcal disease, reported to GERMS-SA, in children <5 years, South Africa, 2009-2015.



2009: N=1337, n=1,009 with viable isolates; 2010: N=909, n=649 with viable isolates; 2011: N=695, n=464 with viable isolates; 2012: N=509, n=353 with viable isolates; 2013: N=498, n=322 with viable isolates; 2014: N=464, n=300 with viable isolates; 2015: N=381, n=216 with viable isolates.

Table 19: Numbers and percentages of invasive pneumococcal cases reported amongst children less than 5 years of age caused by the serotypes contained in the 7-valent, 10-valent and 13-valent pneumococcal conjugate vaccines, South Africa, 2015, n=381 (n=216 with viable isolates).

Province	Total isolates available for serotyping	7-valent serotypes*		Serotype 6A#		10-valent serotypes**		13-valent serotypes***	
		n	(%)	n	(%)	n	(%)	n	(%)
Eastern Cape	15	3	(20)	0	(0)	3	(20)	4	(27)
Free State	9	1	(11)	0	(0)	1	(11)	1	(11)
Gauteng	90	8	(9)	1	(1)	11	(12)	19	(21)
KwaZulu-Natal	26	6	(23)	0	(0)	6	(23)	8	(31)
Limpopo	8	0	(0)	0	(0)	0	(0)	1	(13)
Mpumalanga	8	0	(0)	0	(0)	0	(0)	0	(0)
Northern Cape	5	0	(0)	1	(20)	0	(0)	1	(20)
North West	7	0	(0)	1	(14)	0	(0)	1	(14)
Western Cape	48	5	(10)	0	(0)	5	(10)	10	(21)
South Africa	**216**	**23**	**(11)**	**3**	**(0.01)**	**26**	**(12)**	**45**	**(21)**

*7-valent serotypes: 4, 6B, 9V, 14, 18C, 19F, 23F
**10-valent serotypes: 4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F
***13-valent serotypes: 4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F, 19A, 3, 6A.
Cross-protection with 6B has been demonstrated.[5]

Case-control study to estimate effectiveness of a pneumococcal conjugate vaccine (PCV) against invasive pneumococcal disease (IPD) in South Africa

South Africa introduced PCV-7 in April 2009, and PCV-13 replaced PCV-7 in May/June 2011. A case-control study to assess the effectiveness of PCV against invasive pneumococcal disease (IPD) was started in March 2010 and completed in March 2015. The results for the PCV-7 component of the study were reported previously.[6]

For the PCV-13 component of the study, 315 cases (240 (52 [22%] PCV13 serotype) HIV-uninfected and 75 (21 [28%] PCV13 serotype) HIV-infected cases) were enrolled from January 2012 to December 2014 including 1,401 controls (1,118 HIV-uninfected and 283 HIV-infected) aged ≥16 weeks. Overall, HIV-uninfected cases had a higher average number of controls per case (5 controls) than HIV-infected cases (4 controls). The effectiveness of two or more doses of PCV-13 against PCV-13-serotype IPD was 85% (95% CI 37,96) among HIV-uninfected and 91% (95% CI -35,100) among HIV-infected children. Vaccine effectiveness (VE) was also explored for other high risk groups using all the PCV7 and PCV13 data. The VE against PCV-7-serotype IPD in HIV-exposed-uninfected children was 87% (95% CI 38,97) and in HIV-uninfected malnourished children was 90% (95% CI 53,98).

Staphylococcus aureus

Results

There were 930 cases of *Staphylococcus aureus* bacteraemia reported to GERMS-SA from January through December 2015 from Gauteng and Western Cape Province (Table 20). Of these, the majority of cases were detected from sentinel sites in Johannesburg and Pretoria, Gauteng (56%), followed by Cape Town and Tygerberg, Western Cape (44%) (Table 20). The number of cases was almost equally distributed throughout the whole year, although there was a decline during the winter season, which picked up in the summer and autumn months (Figure 11). Resistance to oxacillin (MRSA) was determined in 243/744 (33%) isolates (Table 21 and Figure 12). We analysed the trend in oxacillin resistance in Gauteng Province, which showed a mild increase in 2015: 243/744 cases (33%) compared to 186/602 cases in 2014 (31%) (Figure 12). On m*ec*A-confirmed *S. aureus* isolates (239/744, 32%), SCCmec typing was performed and showed predominance of type III in Gauteng Province (105/239, 44%) and type IV in Western Cape (50/239, 21%) (Figure 13). From a total of 744 viable *S. aureus* isolates, 215 (29%) were non-susceptible to clindamycin; in addition, from 205 erythromycin-resistant isolates 161 (78%) expressed positive D-zone tests. All isolates were susceptible to vancomycin in 2015. A total of 704/744 (95%) isolates were susceptible to mupirocin and 743/744 (99.9%) to daptomycin (Table 21 and Figure 12). Patient data were available for 97% (904/930) of patients. Of 509 patients with known HIV status, 138 (27%) were HIV positive, 50 (36%) of whom died.

Discussion

Molecular tests indicating community vs. hospital acquired MRSA were performed: SCCmec type III was the most predominant amongst the two provinces though highly distributed in Gauteng, while type IV was dominant in the Western Cape. Thirty-three percent of *S. aureus* isolates submitted to the AMRL were confirmed as MRSA; a slight increase compared to 2014 (31%). Positive HIV status (27%) was recorded as a risk condition for MRSA blood stream infections. Clindamycin-resistant *S. aureus* isolates occurred at high rates (29%). Additionally, 78% of erythromycin-resistant isolates presented with positive clindamycin D-zone tests. No vancomycin non-susceptible isolates were identified. We noted one isolate non-susceptible to daptomycin.

Table 20: Numbers of *Staphylococcus aureus* cases reported to GERMS-SA sentinel sites by province, South Africa, 2015, n=930 (including audit cases).

Province	n	%
Gauteng	517	56
Western Cape	413	44
Total	**930**	**100**

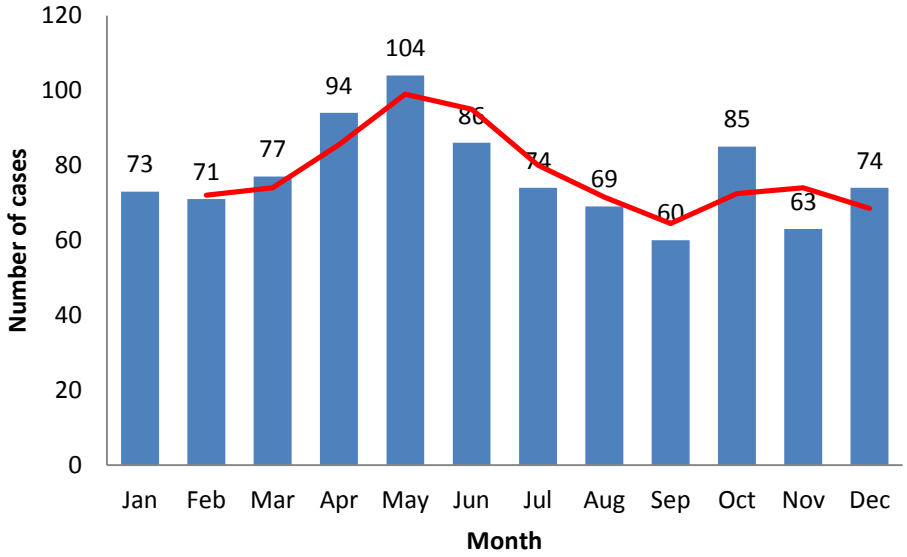


Figure 11: Numbers of cases of laboratory-confirmed *Staphylococcus aureus* bacteraemia cases reported to GERMS-SA sentinel sites by month, 2015, and trend line analysis, n=930.

Table 21: Numbers of viable, laboratory-confirmed *Staphylococcus aureus* reported by GERMS-SA sentinel sites, with reported susceptibility testing to oxacillin (n=744), clindamycin (n=744), vancomycin (n=744), and mupirocin (n=744), 2015.

Province	Antimicrobial agents							
	Oxacillin		Clindamycin		Vancomycin		Mupirocin	
	S*	NS**	S	NS	S	NS	S	NS
Gauteng	242 (63)	140 (37)	258 (68)	124 (32)	382 (100)	0 (0)	368 (96)	14 (4)
Western Cape	259 (72)	103 (28)	271 (75)	91 (25)	362 (100)	0 (0)	336 (93)	26 (7)
Total	**501 (67)**	**243 (33)**	**529 (71)**	**215 (29)**	**744 (100)**	**0 (0)**	**704 (95)**	**40 (5)**

*S:=susceptible; **NS=non-susceptible

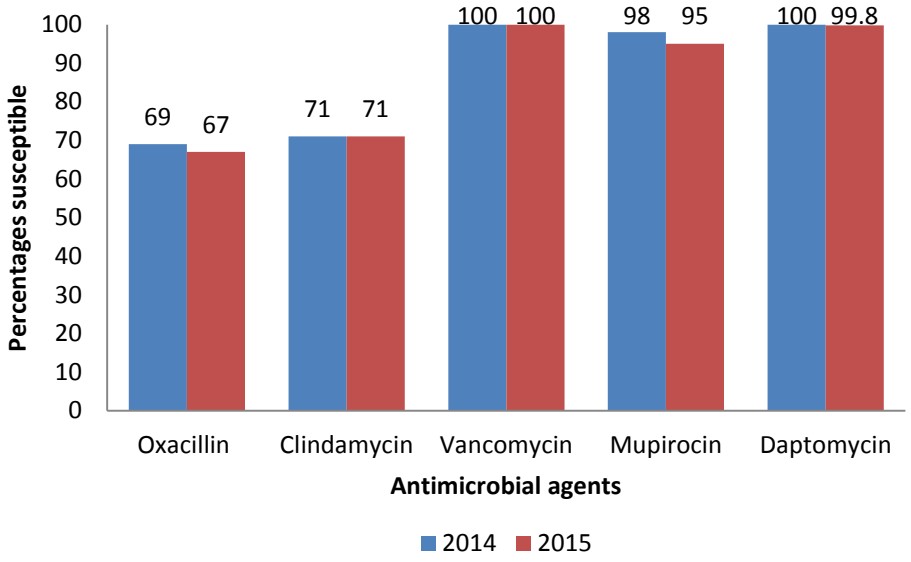


Figure 12: Percentages of susceptibility patterns of cases of laboratory-confirmed *Staphylococcus aureus* bacteraemia reported by GERMS-SA sentinel sites in Gauteng, and trend analysis, 2014 and 2015.

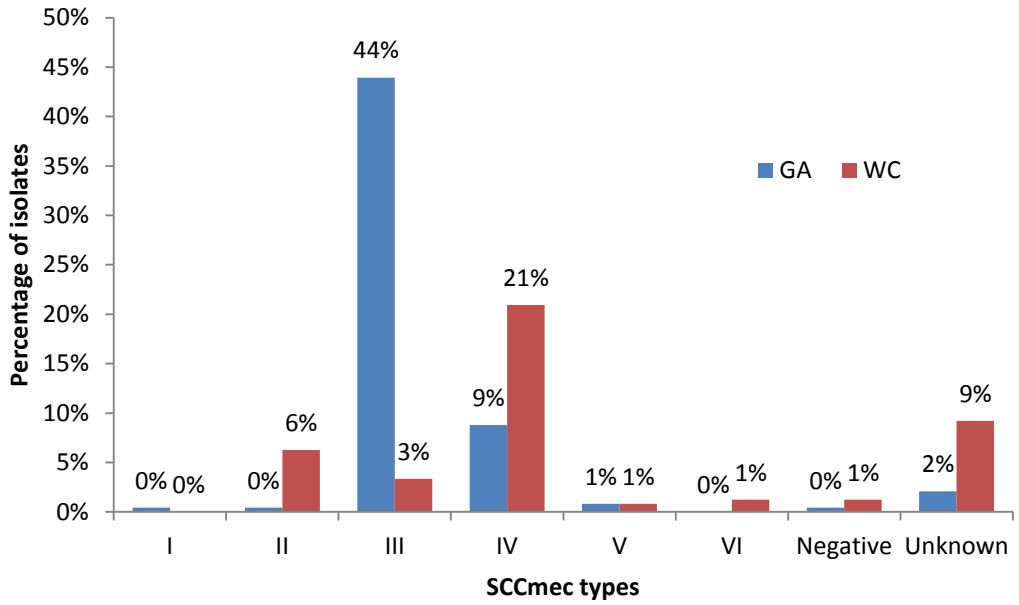


Figure 13: Distribution of SCCmec types of cases of laboratory-confirmed *Staphylococcus aureus* bacteraemia reported by GERMS-SA sentinel sites per province, 2015.

Pseudomonas aeruginosa

Results

There were 560 cases of *Pseudomonas aeruginosa* bacteraemia reported to GERMS-SA from January through December 2015 from Gauteng, Free State, KwaZulu-Natal and Western Cape Provinces (Table 22). The highest number of the cases with *P. aeruginosa* was noted during the early winter months (Figure 14). Resistance to *Pseudomonas* antimicrobial agents was recorded for piperacillin/tazobactam (25%), imipenem (29%), ciprofloxacin (27%) and ceftazidime (21%). Resistance to colistin was 2.5% (Table 23 and Figure 15). In Figure 15, a comparison to 2014 data on susceptibility is shown where a 2-5% decrease was recorded for these antimicrobial agents.

Discussion

On average, one quarter of *P. aeruginosa* isolates were resistant to recommended agents, the most important of which was the high resistance to ceftazidime, imipenem and piperacillin/tazobactam. Resistance to colistin was low and none were confirmed to carry the *mcr*-1 gene.

Table 22: Numbers of *Pseudomonas aeruginosa* cases reported to GERMS-SA sentinel sites by province, South Africa, 2015, n=560 (including audit cases).

Province	n	%
Free State	24	4
Gauteng	328	59
KwaZulu-Natal	67	12
Western Cape	141	25
Total	**560**	**100**

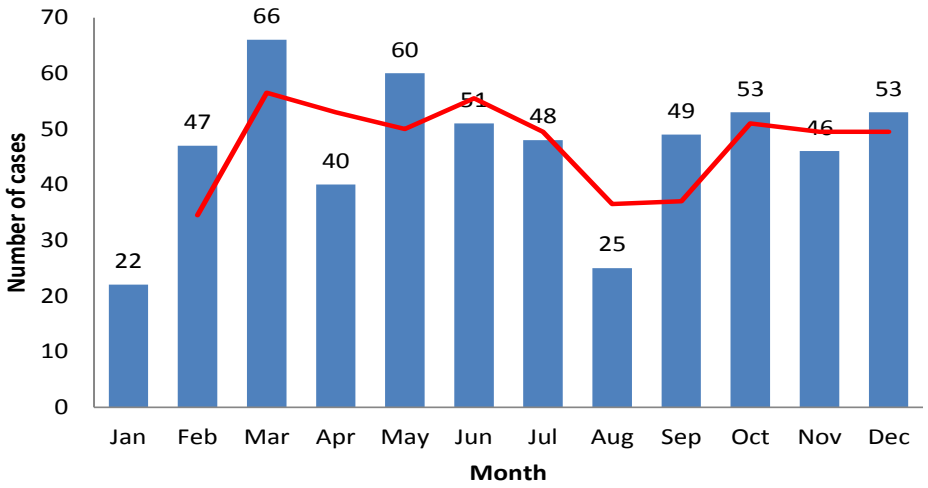


Figure 14: Numbers of cases of laboratory-confirmed *Pseudomonas aeruginosa* bacteraemia cases reported to GERMS-SA sentinel sites by month, 2015, and trend line analysis, n=560.

Table 23: Numbers of viable, laboratory-confirmed *Pseudomonas aeruginosa* reported by GERMS-SA sentinel sites, with reported susceptibility testing to piperacillin/tazobactam (n=365), ceftazidime (n=365), imipenem (n=365), ciprofloxacin (n=365) and colistin (n=365), 2015.

Province	Antimicrobial agents									
	Piperacillin/ tazobactam		Ceftazidime		Imipenem		Ciprofloxacin		Colistin	
	S*	NS**	S	NS	S	NS	S	NS	S	NS
Free State	8 (50)	8 (50)	8 (50)	8 (50)	8 (50)	8 (50)	8 (50)	8 (50)	16 (100)	0 (0)
Gauteng	157 (76)	49 (24)	155 (75)	51 (25)	150 (73)	56 (27)	154 (75)	52 (25)	192 (93)	14 (7)
KwaZulu-Natal	21 (66)	11 (34)	26 (81)	6 (19)	21 (66)	11 (34)	21 (66)	11 (34)	30 (94)	2 (6)
Western Cape	81 (73)	30 (27)	83 (75)	28 (25)	66 (59)	45 (41)	63 (57)	48 (43)	106 (95)	5 (5)
Total	**267 (73)**	**98 (27)**	**272 (75)**	**93 (25)**	**245 (67)**	**120 (33)**	**246 (67)**	**119 (33)**	**344 (94)**	**21 (6)**

*S:=susceptible; **NS=non-susceptible

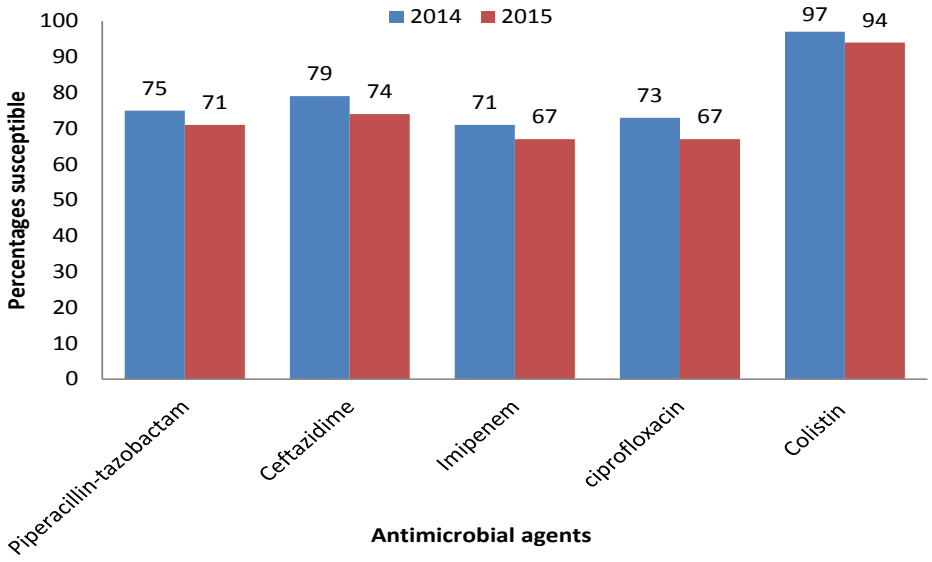


Figure 15: Percentages of susceptibility patterns of cases of laboratory-confirmed *Pseudomonas aeruginosa* bacteraemia reported by GERMS-SA sentinel sites in Gauteng, and trend analysis, 2014 and 2015.

Salmonella enterica serotype Typhi and *S. enterica* serotypes Paratyphi A, Paratyphi B and Paratyphi C

Results

Salmonella Typhi isolates from both invasive and non-invasive sites are reported in Table 24. Cases of enteric fever were highest in November, although there was no marked seasonality (Figure 16). The number of isolates within each age group is reported in Table 25, indicating that most isolates are from patients in the 5 to 14 year and 15 to 44 year age groups, although infection is seen in both older and younger age groups including younger children (less than five years). Ciprofloxacin resistance is problematic although azithromycin remains susceptible (Table 26) following CLSI guidelines .[7] Five isolates of *Salmonella* Paratyphi A were identified. No antimicrobial susceptibility testing was conducted on *Salmonella* Paratyphi A.

Discussion

Salmonella Typhi isolates from both invasive and non-invasive sites are included in these analyses as both add to burden of infection in South Africa and thus represent a public health risk, although data may not reflect actual burden of disease numbers they were comparable with previous non-outbreak years.[8] This is compounded by the challenges of alternative diagnostic methods for typhoid fever, including both clinical and serological. These data thus exclude those patients in whom alternative methods were used without culture confirmation. Strict seasonality was not observed although a greater number of cases were seen between January and April, with numbers rising in November. The greater numbers reported from Gauteng and the Western Cape may reflect health care seeking behavior. The number of reported *Salmonella* Typhi isolates was regarded as an underestimate and thus incidence rates were not calculated. Susceptibility testing was undertaken against limited numbers of antimicrobials due to resource constraints. *Salmonella* Typhi should be tested against azithromycin, which is an alternative treatment option, as ciprofloxacin resistance emerges.[7] Continual monitoring of resistance to these two antimicrobials has become mandatory.[9] Ceftriaxone may also be used as an alternative therapy in these cases. Paratyphoid fever remains rare in South Africa.[10]

Table 24: Numbers of invasive and non-invasive *Salmonella* Typhi cases reported to GERMS-SA, South Africa, 2015, n=76 (including audit reports, missing isolates, mixed and contaminated cultures).

Province	Non-invasive *Salmonella* Typhi	Invasive *Salmonella* Typhi
Eastern Cape	3	1
Free State	1	0
Gauteng	4	24
KwaZulu-Natal	1	8
Limpopo	0	1
Mpumalanga	4	8
Northern Cape	0	0
North West	0	1
Western Cape	2	18
South Africa	**15**	**61**

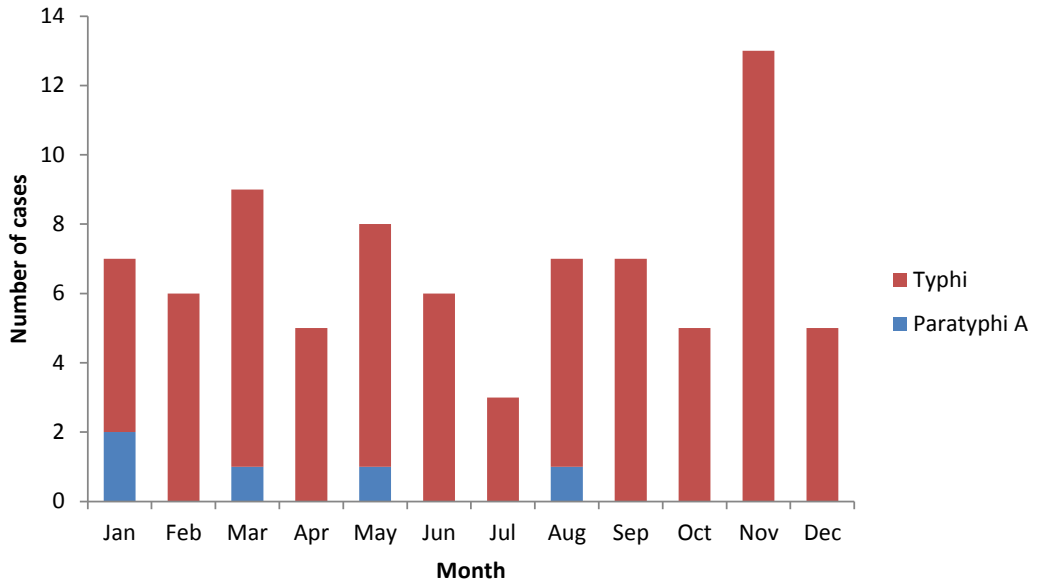


Figure 16: Numbers of non-invasive and invasive cases of *Salmonella* Typhi (n=76) and Paratyphi (n=5) reported to GERMS-SA, by month of specimen collection, South Africa, 2015 (including audit reports). Note *Salmonella* Paratyphi B and Paratyphi C were not identified in 2015.

Table 25: Numbers of *Salmonella* Typhi isolates reported to GERMS-SA by age category, South Africa, 2015, n=72 (including audit reports, missing isolates, mixed and contaminated cultures).

Age category (years)	*Salmonella* Typhi isolates
0 - 4	10
5 - 14	19
15 - 24	8
25 - 34	17
35 - 44	11
45 - 54	7
55 - 64	0
≥ 65	0
Total	**72**

Table 26: Antimicrobial susceptibility test results for all *Salmonella* Typhi isolates received by GERMS-SA, South Africa, 2015, n=71 (excluding audit reports, missing isolates, mixed and contaminated cultures). Clinically relevant antimicrobials are reported.[7]

Antimicrobial agent	Susceptible (%)	Resistant (%)
Ciprofloxacin	61 (86)	9 (14)
Azithromycin	71 (100)	0 (0)

Non-typhoidal *Salmonella enterica* (NTS)

Results

Invasive disease does not appear to have a seasonal prevalence. Increased numbers of non-invasive disease due to NTS in the earlier months of the year and October through December reflect seasonality whereby a lower incidence was observed in the winter months (Figure 17). The number of cases of invasive and non-invasive disease by province, reported to GERMS-SA, is shown in Table 27. The number of cases of invasive and non-invasive disease by age group is shown in Table 28. Most invasive isolates were identified from blood cultures (20.8%), although isolates were frequently identified from both blood culture and another site, including stool and other normally-sterile sites (Table 29). Resistance to the fluoroquinolones was noted (Table 30) and limited azithromycin resistance was noted (7). *Salmonella* Enteritidis was the commonest NTS isolated (Table 31).

Discussion

Non-typhoidal salmonellosis may be food-borne - the patients normally presenting with gastroenteritis - or may be AIDS-defining, in which case the organism frequently becomes invasive. Invasive *Salmonella* Typhimurium ST313 has been documented to occur in South Africa in association with HIV.[11] Seasonal prevalence was noted in 2015 for non-invasive disease. Incidence rates have only been calculated for invasive NTS due to differences in stool-taking practices in adult and paediatric medical care and between different medical facilities. Antimicrobial resistance remains a cause for concern in invasive and non-invasive cases including emerging resistance to azithromycin. *Salmonella* Enteritidis has replaced *Salmonella* Typhimurium as the commonest serotype, as noted in 2011, 2012 and 2013.[12-14]

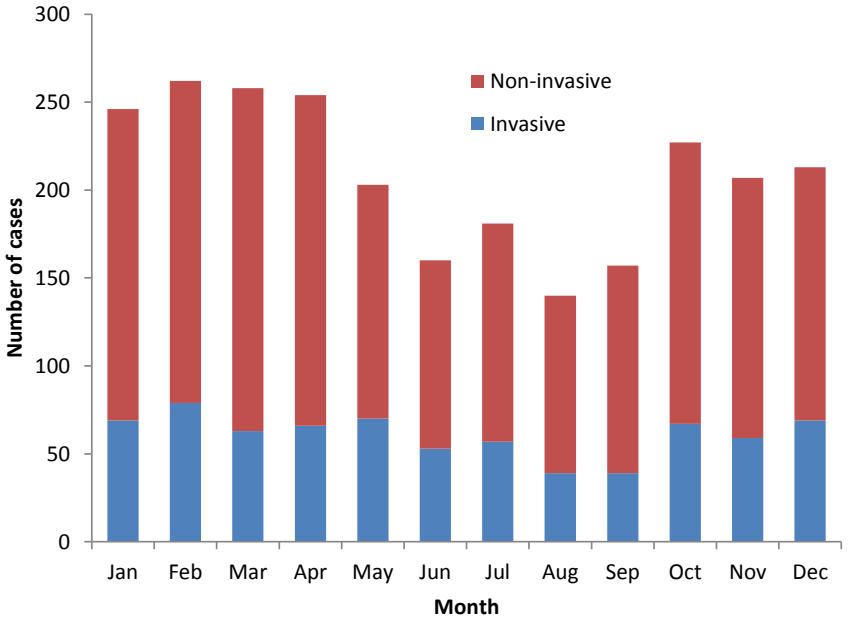


Figure 17: Numbers of non-invasive (n=1,778) and invasive (n=730), non-typhoidal *Salmonella* (NTS) cases, reported to GERMS-SA, by month of specimen collection, South Africa, 2015 (including audit reports).

Table 27: Numbers* of invasive and non-invasive non-typhoidal *Salmonella* cases reported to GERMS-SA, by province, South Africa, 2015, n=2,508 (including audit reports, missing isolates, mixed and contaminated cultures).

Province	Non-invasive, non-typhoidal *Salmonella* isolates	Invasive, non-typhoidal *Salmonella* isolates
Eastern Cape	179	84
Free State	57	22
Gauteng	603	296
KwaZulu-Natal	336	93
Limpopo	68	24
Mpumalanga	137	38
Northern Cape	14	10
North West	15	10
Western Cape	369	153
South Africa	**1,778**	**730**

*Incidence rates were not calculated as there may have been regional differences in specimen collection practices.

Table 28: Numbers* of invasive and non-invasive non-typhoidal *Salmonella* cases reported to GERMS-SA by age category, South Africa, 2015, n=2,379 (including audit reports, missing isolates, mixed and contaminated cultures).

Age Category (years)	Non-invasive, non-typhoidal *Salmonella* isolates	Invasive, non-typhoidal *Salmonella* isolates
0 - 4	497	135
5 - 14	160	29
15 - 24	99	37
25 - 34	206	121
35 - 44	176	121
45 - 54	174	77
55 - 64	111	53
≥ 65	149	51
Unknown	106	77
Total	**1,678**	**701**

*Incidence rates were not calculated because specimens may not have been submitted for culture from all patients with gastroenteritis due to non-typhoidal *Salmonella* in clinical practice.

Table 29: Number of non-typhoidal *Salmonella* cases reported to GERMS-SA by primary anatomical site of isolation*, South Africa, 2015, n=2,379 (including audit reports, missing, mixed and contaminated cultures).

Specimen	n	%
CSF	24	1
Blood culture	567	24
Stool	1,365	57
Other	423	18
Total	**2,379**	**100**

*Certain cases had multiple isolates of the same serotype including those with isolates from an invasive site of origin and a second isolate from stool, or isolates from two different normally-sterile sites.

Table 30: Antimicrobial susceptibility test results for all non-typhoidal *Salmonella* isolates received by GERMS-SA, South Africa, 2015, n=541 (excluding audit reports, missing isolates, mixed and contaminated cultures). Limited antimicrobials for non-invasive and invasive strains were tested due to resource constraints (CLSI 2015).

Antimicrobial agent	Susceptible (%)	Resistant (%)
Azithromycin	537 (99)	4 (1)
Ciprofloxacin	428 (79)	113 (21)

Table 31: Commonest invasive and non-invasive non-typhoidal *Salmonella* serotypes reported to GERMS-SA by province, South Africa, 2015, n=1,294 (excluding audit reports, missing isolates, mixed and contaminated cultures).

Province	Serotype				
	Dublin	Enteritidis	Heidelberg	Isangi	Typhimurium
Eastern Cape	9	26	2	5	117
Free State	2	21	0	0	22
Gauteng	6	323	19	19	119
KwaZulu-Natal	16	82	7	0	69
Limpopo	0	15	2	7	2
Mpumalanga	2	44	6	12	20
Northern Cape	0	2	1	0	11
North West	1	4	1	0	5
Western Cape	5	153	4	1	132
South Africa	**41**	**670**	**42**	**44**	**497**

Shigella species

Results

Slightly increased numbers from January through March and October through December in 2015 suggest seasonality (Figure 18). The primary burden of disease due to *Shigella* is non-invasive dysentery or diarrhoea, although invasive disease cases continue to occur (Table 32). The predominant burden of disease, including both invasive and non-invasive shigellosis, is in the under-five-year age group (Table 33). Fluoroquinolone resistance appears to be emerging (Table 34). Predominant serotypes confirm that *S. flexneri* 2a remains the commonest cause of shigellosis in South Africa (Table 35). *Shigella dysenteriae* type 1 was not isolated in 2015 (data not shown).

Discussion

Shigella infection is associated with water-borne outbreaks in South Africa, although person-to-person transmission plays an important role. Invasive disease appears to be decreasing. [12-15] Resistance to fluoroquinolones remains low but should continue to be monitored. ESBL-production is rarely documented. *Shigella dysenteriae* type 1 isolates were not reported and appear to be rare as there were no isolates in South Africa in 2015 or preceding years when systematic surveillance was conducted. [12-14]

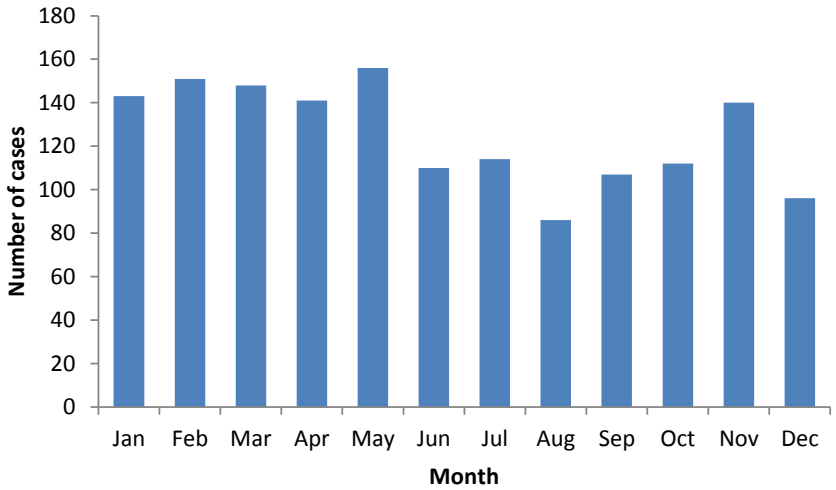


Figure 18: Numbers of non-invasive and invasive *Shigella* isolates, reported to GERMS-SA, by month of specimen collection, South Africa, 2015, n=1,504 (including audit reports).

Table 32: Numbers of invasive and non-invasive *Shigella* isolates reported to GERMS-SA by province, South Africa, 2015, n=1,503 (including audit reports, missing isolates, mixed and contaminated cultures).

Province	Non-invasive *Shigella*	Invasive *Shigella*
Eastern Cape	168	4
Free State	53	0
Gauteng	331	18
KwaZulu-Natal	304	6
Limpopo	18	0
Mpumalanga	32	4
Northern Cape	7	1
North West	15	0
Western Cape	534	8
South Africa	**1,462**	**41**

Table 33: Numbers* of invasive and non-invasive *Shigella* cases reported to GERMS-SA by age category, South Africa, 2015, n=1,503 (including audit reports, missing isolates, mixed and contaminated cultures).

Age Category (years)	Non-invasive *Shigella*	Invasive *Shigella*
0 - 4	639	11
5 - 14	207	4
15 - 24	72	1
25 - 34	156	7
35 - 44	105	5
45 - 54	88	4
55 - 64	49	1
≥ 65	82	3
Unknown	64	5
Total	**1,462**	**41**

*Incidence rates were not calculated because specimens may not have been submitted for culture from all patients with gastroenteritis due to *Shigella* in clinical practice.

Table 34: Antimicrobial susceptibility test results for selected *Shigella* isolates received by GERMS-SA, South Africa, 2015, ciprofloxacin, n=1,097 and azithromycin, n=1,010 (excluding audit reports, missing isolates, mixed and contaminated cultures). Clinically relevant antimicrobials for non-invasive and invasive strains are reported (CLSI 2015). Complete antimicrobial testing was not undertaken due to resource constraints.

Antimicrobial agent	Susceptible	(%)	Resistant	(%)
Ciprofloxacin	1088	(99)	9	(1)
Azithromycin	1001	(99)	9	(1)

Table 35: Commonest invasive and non-invasive *Shigella* serotypes reported to GERMS-SA by province, South Africa, 2015, n=959 (excluding audit reports, missing isolates, mixed and contaminated cultures).

Province	*S. flexneri* type 1b	*S. flexneri* type 2a	*S. flexneri* type 3a	*S. flexneri* type 6	*S. sonnei*
Eastern Cape	7	66	8	8	15
Free State	1	14	5	5	16
Gauteng	10	54	33	32	120
KwaZulu-Natal	18	63	27	20	66
Limpopo	0	2	1	2	2
Mpumalanga	0	6	1	5	11
Northern Cape	0	2	1	1	1
North West	0	1	1	0	5
Western Cape	38	202	34	20	35
South Africa	**74**	**410**	**111**	**93**	**271**

Diarrhoeagenic *Escherichia coli* (DEC)

Results

Very few isolates were received in 2015 and true pathogens represented only 44/153 (28.8%) of isolates (Figure 19). Enteropathogenic *E. coli* (EPEC) remains the commonest cause of diarrhoea in South Africa (Table 36). Most cases were identified in children less than 5 years of age (Table 37).

Discussion

Low numbers of isolates prevented ascertainment of seasonality. The predominance of cases in younger children under five years of age may reflect, in part, specimen-taking practices as well as the burden of diarrhoeal disease in this age group (Table 37). Burden of disease due to diarrhoeagenic *E. coli* is probably greatly underestimated in South Africa, as management is primarily syndromic and centres on rehydration. As a result, clinicians are unlikely to prioritise stool-taking in uncomplicated cases of diarrhoea. Identification of two cases of Shiga toxigenic *E. coli* (STEC) was incidental as there are currently no useful biochemical markers in sorbitol-positive isolates.[16] Terminology of this pathogen is evolving.[17]

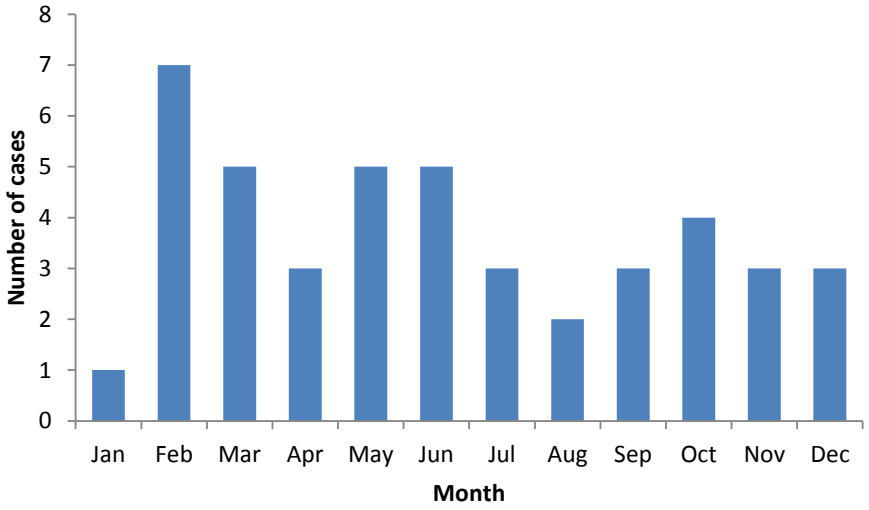


Figure 19: Numbers of diarrhoeagenic *Escherichia coli* isolates, reported to GERMS-SA, by month of specimen collection, South Africa, 2015, n=44.

Table 36: Numbers of diarrhoeagenic *Escherichia coli* isolates reported to GERMS-SA by province, South Africa, 2015, n=44.

Province	DAEC	EAggEC	STEC/ EHEC	EIEC	EPEC	ETEC	Mixed pathotype*
Eastern Cape	2	0	0	0	4	0	1
Free State	0	0	0	0	0	0	0
Gauteng	5	3	0	0	5	0	0
Kwazulu-Natal	3	0	1	2	4	0	1
Limpopo	0	0	0	0	0	0	0
Mpumalanga	5	1	0	0	2	0	0
Northern Cape	0	0	0	0	0	0	0
North West	1	0	0	0	0	0	0
Western Cape	1	1	0	0	2	0	0
South Africa	**17**	**5**	**1**	**2**	**17**	**0**	**2**

DAEC: diffusely-adherent *E. coli*; EAggEC: enteroaggregative *E. coli*; STEC/EHEC: Shiga-toxigenic *E. coli* or enterohaemorrhagic *E. coli*; EIEC: enteroinvasive *E. coli*; EPEC: enteropathogenic *E. coli*; ETEC: enterotoxigenic *E. coli.*
*Mixed pathotype: contained virulence genes from more than one pathotype.

Table 37: Number of diarrhoeagenic *E. coli* isolates reported to GERMS-SA by age category, South Africa, 2015, n=44.

Age category (years)	DAEC	EAggEC	STEC/ EHEC	EIEC	EPEC	ETEC	Mixed pathotype*
0 - 4	11	3	0	0	16	0	2
5 - 14	0	1	0	1	0	0	0
15 - 24	1	0	0	0	1	0	0
25 - 34	3	0	0	0	0	0	0
35 - 44	0	0	0	1	0	0	0
45 - 54	1	0	1	0	0	0	0
55 - 64	0	0	0	0	0	0	0
≥ 65	1	0	0	0	0	0	0
Unknown	0	1	0	0	0	0	0
Total	**17**	**5**	**1**	**2**	**17**	**0**	**2**

DAEC: diffusely-adherent *E. coli*; EAggEC: enteroaggregative *E. coli*; STEC/EHEC: Shiga-toxigenic *E. coli* or enterohaemorrhagic *E. coli*; EIEC: enteroinvasive *E. coli*; EPEC: enteropathogenic *E. coli*; ETEC: enterotoxigenic *E. coli.*
*Mixed pathotype: contained virulence genes from more than one pathotype.

Vibrio cholerae O1

Results

No cases of *Vibrio cholerae* O1 were identified in 2015.

Discussion

The lack of outbreaks of cholera in 2015 supports the importance of heightened awareness and rapid responses in years past in the event of disease being identified.[12-14]

Rifampicin-resistant Tuberculosis

Results

During 2015 a total of 1,286 cases of rifampicin-resistant tuberculosis (TB) were eligible for inclusion into the surveillance, of which 943 (73.3%) were successfully enrolled and a Case Report Form (CRF) completed. Of those with completed CRFs, 94.5% knew their HIV status and of these, 74.7% were HIV positive. Among the HIV-positive cases, 56% were on antiretroviral treatment while among these HIV-positive cases, 53% were females with a median age of 35 years (IQR 30-43). In the HIV-negative group, 38% were female and had a median age of 33 years (IQR 23-47). Limited risk factors were analysed and Table 38 shows the comparison of factors by province. Results of the molecular typing are shown in Figure 20, accumulating data for 2014-2015 across seven provinces.

Discussion

The HIV co-infection rate with TB was 75% across all areas under surveillance, highlighting the important role of HIV infection and the need for integrated management of these two diseases. Unsurprisingly the rates were highest in Gauteng, KwaZulu-Natal and Mpumalanga. It was, however, exceptionally high in Gauteng (92%) and this was likely due to the surveillance site being a tertiary hospital, unlike the other sites which included cases diagnosed at primary health care level. The proportion on antiretroviral treatment (ART) was only 56%, this despite the guidelines published several years ago, indicating that all HIV-positive patients with drug-resistant TB should be started on ART irrespective of CD4+ count. The recent announcement of the test-and-treat strategy for HIV infection is a good initiative and will likely ensure earlier initiation of ART and potentially also impact positively on the drug-resistant TB program and treatment outcomes.

Patients reporting a previous episode of TB treatment accounted for 49% of cases with the remainder experiencing their first episode with drug-resistant TB. This is concerning and indicates that transmission of drug-resistant TB is common. The role of the household as a potential source of transmission was also identified as important with almost half the number of cases having a household member previously diagnosed with TB, though the frequency varied by geographic area. The molecular epidemiological data further confirms the role of transmission, with Beijing strains the dominant type observed across all areas. This was most evident in Eastern Cape with 56% of strains being of the Beijing lineage, indicating the establishment in this province of the Beijing lineage which is known to show a fitness advantage. Interestingly, a high occurrence of the East African Indian lineage was found in Mpumalanga and these isolates were predominantly rifampicin mono-resistant and need to be closely monitored. Among the other risk factors analysed, smoking occurred in approximately one in three patients and needs to be addressed to improve lung health and reduce the risk for TB disease in the community. Prior mining or prison exposure, potentially playing a role in selected surveillance areas/sites, however, was only evident in very low proportions of patients, indicating that mining and imprisonment are unlikely to be major drivers of the epidemic in the community. The surveillance system, although fairly new, has produced important insights into the drug-resistant TB epidemic, and expansion of the surveillance system to cover districts in four provinces has allowed for the molecular typing of data to better assess transmission risks in the community and the risk factor data to also be more representative. Further expansion of this surveillance is planned to cover provinces with a high TB burden not currently included in the surveillance.

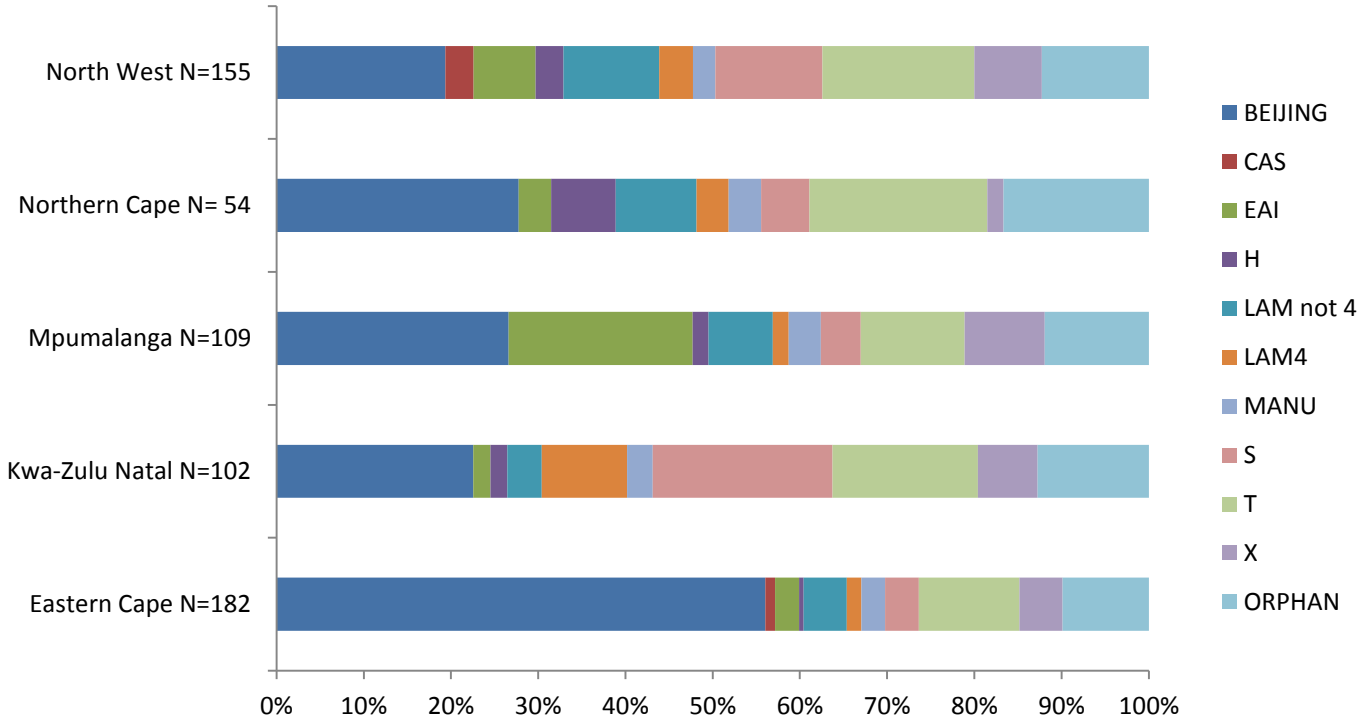


Figure 20: Tuberculosis spoligotypes of culture positive specimens by province, South Africa, 2014 and 2015, n=609.

Table 38: Selected risk factors for rifampicin-resistant tuberculosis (TB) by province using CRF data, South Africa, 2014 and 2015.

Risk Factor	Province*							
	EC N=294	GA N=150	KZ N=114	LP N=14	MP N=159	NC N=74	NW N=138	Total N=943
HIV status								
Yes	175	117	84	8	125	45	112	666
No	105	10	24	6	32	26	22	225
Unknown	14	23	6	0	2	3	4	40
HIV positive % of known status	**63%**	**92%**	**78%**	**57%**	**80%**	**63%**	**84%**	**75%**
HIV positive patients on ARV treatment								
Yes	108	50	45	5	69	25	68	370
No	60	56	34	3	52	17	39	261
Unknown	7	11	5	0	4	3	5	35
Proportion of HIV% on ARTs	**62%**	**43%**	**54%**	**63%**	**55%**	**56%**	**61%**	**56%**
Previous TB treatment								
Yes	174	74	46	4	57	42	65	462
No	108	64	62	10	95	27	64	430
Unknown	12	12	6	0	7	5	9	51
Proportion previous treatment exposure	**59%**	**49%**	**40%**	**29%**	**36%**	**57%**	**47%**	**49%**
Household contact with TB								
Yes	174	74	46	4	57	42	65	462
No	108	64	62	10	95	27	64	430
Unknown	12	12	6	0	7	5	9	51
Proportion with household TB contact	**59%**	**49%**	**40%**	**29%**	**36%**	**57%**	**47%**	**49%**
Smoked in the last 5 years								
Yes	138	44	18	6	37	46	46	335
No	146	90	87	8	116	23	86	556
Unknown	10	16	9	0	6	5	6	52
Proportion positive smoking history	**47%**	**29%**	**16%**	**43%**	**23%**	**62%**	**33%**	**36%**
Worked in mine / quarry								
Yes	3	2	1	0	11	9	13	39
No	285	128	101	14	144	57	119	848
Unknown	6	20	12	0	4	8	6	56
Proportion with prior mining exposure	**1%**	**1%**	**1%**	**0%**	**7%**	**12%**	**9%**	**4%**
Previous imprisonment in last 10 years								
Yes	20	12	2	0	16	6	10	66
No	265	118	100	14	131	62	120	810
Unknown	9	20	12	0	12	6	8	67
Proportion with prior prison exposure	**7%**	**8%**	**2%**	**0%**	**10%**	**8%**	**7%**	**7%**
Regular Alcohol Use								
Yes	27	18	13	3	30	16	35	142
No	253	115	95	11	118	50	97	739
Unknown	14	17	6	0	11	8	6	62
Proportion with regular alcohol intake	**9%**	**12%**	**11%**	**21%**	**19%**	**22%**	**25%**	**15%**
Recreational drug use								
Yes	18	1	1	0	2	9	2	33
No	259	130	106	14	126	57	126	818
Unknown	17	19	7	0	31	8	10	92
Proportion using recreational drugs	**6%**	**1%**	**1%**	**0%**	**1%**	**12%**	**1%**	**3%**

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

Discussion

The GERMS-SA laboratory-based surveillance continues to be useful in reporting trends in pathogen-specific data. Going forward, the GERMS-SA surveillance data will be published per NICD Centre in the NICD Communicable Diseases Surveillance Bulletin (a quarterly publication available at www.nicd.ac.za).

In 2015 there were still challenges moving over from DISA*Lab to TrakCare Lab and mapping data onto the Corporate Data Warehouse. For enhanced sentinel surveillance, the percentage of case report forms done on interview was over 80% and ongoing training and auditing of our surveillance officer data quality is done to continually improve that aspect.

Opportunistic infections: For *Cryptococcus*, a large number of cases of cryptococcal antigenaemia were detected at microbiology/clinical pathology laboratories through provider requests. This follows inclusion of a cryptococcal antigen (CrAg) screen-and-treat intervention in the 2015 national consolidated guidelines for management of HIV. From our sentinel sites, clinical data showed that 97% of 412 patients were HIV-infected. Rifampicin-resistant TB surveillance was increased to seven provinces in 2015 and 75% of 943 enrolled patients were found to be HIV-infected. This supports the recommendation that ART should be started in this group of patients. Transmission of drug-resistant TB is high, with 51% reporting a household contact with TB. The molecular epidemiological data showed the Beijing strains predominating in all areas and establishing itself in the Eastern Cape. A high occurrence of the East African Indian lineage was found in Mpumalanga. These isolates were mostly rifampicin mono-resistant and need close monitoring.

Vaccine-preventable diseases: The 2015 data continues to monitor the trends in vaccine-preventable diseases of IPD and Hib post-EPI vaccine introduction of PCV13 and the Hib booster. It shows a continued decrease in IPD with an increase in non-vaccine serotypes. Hib disease in children <1 year continues to decrease and serotype b is no longer the commonest serotype causing disease in children <5 years. Non-typeable strains are becoming more important. Non-vaccine-type disease for *Haemophilus influenzae* and IPD needs to be monitored. Clinicians should remember that children with missed vaccine doses should receive appropriate catch-up doses and that Hib is a notifiable medical condition.

Epidemic-prone diseases: The incidence of meningococcal disease remained low. Penicillin is, at present, still being recommended as the drug of choice for therapy for confirmed meningococcal disease. For enteric organisms there was nothing to compare to in 2014 since surveillance was stopped for that year. There is a great underestimation of enteric disease because of stool-taking practices. For *Salmonella* Typhi, azithromycin is an alternative treatment option since the emergence of ciprofloxacin resistance. For non-typhoidal salmonellosis, *Salmonella* Enteritidis has replaced *S.* Typhimurium as the commonest serotype. For shigellosis, fluoroquinolone resistance appears to be emerging and *Shigella flexneri* 2a remains the commonest serotype. *Shigella dysenteriae* type 1 has not been isolated in the last few years. No cases of *Vibrio cholerae* O1 were identified.

Hospital infections: The 2015 candidaemia surveillance covered all provinces except the Western Cape and only one hospital in Gauteng, compared to 2014 where it included only Gauteng and the Western Cape. Candidaemia cases were mostly in young children, predominantly neonates. Resistance to fluconazole is high and local knowledge should guide empiric treatment choices. Conventional amphotericin B remains the empiric drug of choice for candidaemia in the public-sector because of the high prevalence of azole-resistant *C. parapsilosis* isolates. *Staphylococcus*

aureus surveillance is ongoing in Gauteng and the Western Cape. One third of isolates received were confirmed as MRSA. SCC mec type III was more common in Gauteng and SCC mec IV in the Western Cape. All isolates were susceptible to vancomycin. *Pseudomonas aeruginosa* surveillance was done at selected sentinel sites in four provinces. A quarter of isolates were resistant to recommended agents.

Information from our enhanced surveillance show that approximately one third of patients die in hospital and the majority of deaths occur early on in admission, suggesting that access to healthcare is late. At 76%, the percentage of patients with known HIV status was high, although of those who were HIV-infected, only about half were on antiretroviral treatment.

The GERMS-SA publications and effects on policy are as a result of the isolates that your participating laboratories submit. We encourage all laboratory staff to continue participating in the NICD surveillance programmes. We thank you for your ongoing service to the health of all South Africans.

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ANTIMICROBIAL RESISTANCE SURVEILLANCE FROM SENTINEL PUBLIC HOSPITALS, SOUTH AFRICA, 2015

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Introduction

Antimicrobial resistance (AMR) is a significant public health concern that threatens effective treatment of severe infections, both locally and globally. Surveillance is conducted to determine the extent and pattern of resistance amongst the most common pathogens causing infections in humans.[1] Integrated data on bacterial resistance are obtained from an electronic database of bacterial antimicrobial susceptibility results generated by public sector diagnostic laboratories in South Africa.

The objectives of the AMR surveillance programme are to determine the number of isolates of selected pathogens reported from selected hospitals by month and to describe antimicrobial susceptibility to the most important treatment regimens by pathogen and by hospital.

Methods

All data for this report were sourced from the National Health Laboratory Service (NHLS) Corporate Data Warehouse (CDW). This is a national repository for laboratories serving all public sector hospitals in South Africa and contains archived data from the Laboratory Information System (LIS).[2]

Bloodstream infections over the period January-December 2015 were extracted for the following ESKAPE pathogens: *Acinetobacter baumannii* complex, *Enterobacter cloacae* complex, *Escherichia coli, Enterococcus faecalis, Enterococcus faecium, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Staphylococcus aureus.* Routine electronic data were collected from sentinel sites (mostly tertiary academic hospitals) (Table 1).

Antimicrobial susceptibility reporting was based on Clinical Laboratory Standards Institute (CLSI) guidelines.[3] The various laboratory methods used included Microscan, Vitek and disk diffusion. Due to site-specific differences in testing methodologies and data capture on the LIS, extensive cleaning and recoding of data were necessary. This was done within the CDW. The CDW linking algorithm was used to create unique patient identifiers that enabled the generation of patient-level data and de-duplication within a 21-day patient episode, which was initiated from the first occurrence of resistance to a given antibiotic for a given pathogen.

Vancomycin resistance is not reported for *Staphylococcus aureus* due to the lack of confirmatory test methods (pending agreement with the South African Society for Clinical Microbiology (SASCM)). Data were omitted for those sites that tested fewer than 30 organisms for resistance to a particular antibiotic.

Table 1: Hospitals participating in antimicrobial resistance surveillance by province, South Africa, and their characteristics.

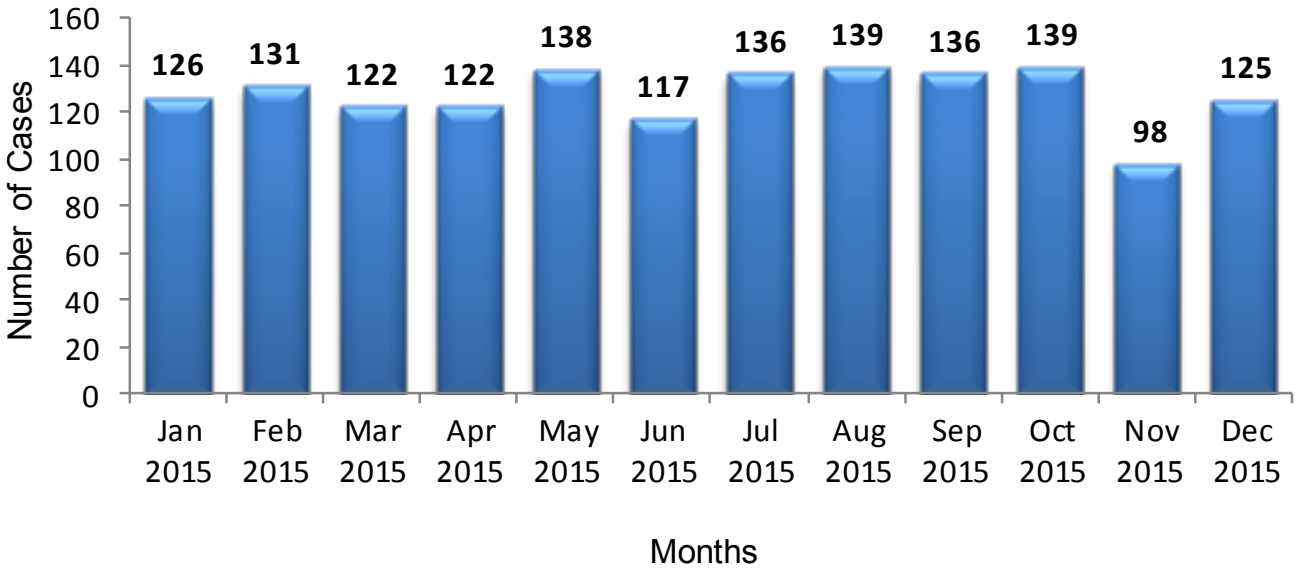
Hospital Site	Province	Academic Hospital	No of beds
Frere Hospital	Eastern Cape	No	916
Livingstone Hospital	Eastern Cape	Yes	616
Nelson Mandela Academic Hospital/Mthatha Tertiary (NMAH)	Eastern Cape	Yes	520
Universitas Hospital (UH)	Free State	Yes	650
Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)	Gauteng	Yes	1088
Chris Hani Baragwanath Hospital (CHBH)	Gauteng	Yes	3200
Dr George Mukhari Hospital (DGMH)	Gauteng	Yes	1200
Steve Biko Academic Hospital (SBAH)	Gauteng	Yes	832
Helen Joseph Hospital (HJH)	Gauteng	Yes	700
Grey's Hospital (GH)	KwaZulu-Natal	Yes	530
Inkosi Albert Luthuli Central Hospital (IALCH)	KwaZulu-Natal	Yes	846
King Edward VIII Hospital (KEH)	KwaZulu-Natal	Yes	922
Mahatma Gandhi Hospital (MGH)	KwaZulu-Natal	No	350
RK Khan Hospital (RKKH)	KwaZulu-Natal	No	543
Tygerberg Hospital (TH)	Western Cape	Yes	1310
Groote Schuur Hospital (GSH)	Western Cape	Yes	893

Results

Data for bloodstream infections and antimicrobial susceptibility tests are summarised for *Acinetobacter baumannii* complex (Figure 1), *Enterobacter cloacae* complex (Figure 2), *Enterococcus faecalis* (Figure 3), *Enterococcus faecium* (Figure 4), *Escherichia coli* (Figure 5), *Klebsiella pneumoniae* (Figure 6), *Pseudomonas aeruginosa* (Figure 7) and *Staphylococcus aureus* (Figure 8). For each organism, the total number of isolates, as well as their susceptibility profiles and percentage susceptibility to selected antimicrobial agents by site were analysed (Figures 1-8).

***Acinetobacter baumannii* complex**

Acinetobacter baumannii showed resistance to the majority of antimicrobial agents tested. This was likely due to its ability to encode and upregulate various mechanisms of resistance such as the loss of outer membrane porins and permeability, efflux systems, AmpC β-lactamases and others. The proportions of isolates resistant to imipenem, cefepime and ceftazidime were high at 82%, 81% and 78%, respectively, whereas resistance proportions were 68% to ciprofloxacin, 50% to amikacin and 61% to tobramycin. The extent of resistance to most agents changed in comparison to 2014 i.e. there was a significant decrease in resistance to imipenem (23% in 2014 vs. 18% 2015; $p<0.001$) while resistance to carbapenems, cephalosporins (3rd and 4th generations) and aminoglycosides increased in 2015, with the exception of resistance to colistin which was only 2% in 2015 compared to 5% in 2014. From referral isolates sent to the Antimicrobial Resistance Laboratory (AMRL) of the NICD, no colistin resistance conferred by the *mcr*1 gene was confirmed. Except for these few isolates no confirmation of colistin resistance is performed at the AMRL.



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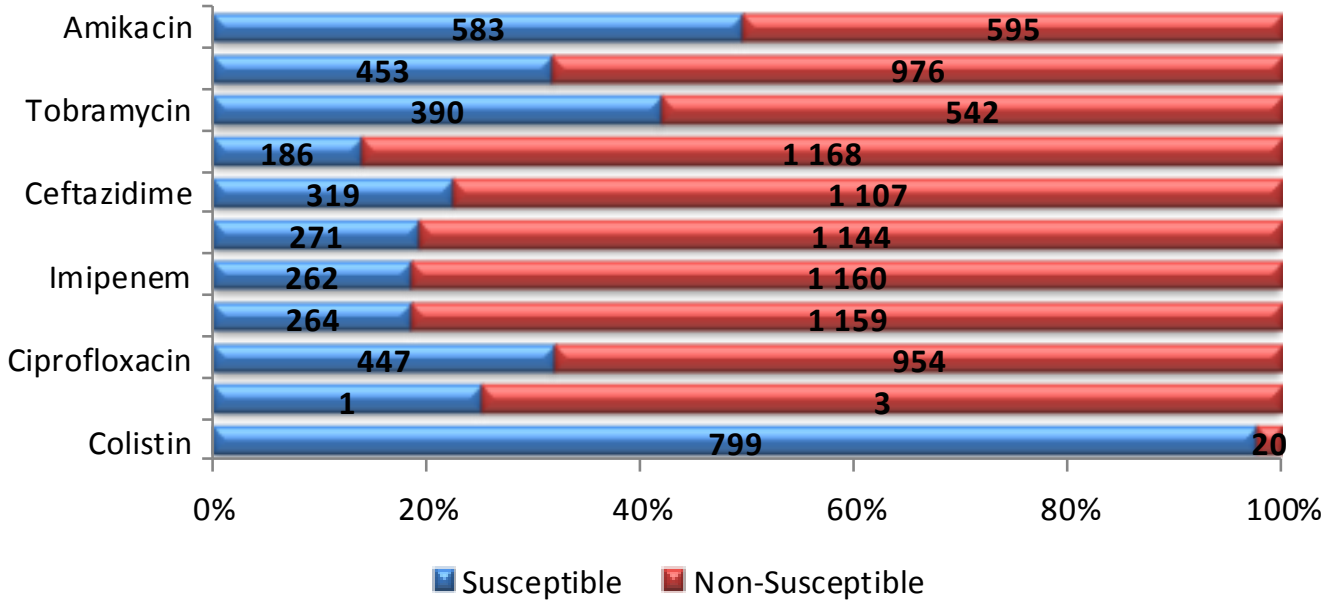
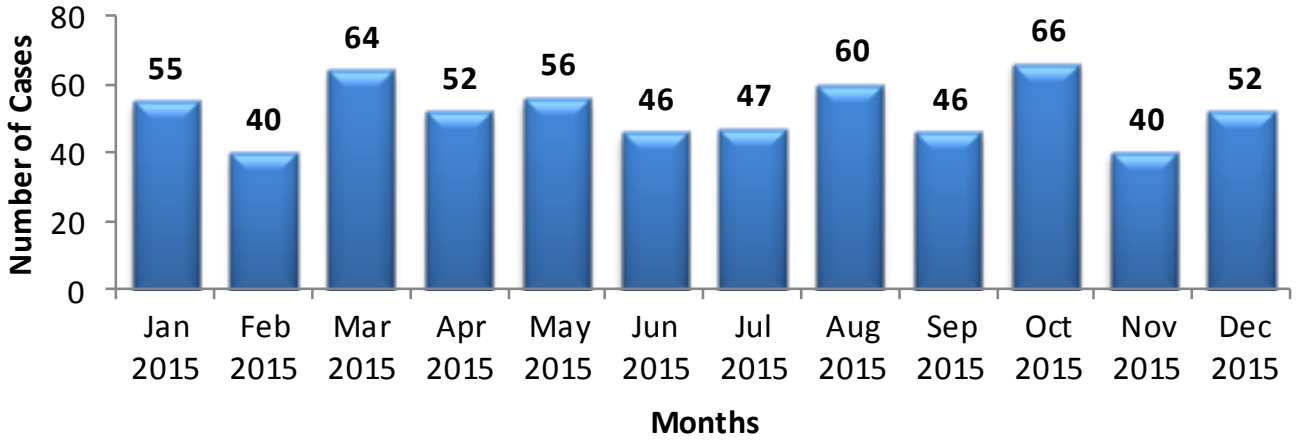


B

Figure 1: A. *Acinetobacter baumannii* cases by month, and B. Numbers and percentages of susceptible and resistant *A. baumannii* complex isolates from blood cultures at public-sector sentinel sites, 2015. Total number of isolates analyzed = 1529.

***Enterobacter cloacae* complex**

The prevalence of presumptive (i.e. no molecular confirmation) resistance of *Enterobacter cloacae* complex to ertapenem of 8% has decreased in comparison to the 2014 resistance prevalence of 11%. Resistance to imipenem and meropenem has remained stable at 2%. Resistance to ceftazidime has decreased since 2014 (p=0.02) while resistance to piperacillin-tazobactam remained stable in 2015. Resistance to cefepime (31%) is suggestive of AmpC hyper-production due to de-repressed AmpC mutants which confer resistance to all cephalosporins. These data may also indicate co-carriage of an extended-spectrum β-lactamase (ESBL).



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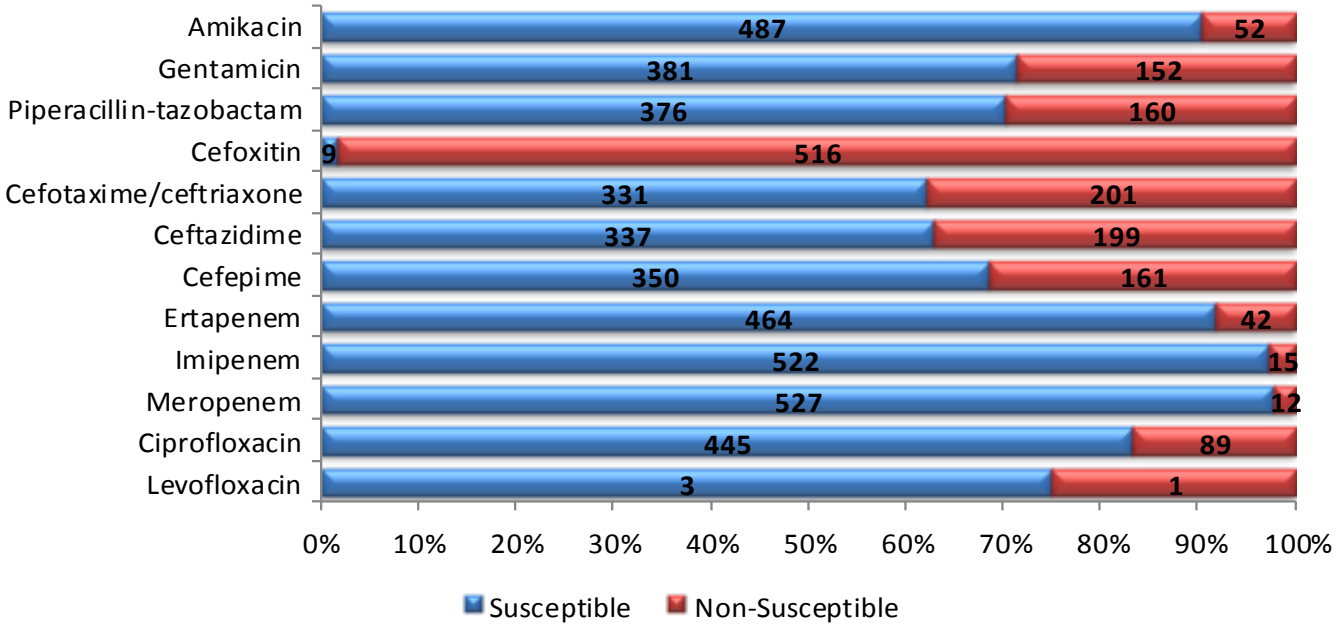

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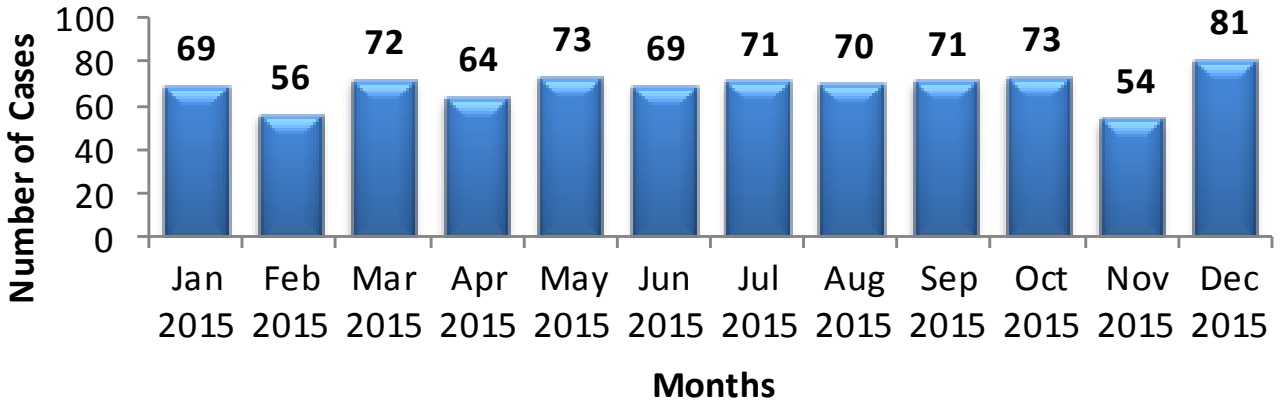
Figure 2: A. *Enterobacter cloacae* cases by month, and B. Numbers and percentages of susceptible and resistant *E. cloacae* complex isolates from blood cultures at public-sector sentinel sites, 2015. Total number of isolates analyzed = 624.

Enterococcus faecalis

Enterococcus faecalis exhibited 14% resistance to penicillins and 1% (non-confirmed) resistance to vancomycin, both of which are slightly reduced from the corresponding prevalences of 2014 (17% to penicillins and 2% to vancomycin). There were no other significant changes in comparison to 2014.



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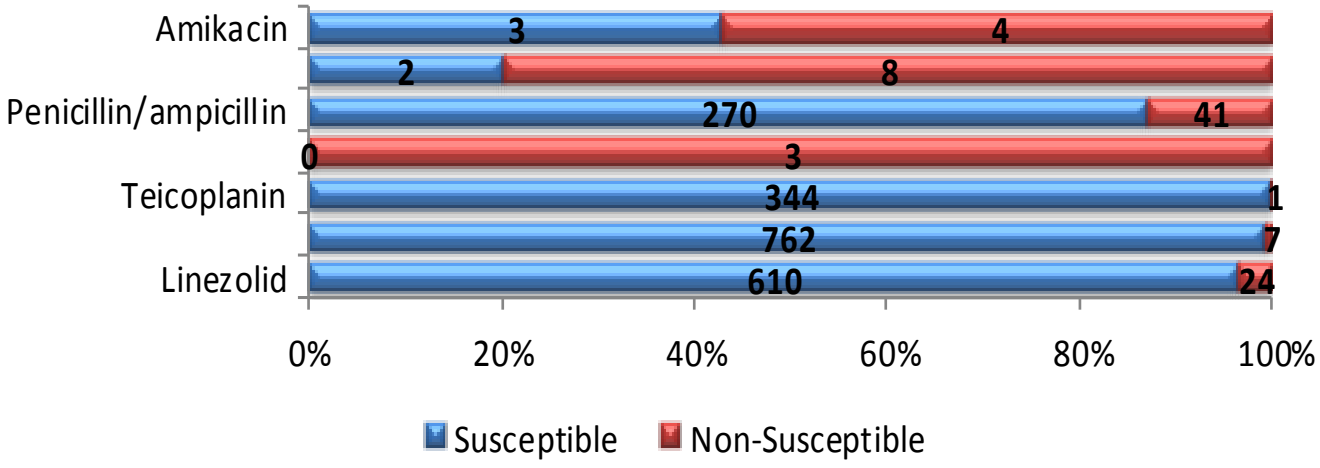

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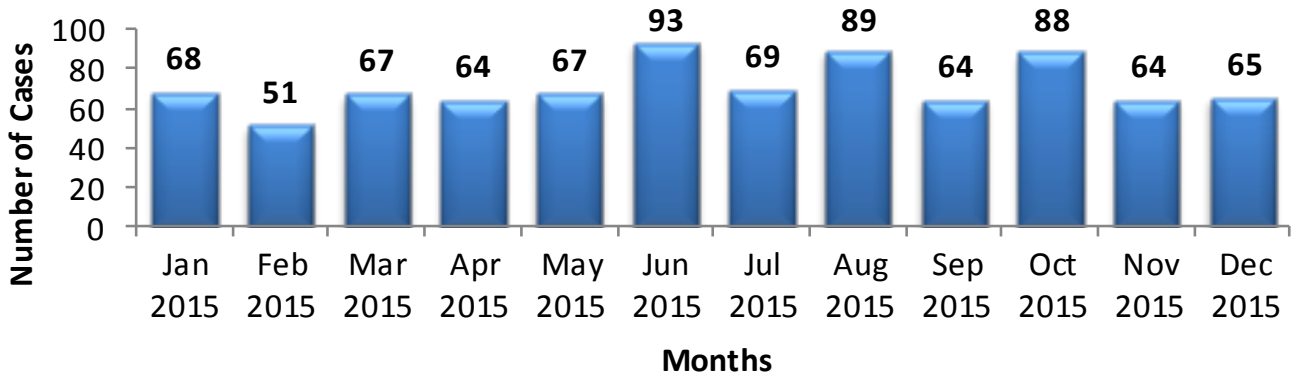
Figure 3: A. *Enterococcus faecalis* cases by month, and B. Numbers and percentages of susceptible and resistant *E. faecalis* isolates from blood cultures at public-sector sentinel sites, 2015. Total number of isolates analyzed = 823.

Enterococcus faecium

Enterococcus faecium is inherently resistant to β-lactam agents. Resistance to vancomycin remained unchanged at 5% in 2015.



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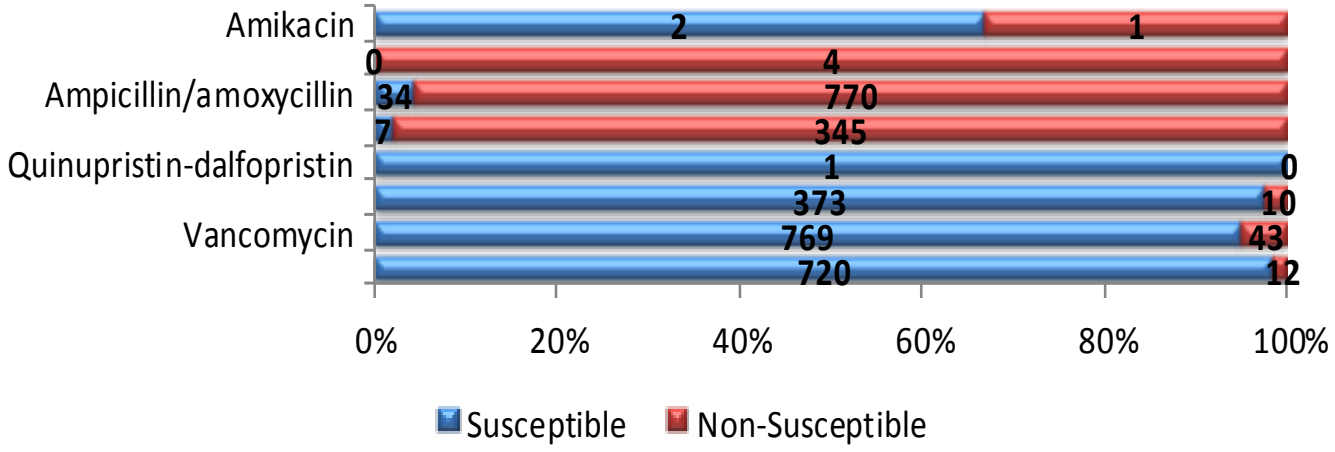
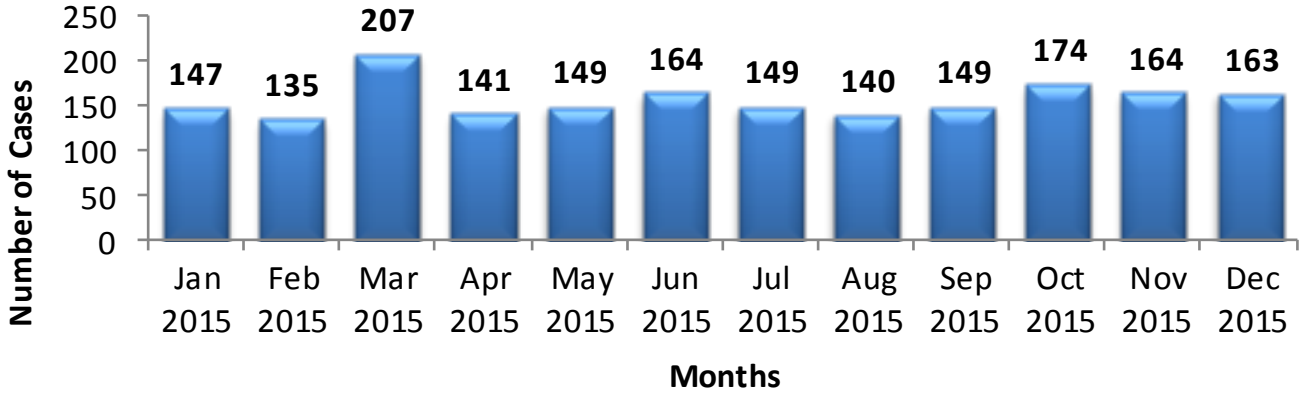


B

Figure 4: A. *Enterococcus faecium* cases by month, and B. Numbers and percentages of susceptible and resistant *E. faecium* isolates from blood cultures at public-sector sentinel sites, 2015. Total number of isolates analyzed = 849.

Escherichia coli

Escherichia coli showed no change in resistance to piperacillin-tazobactam and ciprofloxacin compared to 2014 and no significant increased resistance to the β-lactam group over a two-year period. Resistance to 3rd generation cephalosporins indicates the presence of extended spectrum β-lactamases (ESBLs) and was recorded in 22% of isolates.



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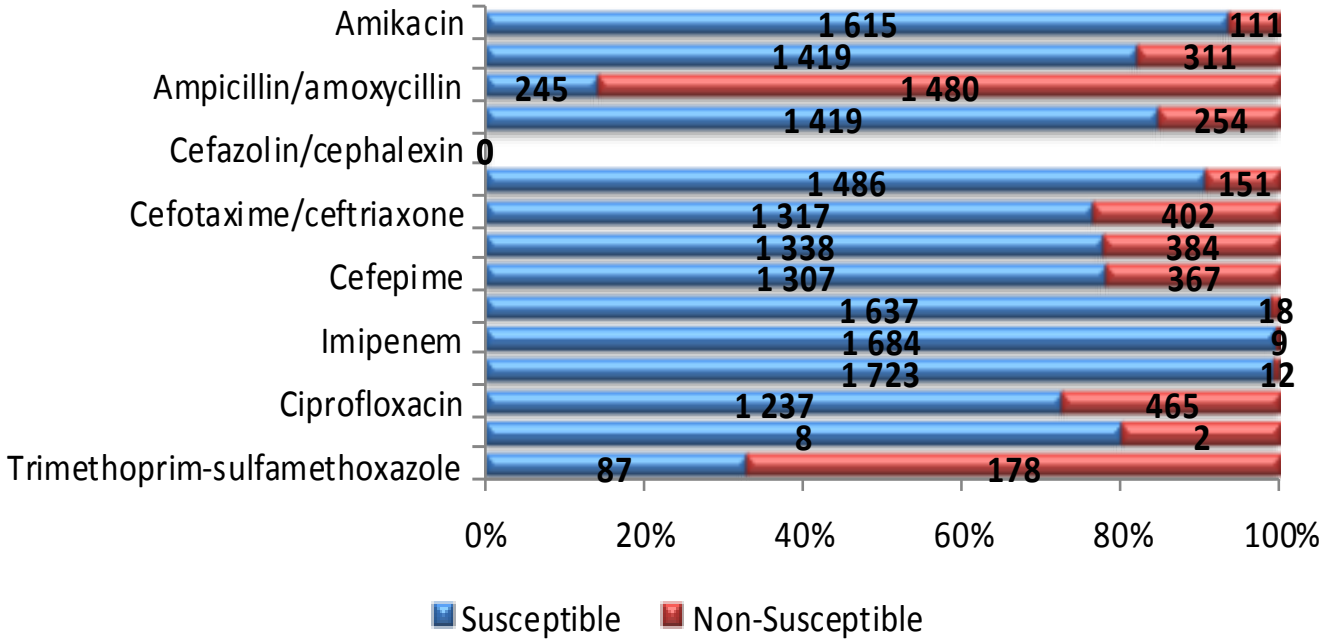
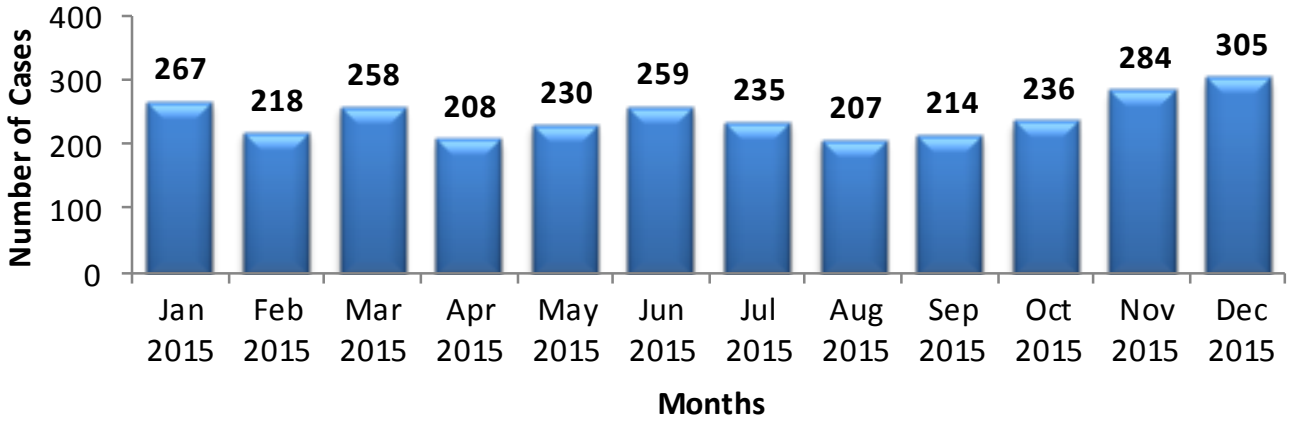


B

Figure 5: A. *Escherichia coli* cases by month, and B. Numbers and percentages of susceptible and resistant *E. coli* isolates from blood cultures at public-sector sentinel sites, 2015. Total number of isolates analyzed = 1882.

Klebsiella pneumoniae

Klebsiella pneumoniae was resistant to multiple antimicrobials, including 3rd generation cephalosporins that indicate production of ESBLs (69%), ciprofloxacin (33%) and piperacillin-tazobactam (50%). The proportion of isolates resistant to ertapenem (4%) has remained unchanged over a 2-year period. Resistance prevalences to imipenem (6%) and meropenem (6%) showed significant increases compared to 2014 ($p<0.001$). Although resistance to other carbapenems was generally low, the rapid emergence of strains with carbapenemase production threatens the efficacy and use of this vital class of antimicrobials as a therapeutic option. Thus, knowledge of local hospital epidemiology and monitoring of carbapenem resistance is essential.



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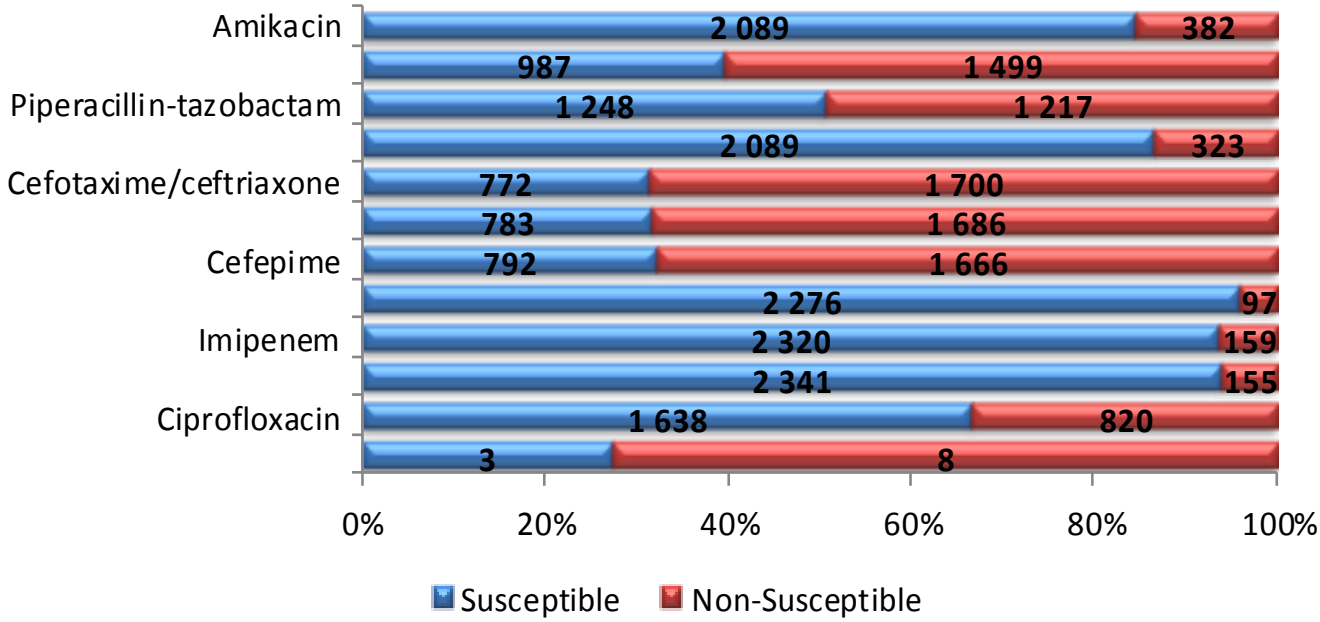
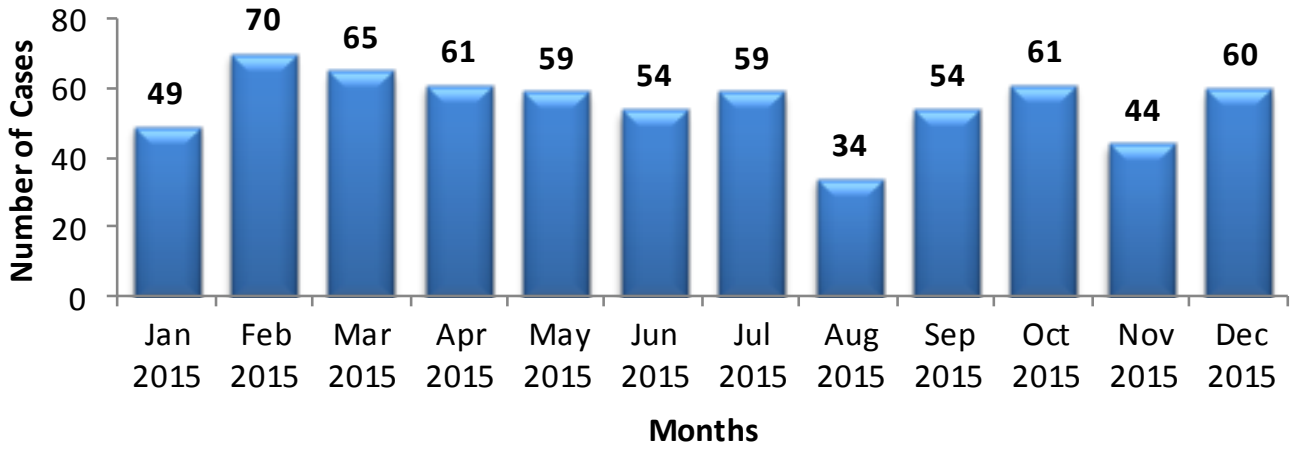


B

Figure 6: A. *Klebsiella pneumoniae* cases by month, and B. Numbers and percentages of susceptible and resistant *K. pneumoniae* isolates from blood cultures at public-sector sentinel sites, 2015. Total number of isolates analyzed = 2921.

Pseudomonas aeruginosa

Thirty percent of *Pseudomonas aeruginosa* isolates were resistant to piperacillin-tazobactam and 27% were resistant to cefepime. Colistin resistance was low (1%). However, this was not confirmed by reference or molecular methods.



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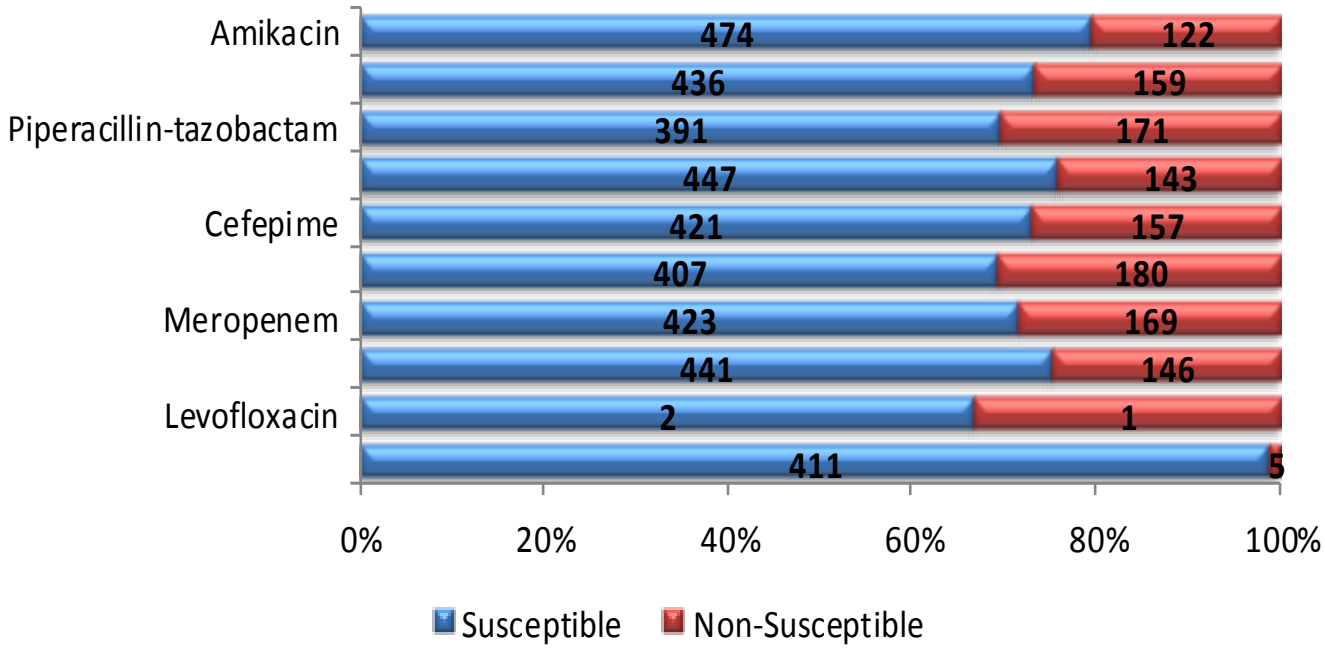
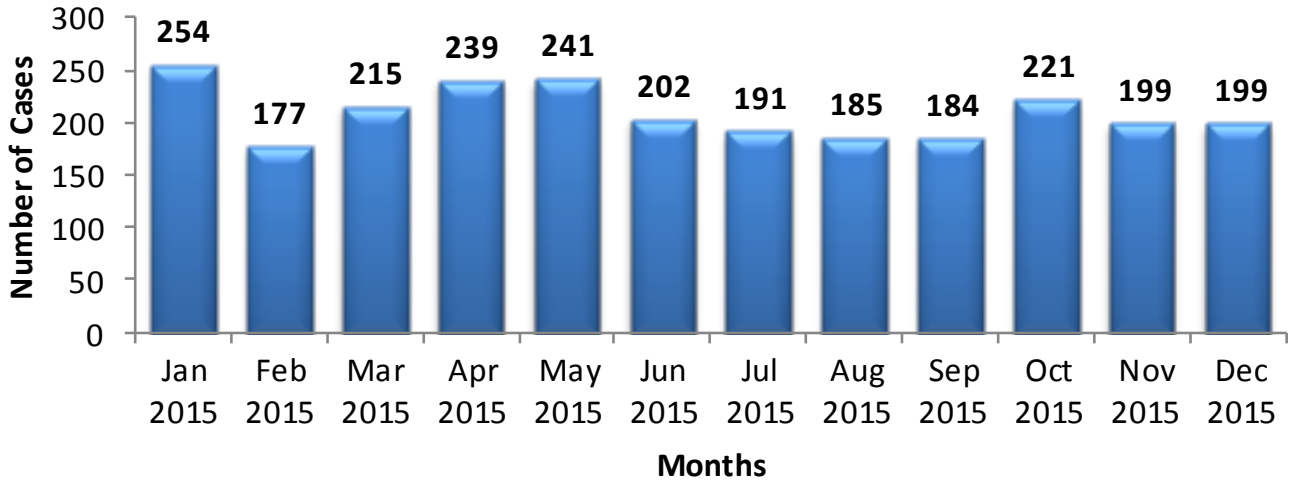


B

Figure 7: A. *Pseudomonas aeruginosa* cases by month, and B. Numbers and percentages of susceptible and resistant *P. aeruginosa* isolates from blood cultures at public-sector sentinel sites, 2015. Total number of isolates analyzed **=** 670.

Staphylococcus aureus

No *S. aureus* isolates were reported to be vancomycin resistant in 2015. Resistance to methicillin/oxacillin and all other β-lactams showed a minor increase compared to 2014. Cefoxitin resistance was indicative of methicillin resistance (MRSA). Resistance rates to erythromycin and clindamycin remained unchanged.



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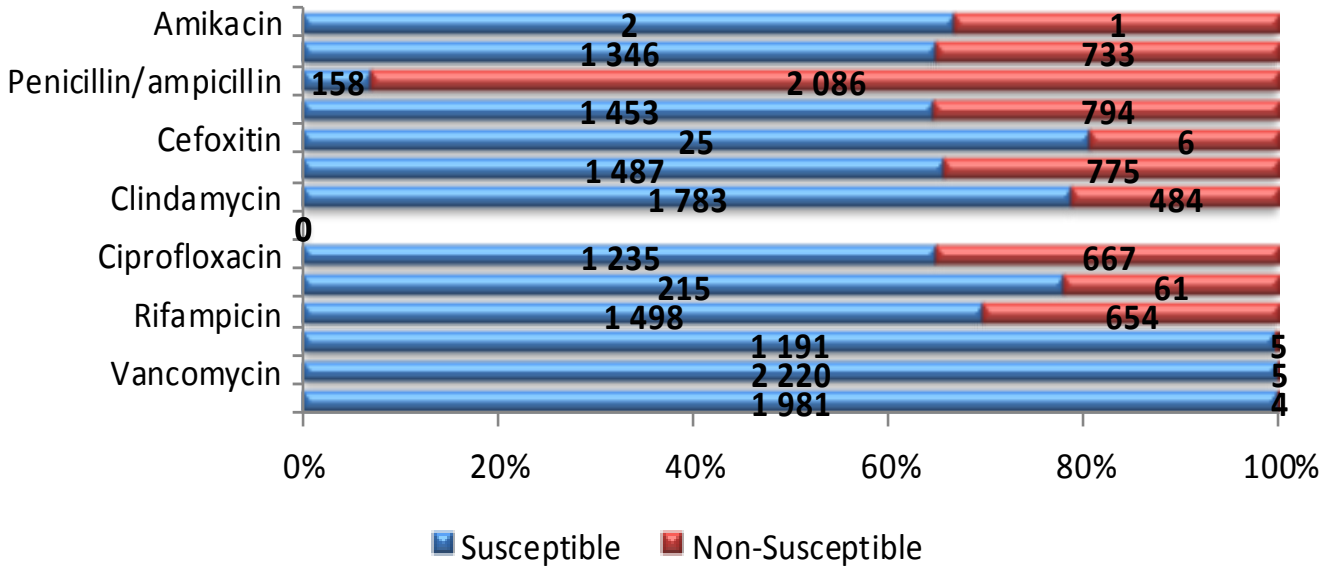

B

Figure 8: A. *Staphylococcus aureus* cases by month, and B. Numbers and percentages of susceptible and resistant *S. aureus* isolates from blood cultures at public-sector sentinel sites, 2015. Total number of isolates analyzed = 2507.

Carbapenemase-producing Enterobacteriaceae (CPE)

The Antimicrobial Resistance Laboratory confirmed the presence of carbapenemase genes in Enterobacteriaceae isolates that were referred from public laboratories following phenotypic confirmation of carbapenem resistance (Table 2). Few organisms presented with more than one CPE gene.

Table 2: Numbers of confirmed carbapenemase-producing *Enterobactericeae* by species and genoptype

Carbapenemases producing Enterobacteriaceae	**No. of isolates**
Species	
Citrobacter freundii	19
Enterobacter aerogenes	8
Enterobacter asburiae	3
Enterobacter cloacae	114
Enterobacter kobei	2
Enterobacter spp.	2
Escherichia coli	64
Klebsiella oxytoca	20
Klebsiella pneumoniae	552
Klebsiella spp.	3
Morganella morganii	10
Proteus mirabilis	2
Proteus spp.	1
Providencia rettgeri	23
Providencia vermicola	1
Raoutella ornithinolytica	1
Serratia marcescens	55
Genotype	
OXA-48$_{like}$	234
VIM	55
NDM	438
GES	12
KPC	11
IMP	8

Discussion and conclusion

Certain limitations are inherent in the data presented. Data may be incomplete due to missing cases not captured on the LIS or non-standardised coding of pathogens and antibiotics. Testing methods and microbiological practice vary between sites and this could account for variation in the results presented. Confirmatory antimicrobial susceptibility test (AST) methods were not performed for any of these organisms and results presented here are reported as captured on the LIS. Thus, while some results may suggest the occurrence of an outbreak, it is not possible to confirm this. For certain sites, not all organisms are represented. This may be due to organisms not being identified at a particular site for 2015.

Surveillance for CPEs is currently being conducted at 14 national sites. Due to the limitations mentioned above

there is a continuous need for improvement in the quality of data obtained by electronic surveillance. The data presented in this report nevertheless highlight the importance of surveillance for antimicrobial resistance patterns.

Disclaimer

Data are reported as received through the CDW. No demographic, epidemiological, clinical or molecular data were available to distinguish between hospital-associated and community-acquired infections.

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