Antimicrobial susceptibility surveillance of bloodstream pathogens

The South African Society of Clinical Microbiology (SASCM) is responsible for the oversight of antimicrobial surveillance activities and it is incumbent upon the society to educate and raise awareness around antimicrobial susceptibility testing issues that have implications for treatment and surveillance data. SASCM's role in providing oversight and guidance on interpretation of antimicrobial susceptibility data remains critical against a backdrop of increasing complexity in this field.

SASCM proposes to expand on the surveillance data that NICD collates and to direct a parallel channel of information using the FIDSSA infrastructure. SASCM aims to raise awareness around antimicrobial susceptibility testing (AST), the challenges around AST and how these impact on surveillance, antimicrobial stewardship (AMS) and antimicrobial resistance (AMR). The existing surveillance data will be used to present more focused perspectives on the data to achieve this aim.

This is the first instalment of updates to follow, and the primary focus of the update series will be on the ESKAPE pathogens. Both private and public sector data will be utilized however, given that the NICD dashboard provides more granular detail for the public sector (sentinel sites and facility level data available) the 2019 private sector data will be elaborated on and highlighted. The specific issues raised around AST do pertain to both sectors and remain relevant at a national level.

Antimicrobial susceptibility surveillance data for *Klebsiella pneumoniae* bloodstream isolates from the South African private sector: 2019

SASCM surveillance data methodology

Source of data: Aggregated data from the laboratory information systems of 4 accredited private laboratories in South Africa [Ampath, Lancet, PathCare & PathCare/Vermaak].

Specimen type: Blood cultures, deduplicated by unique identifier, isolates separated by minimum interval of 3 weeks.

Antimicrobial susceptibility reporting: Two different antimicrobial susceptibility guidelines are currently in utilization. These are the Clinical Laboratory Standards Institute [CLSI] and the European Committee on Antimicrobial Susceptibility Testing [EUCAST]. Clinical breakpoints differ for certain drug-bug combinations and hence categorical, clinical breakpoint data [e.g., susceptible (S) or resistant (R)] is used in the analysis].
Reporting is not standardized between all laboratories and therefore antibiogram profiles and reporting interpretations may differ. This accounts for differences in number of isolates tested against certain antimicrobials and totals may not always add up to the cumulative number of isolates.

Data is presented as percentage susceptible (%S). Numbers of isolates are provided where possible.

Regional (provincial) data is provided based on the data submitted by individual laboratories which either reflects a specific region or hospital. The designation is thus based on site of submission and not necessarily site of acquisition.

Where relevant interpretation of the "I" category is elaborated on and included in the susceptibility analysis.

Klebsiella pneumoniae

The total number of isolates for 2019 was 4852 with a breakdown per province as follows:

Gauteng	2065
WC	879
EC	306
Mpumalanga	107
KZN	409
Free State	252
Limpopo	117
North West	284
NC	51

The susceptibilities to indicator agents that define the important phenotypes of *K. pneumoniae* are represented in figures 1 and 2. Extended-spectrum β-lactamase producers (ESBLs) are defined by resistance to the 3rd generation cephalosporins ceftriaxone and/or cefotaxime.

Carbapenem resistant isolates (CRE) are defined by resistance to ertapenem, irrespective of susceptibility to any of the other carbapenems.
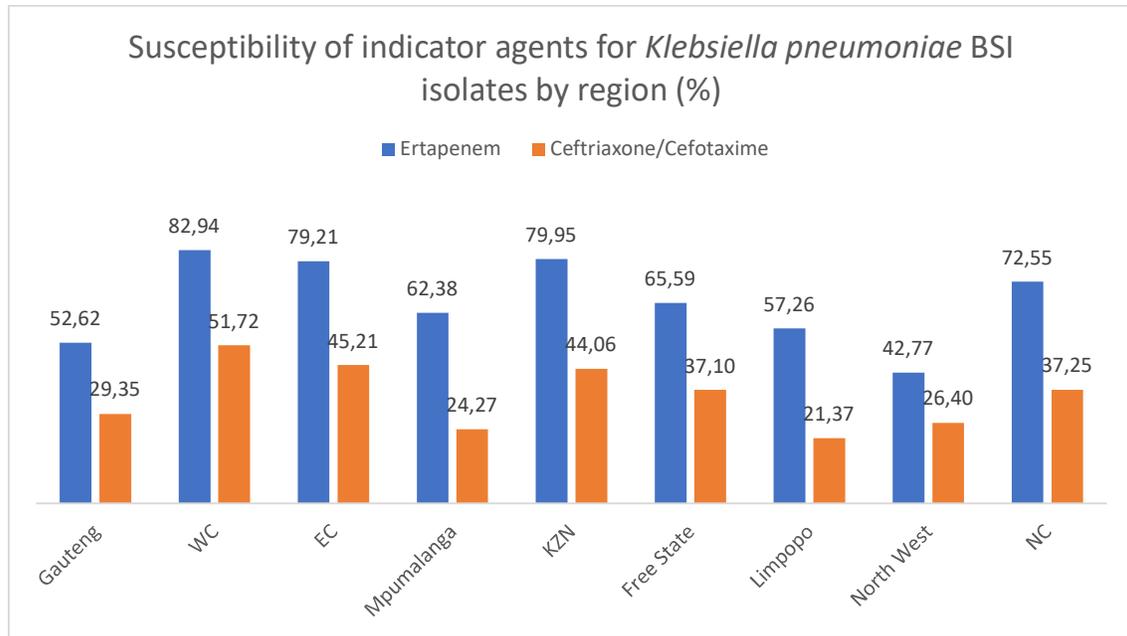
Figure 1. Susceptibility of *K. pneumoniae* to ceftriaxone/cefotaxime and ertapenem for year 2019

WC – Western Cape; EC – Eastern Cape; KZN – Kwazulu Natal; NC – Northern Cape; BSI – bloodstream isolates

A total of 3957 isolates had susceptibility to the 3rd generation cephalosporins ceftriaxone/cefotaxime reported, with an overall susceptibility of 35.15% (range: 21.37 to 51.72%)

A total of 3922 isolates had susceptibility to ertapenem reported, with an overall susceptibility of 61.3% (range: 42.77 to 82.94%)
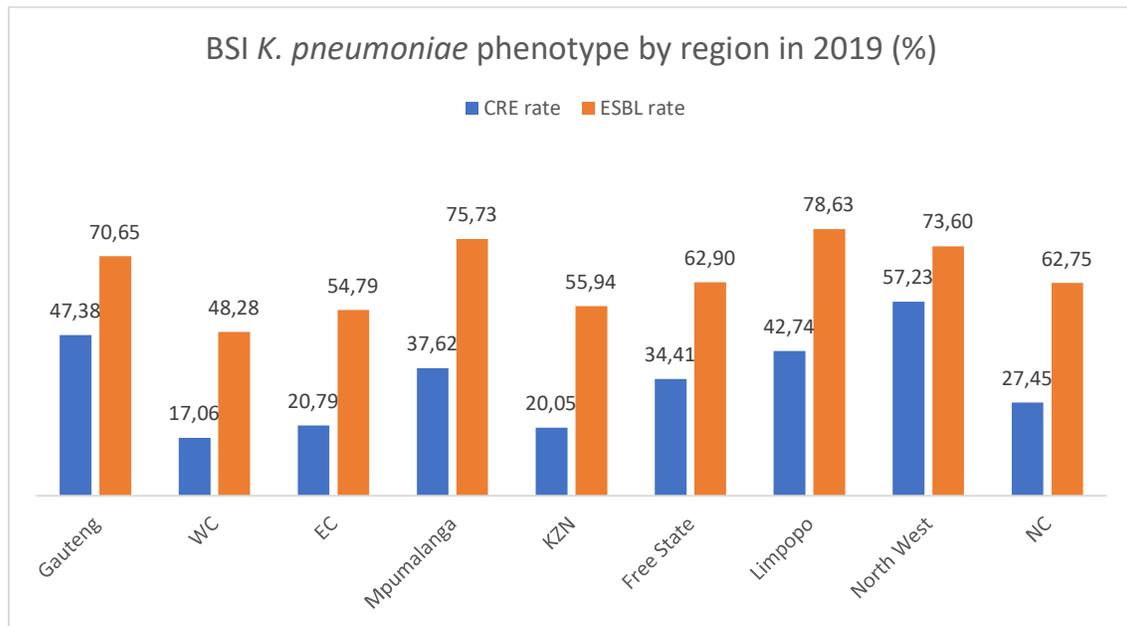

Figure 2. *K. pneumoniae* resistance phenotypes for year 2019

WC – Western Cape; EC – Eastern Cape; KZN – Kwazulu Natal; NC – Northern Cape; BSI – bloodstream isolates

This corresponds to an overall ESBL rate of 64.85% and a CRE rate of 38.7%.
In comparison to 2018 data (N = 3829) the ESBL and CRE rate were 63% and 30%, respectively.
The public sector national data for 2019 reflects an overall ESBL rate of 73% and a CRE rate of 17%, with corresponding 2018 rates of 76% and 10%.

Since 2017, with the introduction of the EUCAST guidelines by some laboratories, it is important to be aware of and to understand the implications of different guidelines on surveillance data. There are differences in interpretation and reporting and these will have an impact on submitted surveillance data that is aggregated. Figure 3 below provides an important example, where there are different breakpoints for the carbapenems meropenem, imipenem and doripenem. The susceptible breakpoint for ertapenem (≤0.5μg/ml) is the same for CLSI and EUCAST and thus remains the best option for defining the CRE phenotype. However, for meropenem the CLSI susceptible breakpoint is ≤1μg/ml and the EUCAST susceptible breakpoint is ≤2μg/ml, a one-fold dilution difference. Considering that the most predominant carbapenemases in South Africa are the OXA-48$_{like}$ carbapenemases, where the carbapenem MICs are elevated but often still within the range of 2 – 8μg/ml, this difference is important. Furthermore, EUCAST defines the "I" category as **"Susceptible, Increased exposure"**. This definition means that meropenem can still be used with high likelihood of successful outcome provided that a higher dosage is used.
This is in contrast to the CLSI definition of "I", which means **"Intermediate"** and is defined as follows: "A microorganism is defined as intermediate by a level of antimicrobial agent activity associated with **uncertain therapeutic effect**. It implies that an infection due to the isolate may be appropriately treated in body sites **where the drugs are physiologically concentrated** or when a **high dosage of drug can be used**; it also indicates a **buffer zone that should prevent small, uncontrolled, technical factors** from causing major discrepancies in interpretations". So there is some similarity in the two definitions but the additional components in the CLSI definition often prohibit its widespread use in terms of the clinical interpretation.

Figure 3 highlights the differences in susceptibility according to different laboratories reporting guidelines and illustrates the potential "susceptibility" gain when interpreting the "I" category as susceptible. Only one laboratory was utilizing EUCAST for the full 2019 period, with 2 others only using CLSI, and the 4th switching to EUCAST midway through 2019. Considering the dramatic rise in the CRE rate and that carbapenems still remain very useful in treatment of these isolates a 10% gain in susceptibility is clinically relevant.
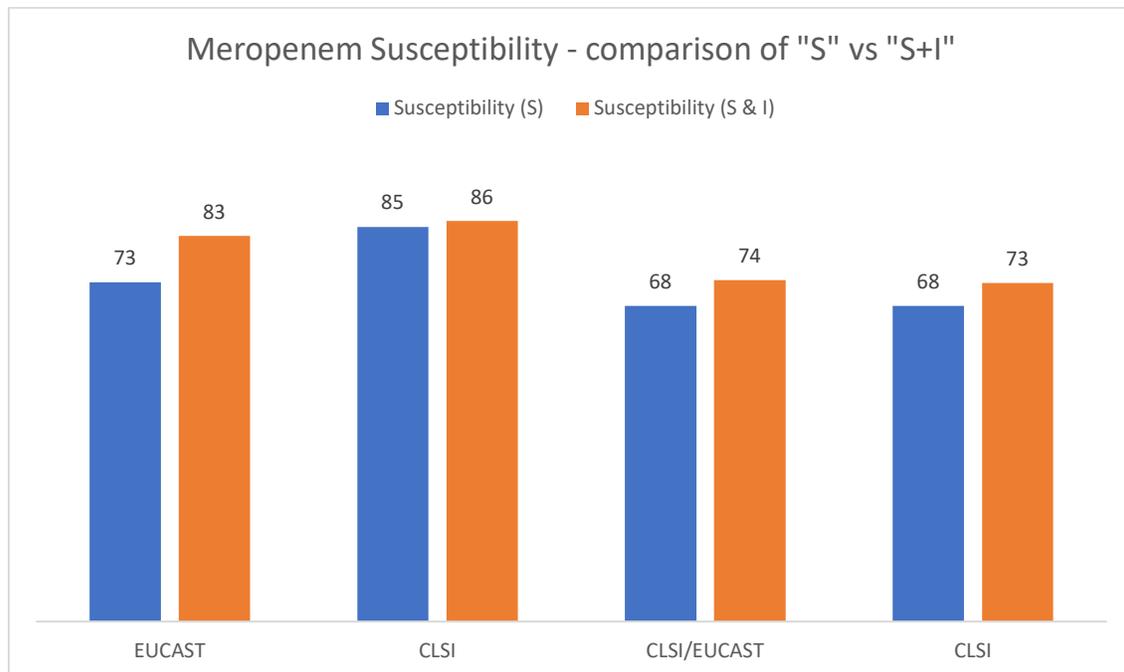
Figure 3. Susceptibility of *K. pneumoniae* to meropenem according to different laboratories antimicrobial susceptibility reporting guidelines.

The dynamic and evolving nature of AST and reporting guidelines has significant implications for treatment and surveillance data, especially with respect to the interpretation of that data. For example, considering overall antimicrobial susceptibility it may be important to report susceptibility with inclusion of the "I" category considering the implied susceptibility within the definitions. To date presented surveillance data has included the "I" category as part of the non-susceptible group.