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REVIEW ARTICLE

Antimicrobial Resistance Surveillance among Nosocomial Pathogens in South Africa: Systematic Review of Published Literature

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There has been a significant increase in the prevalence of antimicrobial drug resistance in sub-Saharan Africa. This may increase health-care costs due to patients' needs for more diagnostic tests, longer hospitalization, and poor outcome. Therefore, monitoring systems for resistance patterns are needed to effectively minimize poor outcome. A systematic review was conducted to find out the prevalence of antimicrobial drugs' resistance among *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, and to understand whether or not such data were part of an ongoing surveillance system for nosocomial infections in South Africa. An online search of main databases, including Cochrane Library, PUBMED, and MEDLINE, was done using the following search terms: "antimicrobial resistance" and "surveillance"; "antimicrobial susceptibility" and "surveillance"; *Staphylococcus aureus* or *Klebsiella pneumoniae* or *Pseudomonas aeruginosa*; "nosocomial" or "hospital acquired"; or South Africa or Africa. We also performed manual search of local conferences, theses, and dissertations to identify relevant articles. In total, 41 manuscripts were identified of which eight were analyzed. There is no evidence of any ongoing antimicrobial resistance surveillance for nosocomial pathogens in South Africa. Data reported in this review seem to have been analyzed on an ad hoc basis and do not show a particular resistance pattern; however, data show evidence of resistance to commonly used antimicrobial drugs in this population: for *S aureus*, resistance to cloxacillin was 29% and to erythromycin 38%; for *K pneumoniae*, resistance to ciprofloxacillin was 35% and to ampicillin 99%; and for *P aeruginosa*, the mean resistance to ciprofloxacillin was 43% and to amikacin 35%. Surveillance of antimicrobial resistance is essential to better understand the complexity of antimicrobial resistance development. Such evidence would be used in developing an effective surveillance program to monitor patterns and trends of resistance over time.

1. Introduction

Antimicrobials are essential for the treatment of infectious diseases. However, a high prevalence of resistance impacts patient outcomes negatively. Antimicrobial resistance increases health-care costs due to a need for more diagnostic tests, additional drugs for treatment, and longer duration of hospitalization.[1,2] Therefore, the emergence and spread of antimicrobial-resistant organisms from hospital to the community is a growing public health challenge in South Africa and worldwide. It is associated with a high level of morbidity and mortality, and for this reason, antimicrobial resistance requires effective monitoring to determine patterns and trends over time.[3–6] For South Africa, such information is particularly important because of the HIV/AIDS epidemic and increased antimicrobial consumption due to frequent episodes of opportunistic infections.

Antimicrobial resistance surveillance is crucial for evaluating the use of empirical antimicrobials for treatment.[7] Continuous monitoring, and a better understanding of the profile and magnitude of antimicrobial resistance are therefore required. This will help address the problem of increasing rates of antimicrobial resistance in South Africa. The European Antimicrobial Resistance Surveillance System (EARSS) is an electronic laboratory information system that has been used as a tool for identifying emerging antimicrobial resistance.[8] In South Africa, an equivalent national surveillance system to monitor the status of antimicrobial resistance for nosocomial pathogens has not yet been established. For this reason and as an interim exercise, this review was initiated to gather scientific evidence of the extent and patterns of

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antimicrobial resistance in selected hospital-acquired pathogens in South Africa.

2. Methodology

2.1. Online search strategy

A comprehensive search of biomedical databases was carried out to find all relevant manuscripts published in English. The search aimed at identifying relevant peer-reviewed epidemiological studies that would provide adequate information on antimicrobial surveillance initiatives in South Africa.

2.2. Search engines, dates of publications, and search words used

The following search terms were using: "antimicrobial resistance" and "surveillance"; "antimicrobial susceptibility" and either "surveillance" or "*Staphylococcus aureus*" or "*Klebsiella pneumoniae*" or "*Pseudomonas aeruginosa*"; "nosocomial" or "hospital acquired"; or "South Africa" or "Africa." We focused on searching pathogen-specific literature and data for this review using manuscripts identified through such an extensive search of the following databases: Cochrane Library (July 2011); MEDLINE (1966 to July 2011); *African Journals Online* (AJOL) (1980 to July 2011), EMBASE (1980 to July 2011); and LILACS (1982 to July 2011) on www.bireme.br.

2.3. Manual search strategy

We also carried out a manual search and review of the reference lists of the identified articles. Additionally, as findings of studies are not always published conventionally, we manually searched the abstracts and proceedings within the past 10 years for the following conferences: "OIE International Conference on Antimicrobial Resistance," "Conference on Antibiotic Resistance Prevention and Control" (ARPAC), "Public Health Association of Southern Africa" (PHASA), "Federation of Infectious Diseases Society of South Africa" (FIDSSA), "Global Antimicrobial Resistance Program" (GARP), "Congress of the European Society of Clinical Microbiology and Infectious Diseases" (ESCMID), and the "Congress of the International Society for Infectious Diseases." Such conference proceedings outline major group sessions for microbiology and infectious disease specialists working within the field of antimicrobial resistance. We did not obtain any relevant data from these searches. In addition, informal approaches were made to individuals and organizations within the field of hospital infection control and antimicrobial resistance surveillance for information regarding unpublished data, dissertations, and theses.

This search yielded four of the eight papers that were included for analysis. Data for rates of antimicrobial resistances were presented as means.

3. Results

3.1. Antimicrobial resistance surveillance for invasive pathogens in South Africa

A good surveillance system for antimicrobial resistance monitoring should involve ongoing collection and collation of both clinical and microbiological data, with an emphasis on timeliness, accuracy, consistent and standardized methods of collection, and analysis, using a centralized laboratory with appropriate control measures, with a focus on reporting on nosocomial pathogens. Such a system has not been present in South Africa. However, although different methods were used, they were all approved by the National Committee for Clinical Laboratory Standards (NCCLS), predecessor of the Clinical Laboratory Standards Institute (CLSI), and therefore suitable for trend analysis e.g. ciprofloxacin resistance in *K. pneumoniae* increased in academic hospitals from 18% (24/1324 isolates) in 1999 to 28% (498/1778) in 2007.

From the included studies, lack of clinical data and quality assurance information are deficiencies requiring attention; nonetheless, some steps have been taken to contain resistance development. Prudent use of antimicrobials (antimicrobial stewardship) has been looked at through the South African Society of Clinical Microbiology, formerly the National Antimicrobial Surveillance Forum (NASF), using passively collating antimicrobial data in public through the National Health Laboratory Services (NHLS) and in private health-care sectors through private microbiology laboratories.

The Antibiotic Study Group of South Africa has been active since 1976[9]; this group joined private sector surveillance in 2002 as NASF, meeting and sharing information, and several publications in the area of antimicrobial resistance have been released.[9–12] More recently, the Group for Enteric, Respiratory and Meningeal Diseases Surveillance (GERMS-SA), an established entity within the National Institutes for Communicable Diseases (NICD), has been established, which operates in all nine provinces, focusing on surveillance of community-acquired pathogens and monitoring resistance profiles. As of 2010, a surveillance to monitor resistance among *S aureus and K pneumoniae* was established as part of GERMS-SA. Another initiative was introduced in KwaZulu Natal for surveillance of *Escherichia coli* in 2000/2001,[13] and the Veterinary Surveillance of Antimicrobial Resistance in South Africa has been involved in monitoring resistance among zoonotic infections.[14] Table 1 illustrates hospitals and laboratories that contributed antimicrobial susceptibility data for the studies that were included in this review.

3.2. Description of study settings and study designs[12,15–22]

A total of 41 manuscripts were identified: 26 identified through database searches and 14 through manual searches in libraries and among personal contacts. Twenty-four manuscripts were excluded, leaving 18 that had full-text article reviews to further assess for eligibility, and 10 more were further excluded. Eight manuscripts published between 2000 and 2011 were identified and included in this review (Figure 1). Of the eight manuscripts, five were published prior to 2007. All manuscripts identified for this review included

Table 1 Public and private sector laboratories that participated in antimicrobial susceptibility data over the period 2000–2011

Public sector hospitals/ NHLS laboratory*	Private sector laboratories†
Chris Hani Baragwanath Hospital	Drs Bouwer & Partners (Ampath)
Charlotte Maxeke Johannesburg Academic Hospital	Drs Dietrich & Voigt (Pathcare)
Steve Biko Academic Hospital	Drs du Buisson, Bruinette & Partners (Ampath)
Dr George Mukhari Hospital	Drs Mauf & Partners (Lancet)
Pelonomi & Universitas Hospital	Drs Swart & Marais (Ampath)
Groote Schuur Hospital	Drs van Rensburg Pathologists
Tygerberg Hospital	Drs Vermaak & Partners
Green Point NHLS Laboratory	Niehaus & Botha
King Edward VIII	
No. 1 Military Hospital	

NHLS = National Health Laboratory Service.

* NHLS from Gauteng province (Johannesburg, Pretoria), Free State province (Bloemfontein), and KwaZulu Natal province (Durban and Western Cape province (Cape Town); † Private laboratories in Gauteng province (Johannesburg, Pretoria), KwaZulu Natal province (Durban), Western Cape province (Cape Town), and Free State province (Bloemfontein).

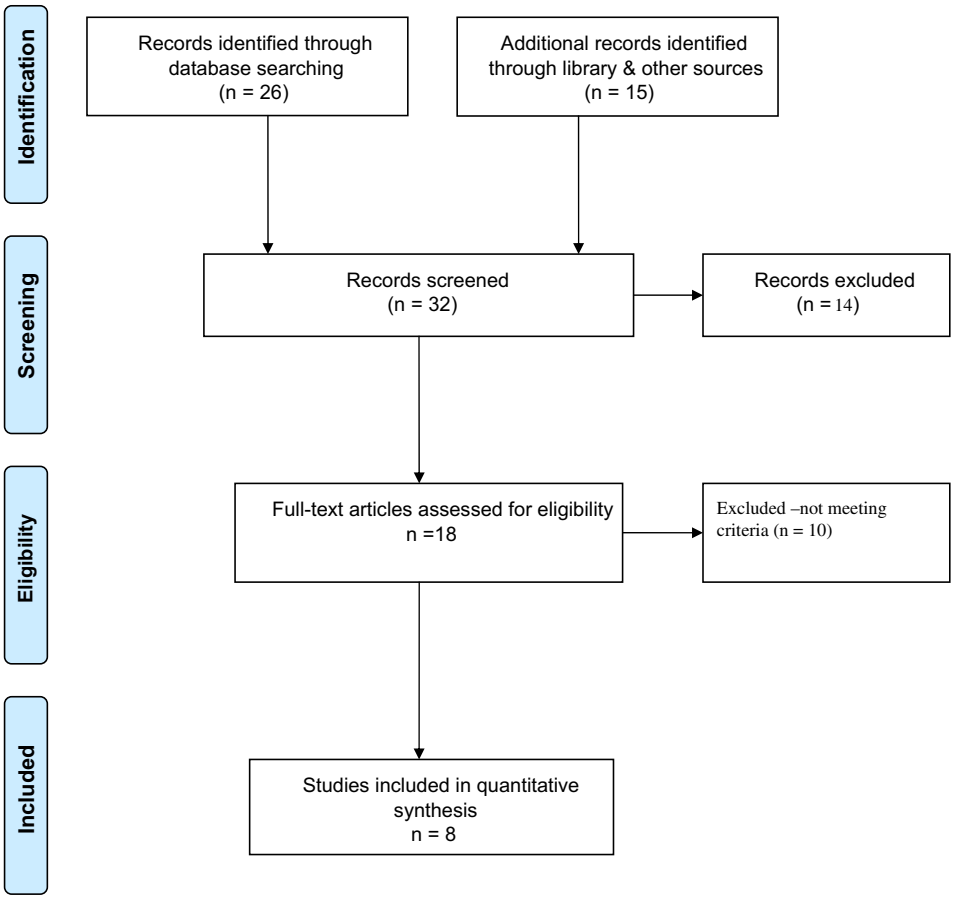

Figure 1 Flow diagram of antimicrobial resistance studies included in the review. *Note.* From PRISMA: www.prisma-statement.org.

susceptibility data from only four of the nine provinces of South Africa. Five of these studies were from public sector tertiary hospitals and three were from private sector laboratories, predominantly from urban settings across South Africa (Table 2).

Seven of these studies produced results from surveillance data aggregated from more than seven sites nationwide, while one study produced results from surveillance data from 16 hospitals within KwaZulu Natal province. None of the eight studies detailed the study design used, other than stating that the study was "multi-site and used data of blood culture isolates from microbiology laboratories." Only one study used isolates from respiratory aspirates[20]; all except one study from various public sector hospitals within KwaZulu Natal province used retrospective laboratory data[21] (Table 2).

3.3. Description of microbiological methods[12,16–19,22]

Seven of the studies used data from blood and cerebral spinal fluid (CSF) cultures[12,16–19]; one study used data from respiratory aspirates.[22] The methodologies of antibiotic susceptibility testing

Table 2 Characteristics of antimicrobial resistance studies in South Africa

Author	Year	Pathogen	Location	Sample type	Source of information	Study design
Bamford et al[16]	2009	SA, KP, PA & others	8 NHLS labs	Blood & CSF	NHLS surveillance data	Not specified
National Antimicrobial Surveillance Forum[22]	2008	SA, KP, EC & others	Private labs, no. of labs involved not mentioned	Blood & urine	Private labs data	Not specified
Brink et al[17]	2007	SA, KP,PA & others	7 private laboratories	Blood	Private labs data	Not specified
Sein et al[19]	2005	SA, KP, EC & others	7 NHLS labs	Blood & CSF	NHLS surveillance data	Retrospective approach
Essack et al[21]	2005	SA, KP, PA & others	Laboratories in 16 hospitals	Blood	Public sector surveillance data	Multicenter study in SA
Liebowitz et al[20]	2003	KP & others	12 private labs	Sputum, bronchial brush, BAL, pleural fluid, sinus tap, MEF, pharyngeal swabs	Private labs data	Multicenter study in SA
Crewe-Brown et al[18]	2001	SA, KP, EC & others	8 NHLS labs	Blood & CSF	Public sector surveillance data	Not specified
Antibiotic Study Group of South Africa[12]	2000	SA, KP & others	8 NHLS labs	Blood & CSF	Public sector surveillance data	Not specified

BAL = bronchial alveolar lavage; CSF = cerebral spinal fluid; EC = *E coli*; HI = *Haemophilus influenzae*; KP = *K pneumoniae*; MEF = middle ear fluid; NHLS = National Health Laboratory Service; PA = *P aeruginosa*; SA (pathogen) = *S aureus*; SA = South Africa; SP = *Streptococcal pneumonia.*

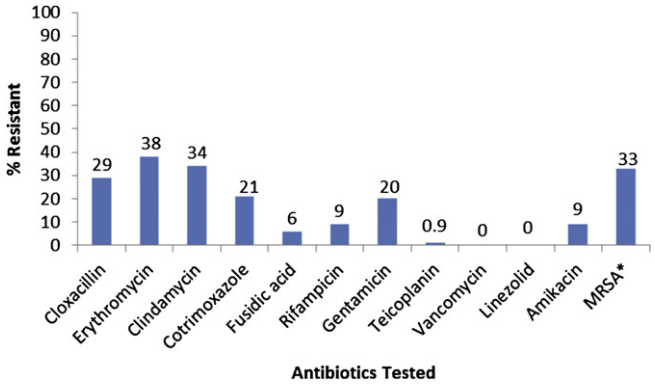

Figure 2 Prevalence of antimicrobial resistance among *S aureus*. *Note*. From seven published studies between 2000 and 2009. *Different methods used to determine MRSA status (Cloxacillin resistance of 29% vs 33% MRSA).

were described in seven studies, all of which mentioned the use of the CLSI breakpoints, formerly NCCLS, to determine antimicrobial susceptibilities. Two studies described in detail other methods used for susceptibility testing of various antibiotics such as Kirby–Bauer disk diffusion, Broth microdilution, E-test, and use of automated Vitek 2 system.[17,20] Only one study mentioned quality control in identification and susceptibility testing as per CLSI recommendations.[17] All studies used only one sample per patient; hence, duplicate samples were excluded to minimize over-representation of the cases that had multiple and frequent cultures. Two studies that reported antimicrobial susceptibility of respiratory tract pathogens mentioned intermediate- and high-level resistance for such organisms.[18,20]

3.4. Resistance rates for different pathogens

3.4.1. Staphylococcus aureus[12,16–19,21,22]

Susceptibility data for *S aureus* were reported in seven studies (Table 2). Five of these studies were from public sector laboratories and two from private sector laboratories.[12,16,18,19,22] Geographically all studies identified were performed in urban areas except one study done in Durban, which included isolates from district and regional hospitals. Specimen types included blood and CSF, except one study that included respiratory aspirates (Table 2). The resistance rate of *S aureus* to cloxacillin was 29%, erythromycin 38%, and gentamicin 20%, and methicillin resistance (MRSA) was 33%. No resistance has been reported to linezolid since its introduction in 2000, while frequency of resistance to glycopeptides is uncertain due to disagreement on optimization of vancomycin susceptibility testing (Figure 2).

3.4.2. Klebsiella pneumoniae[12,16–22]

Most studies that reported on susceptibility patterns for *K pneumoniae* were published by the Antibiotic Study Group that used data mostly from large public sector academic hospitals that provide services to a diverse population group. Clinical isolates were predominantly from blood and CSF culture (four studies), blood culture only (one study), blood and urine culture (one study), and respiratory aspirates (one study). The resistance of *K pneumoniae* to ciprofloxacillin was 35%, cefuroxime 52%, gentamicin 50%, and ampicillin 99%. Resistance was almost nonexistent for imipenem, meropenem, and moxifloxacin (Figure 3).

3.4.3. Pseudomonas aeruginosa[16,17,21]

Three studies reported resistance rates for *P aeruginosa*, two of which were from blood culture isolates and one from nonspecific sources.[16,17,21] The resistance among *P aeruginosa* to ciprofloxacillin was 43%, gentamicin 50%, amikacin 35%, and aztreonam 42%. Resistance to polymyxin was <5% and was reported in a single study.[16,17,21] Resistance rates to almost all drugs tested were greater than 30% (Figure 4). A study conducted by Perovic et al using data from 1998 to 1999 at Chris Hani – Baragwanath Hospital showed that there was an association between *P aeruginosa* bacteremia and outbreaks caused by multiple-resistant genotypes. In this study, the proportion of nosocomially acquired infection was 57.1%.[24] The resistance profiles and incidence of disease are likely to have changed during the 10-year period, and the current status may be different but is unknown. This review shows high resistance rates of *P aeruginosa* to most conventional antibiotics.

3.5. Presence of extended-spectrum beta-lactamases

Seven studies reported on extended-spectrum beta-lactamases (ESBLs) in *K pneumoniae*. In academic hospitals the rates of ESBLs increased from 33% (436/1324) in 1999 to 49% (869/1778) in 2007. These studies used the double-disk method and reported resistance rates as high as 59% and 62% in private hospitals and public sector hospitals, respectively. A study conducted by Essack Sabiha at

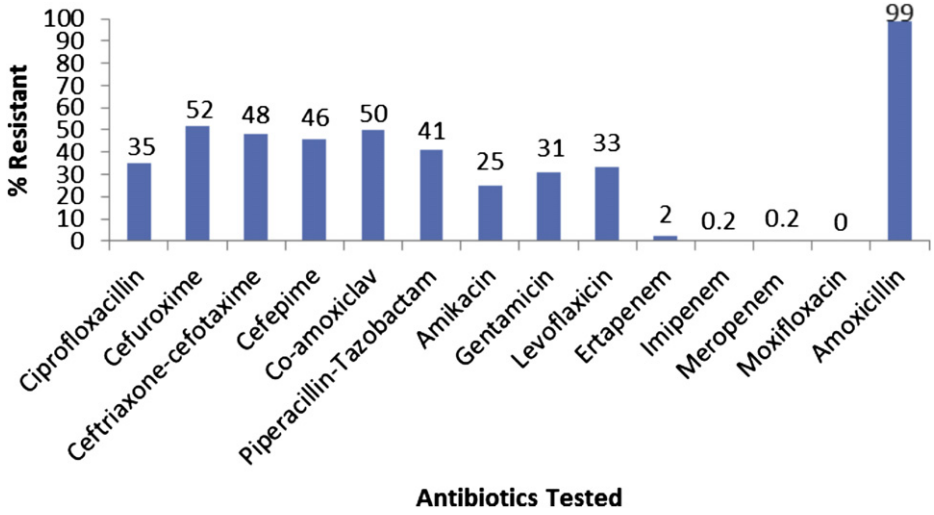

Figure 3 Prevalence of antimicrobial resistance among *K pneumoniae*. *Note*. From eight published studies from 2000 to 2009.

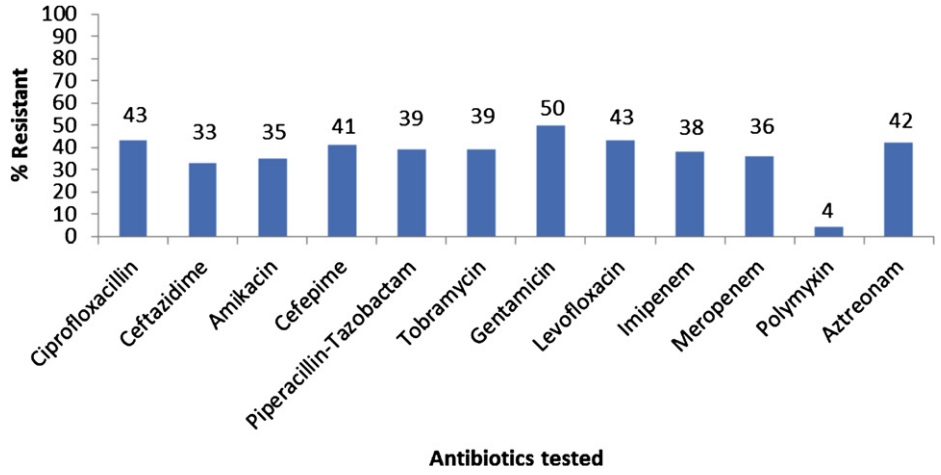

Figure 4 Prevalence of antimicrobial resistance among *P aeruginosa*. *Note*. From three published studies from 2005 to 2009.

a teaching hospital in Durban between 1994 and 1996 investigated ESBL-mediated resistance in South African nosocomial origin of *K pneumoniae* and demonstrated that each of the isolates expressed 1–6 beta-lactamases.[23]

4. Discussion

This systematic review assessed the prevalence of resistance to commonly used antimicrobials as well as whether or not such data were part of an ongoing surveillance system for nosocomial infections in South Africa. We found that no national surveillance system exists that collates and collects data year on year to assess trends and resistance patterns for nosocomial pathogens. In addition, we found that the overall prevalence of resistance to antimicrobials used for empirical treatment is high. Except for polymyxin, with a resistance rate of <5%, most other antibiotics showed high prevalence of *P aeruginosa* resistance to commonly available antimicrobials. The study found a low level of resistance among *K pneumoniae* to moxifloxacin and carbapenems, and a high pattern of resistance to other classes of antimicrobials that are commonly prescribed. *S aureus* showed no resistance to teicoplanin, vancomycin, and linezolid, but high resistance to other classes of antimicrobials. This is similar to the resistance pattern in Central African countries, as shown in a review by Vlieghe et al,[25] even though their study focused mostly on community-acquired pathogens.

Several limitations have been observed in this study: Firstly, studies included in this review reported laboratory data on antimicrobial-resistant isolates, with no clinical data; hence, they could not link resistant isolates to clinical findings. Secondly, most studies aggregated data from different laboratories which employed varied laboratory techniques. This was not ideal for surveillance purposes but all methods were NCCLS/CLSI approved. Thirdly, data used were collected retrospectively, except for a single study by Brink et al that collected data prospectively.[17] Use of retrospective data has several limitations, including incomplete data that are subject to numerous biases. Fourthly, most, if not all, studies lacked demographic data; hence, it was difficult to compare community-acquired versus hospital-acquired infections. Lastly, variation in clinical specimens, taking practices between different institutions, might alter representativeness of data reported from these various studies. Furthermore, this study included invasive pathogens from blood cultures as well as pathogens from respiratory specimens and, in the case of *P. aeruginosa*, also from other sources, including burns."

In spite of the limitations mentioned above, there is growing evidence of escalating rates of antimicrobial resistance to several conventional antimicrobials. Even though vancomycin resistance is still negligible, ESBL and MRSA rates are high in these urban academic centers and private institutions. This emphasizes the fact that surveillance is essential to further our understanding of antimicrobial resistance development and how it relates to prescription practice.[23,25] Such undertaking will pave the way for designing interventions that could overcome resistance development to established antimicrobial agents.

5. Conclusions

Evidence indicates that antimicrobial resistance rate to nosocomial pathogens are generally high in South Africa. This is an emerging threat to public health and clinical management of patients with such infections in the face of dwindling antimicrobial development. We believe that a good surveillance system would enhance effective monitoring of emerging resistance and changes in resistance profiles, and identify significant differences in trends and distribution of antimicrobial resistance.

Authors' contributions

PN searched the relevant papers and drafted the manuscript. JM proposed the topic for this review and helped draft the manuscript. OP and HK participated in critically reviewing the manuscript on intellectual content and scholarly writing. All authors read and approved the final manuscript.

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