Trend Analysis of Antibiotic Resistance in in KwaZulu Natal: A Retrospective Study 2011-2015

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# Trend Analysis of Antibiotic Resistance KwaZulu Natal: A Retrospective Study 2011-2015

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A dissertation submitted to the School of Health Sciences, College of Health Science, University of KwaZulu-Natal, Westville Campus, for the degree of Master of Pharmacy (Pharmacy Practice).

This is the dissertation in which the chapter is written as a research publication, with an overall introduction and final summary.

This is to certify that the content of this dissertation is the original research work of Ms Miriam Patel. As the candidate's supervisor, I have approved this thesis for submission.

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# LIST OF ABBREVIATIONS AND ACRONYMS

ABR	Antibiotic Resistance
AMR	Antimicrobial Resistance
AST	Antimicrobial Susceptibility Testing
BSI	Blood Stream Infection
CAESAR	Central Asian and Eastern European Surveillance of Antimicrobial Resistance
CDC	Centers for Disease Control
CLSI	Clinical Laboratory Standards Institute
CPE	Carbapenemase-Producing Enterobacteriaceae
CRE	Carbapenem Resistant Enterobacteriaceae
EARS-Net	European Antimicrobial Resistance Network
EARSS	European Antimicrobial Resistance Surveillance System
ECDC	European Centers for Disease Control
ESBL	Extended Spectrum β-Lactamase
ESKAPE	Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter
	baumanii, Pseudomonas aeruginosa, and Enterobacter spp.
EUCAST	European Committee on Antimicrobial Susceptibility Testing
GAP	Global Action Plan (on Antimicrobial Resistance)
GARP	Global Antibiotic Resistance Partnership
GASP	Gonococcal Antimicrobial Surveillance Programme
GERMS-SA	Group for Enteric Respiratory and Meningeal Disease Surveillance in South Africa
GLASS	Global Antimicrobial Surveillance System
HAI	Hospital Acquired Infection
HIV	Human Immunodeficiency Virus
ICU	Intensive Care Unit
MCC	Medicines Control Council
MDR	Multi-drug Resistant
MIC	Minimum Inhibitory Concentration

MRSA	Methicillin-resistant Staphylococcus aureus
MYSTIC	Meropenem Yearly Susceptibility Test Information Collection
NDoH	National Department of Health
NDP	National Drug Policy
NGO	Non-Governmental Organization
NICD	National Institute for Communicable Diseases
NTS	Non-typhoidal Salmonella
РАНО	Pan American Health Organization
SAB	Staphylococcus aureus Bacteremia
STG	Standard Treatment Guidelines
STI	Sexually Transmitted Infection
TB	Tuberculosis
TICU	Trauma Intensive Care Unit
UTI	Urinary Tract Infection
WHO	World Health Organization

#### ABSTRACT

**Objective:** Antimicrobial resistance is a global phenomenon which is limiting treatment options for common infections resulting in poor clinical outcomes, increased mortality and increased cost of healthcare. Antibiotic resistance trends in pathogen-drug combinations stipulated in the Global Antimicrobial Surveillance System (GLASS) of the World Health Organization were investigated for the period 2011-2015 in the province of KwaZulu Natal, South Africa.

**Methods:** Antibiotic susceptibility data from blood, urine, faecal and urethral/cervical samples was retrospectively analyzed from six public hospitals. Pathogens included *Escherichia coli*, *Streptococcus pneumoniae, Klebsiella pneumoniae, Salmonella spp., Acinetobacter baumannii, Staphylococcus aureus, Shigella spp. and N. gonorrhoea.* Results were analyzed as MIC50, MIC90, percentage resistance, incidence of monitored infections in the population and proportion of nonsusceptible infections per pathogen. Results were also evaluated against South African treatment guidelines. Significant differences in resistance proportions by year were identified using the Pearson  $\chi^2$  test. Comparison of MIC50 were analysed using the equality-of-medians test.

**Findings:** Urine samples were most abundant (61.22%, n= 33 018) and *E. coli* (52%) was the most common pathogen. Most isolates were multi-drug resistant. Resistance to third and fourth generation cephalosporins and fluoroquinolones increased in *K. pneumoniae*, *E. coli* and *Shigella spp*. over the 5-year period. Notable changes in resistance were: *K. pneumoniae* from blood samples to carbapenems (1 - 26%, p < 0.001) and *A. baumannii* to carbapenems (69% - 50%, p-value not available). Susceptibility to antibiotics recommended in treatment guidelines was >50% for most pathogen-drug combinations.

**Conclusion:** The results of this study show that antibiotic resistance in hospitals in KwaZulu-Natal generally increased from 2011 to 2015, although some pathogen-drug combinations showed a plateau or decline in resistance necessitating a review of the existing treatment guidelines. To our knowledge, this is the first South African report on ABR using GLASS metrics. There is a need for more extensive research in order to build an accurate, comparable picture of ABR in South Africa.

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#### **Chapter 1 Introduction and Literature Review**

### **1.1.Introduction**

The increase in the incidence and spread of infectious diseases has led to an increase in the use of antimicrobial drugs, in turn causing an increase in antimicrobial resistance (AMR) (Mendelson & Matsotso, 2015). The term AMR applies broadly to resistance in all microbial pathogens including bacteria, parasites, viruses and fungi while antibiotic resistance (ABR) refers specifically to resistance of bacterial pathogens to antibiotics (Shaban, *et al.*, 2013). While ABR is an anticipated result of antibiotic use, the spread of resistance is accelerated by preventable factors such as poor infection control, irrational antibiotic use and the use of substandard drugs (Hoffman, *et al.*, 2015) (World Health Organisation, 2015 (c))

ABR is a global concern affecting both developed and developing countries to varying extents. While efforts are being made to delineate the incidence, prevalence and mechanisms of ABR, there is a need for quality, standardised, comparable data to provide an accurate picture of global trends in ABR (World Health Organisation, 2015 (b)).

The impact of the increasing incidence of ABR is far reaching and if measures are not implemented now, the resulting financial burden and mortality due to ABR is projected to be gravely high. The World Health Organisation (WHO) has released various publications with suggested action plans in order to curb the increase in resistance and in developed regions research around ABR has already been established for some years (Hoffman, *et al.*, 2015).

ABR surveillance is vital in providing information to guide the development of strategies to curb the spread of ABR. Established surveillance programmes such as the Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) and the European Antimicrobial Resistance Surveillance Network (EARS-Net) have provided useful data but are limited in a global context due to differences in data collection methods, limited data-sharing and the tendency to focus on specific pathogens or regions (World Health Organisation, 2014 (a)). Limited resources in terms of funding, laboratory capacity and human resources are obstacles in obtaining useable surveillance data in developing countries (Vernet, *et al.*, 2014).

In May 2015 the Global Action Plan (GAP) on AMR was adopted by the World Health Assembly committing WHO member states to developing National Action Plans to combat AMR. A key component of the GAP is surveillance, specifically a uniform system of surveillance and reporting of ABR. Subsequently the Global Antimicrobial Surveillance System (GLASS) was developed, aimed specifically at ABR in specified bacterial pathogens and the WHO has called on member states to implement this programme. The key to the success of GLASS is in the cooperation of as many countries as possible to as large an extent as possible in order to gain baseline data from which further strategies can be developed. The GLASS manual for early implementation was published in 2015 and

outlines a comprehensive system which aims to provide comparable, validated data which can be shared on a global scale in order to guide future interventions against the spread of ABR World Health Organisation, 2015(b)).

In South Africa, AMR in pathogens other than tuberculosis (TB) and Human Immunodeficiency Virus (HIV) has increasingly gained attention. Treatable illnesses such as diarrhoeal infections and urinary tract infections (UTIs) are among the common conditions burdening our public health system (Mendelson & Matsotso, 2015). Budget constraints, especially in public sector healthcare facilities, limit the choice of antibiotics to those stipulated in the Standard Treatment Guidelines published by the national Department of Health. There is a concern that the susceptibility of pathogens to the empiric antibiotics listed in the STGs is limited, which raises concerns about exacerbating resistance, wastage of money on ineffective treatment and most importantly, treatment failure. The treatment strategies for common infections can be greatly enhanced if informed by current surveillance data. (Perovic, *et al.*, 2014) While surveillance studies have been conducted, mainly by academic institutions, the data available is not representative enough to guide national strategies.

# **1.2. Literature Review**

#### 1.2.1. Surveillance of Antimicrobial Resistance:

Public health surveillance can be defined as the collection and analysis of data in order to monitor and manage public health threats and concerns (World Health Organisation, 2017 (a)). The global surveillance report published in 2014 by the WHO, showed the burden of AMR in Member States to be extensive. The report also illustrated the lack of standardised methodology that limited the usefulness of existing surveillance data. Data from hospital based healthcare settings was shown to be more readily available than data from community based facilities and there was also a bias in existing data in that the samples submitted for sensitivity analyses come from patients who were severely ill and were thus more likely to be infected with resistant pathogens. The survey upon which the report was based included the bacterial infections that exhibit high levels of resistance and the corresponding antibiotics commonly used to treat such infections (World Health Organisation, 2014 (c)).

While existing surveillance programmes have contributed towards combatting ABR, it is spreading such that there is still a deficit in the information required in order to develop evidence-based strategies on a global scale.

Surveillance of ABR is needed to guide clinical interventions to provide an optimal level of care, while limiting the spread of resistance. Rapidly spreading resistance is limiting treatment options for common infectious diseases, as is the case with the emergence of strains of untreatable gonorrhoea (World Health Organisation, 2014 (c)). While comprehensive surveillance of all infections caused by

pathogens within a population would be ideal, sentinel surveillance is more realistic and sustainable. Sentinel surveillance is conducted on the population of a limited region seen to be representative of the rest of the population and can thus provide more detailed data over a longer period of time (World Health Organisation, 2016).

When conducting surveillance on ABR, samples that are representative of both hospital and community healthcare settings must be included as different infections are prevalent in each setting. While blood stream infections are prevalent in hospitals, gonorrhoea and food-borne diarrhoea are the common infections seen in a community health setting and urinary tract infections are prevalent in both. (World Health Organisation.(b), 2015) (World Health Organisation, 2014 (c)).

In resource limited regions such as Africa, Latin America and the Eastern Mediterranean region there are big gaps in information available as they are still in the early stages of combatting ABR (World Health Organisation, 2016). In such settings, there is limited financial capacity and inter-institutional collaboration to facilitate the implementation of strategies to curb ABR. In this regard, the Global Antimicrobial Surveillance System (GLASS) methodology provides the resources and guidelines to assist in the development of surveillance programmes. (Hoffman, *et al.*, 2015)

#### 1.2.2. The Global Antimicrobial Surveillance System (GLASS)

Increasing globalisation has increased the ease with which infections, and thus resistance, can spread. This makes ABR in any one region of the world a global concern and the WHO has made much progress in developing means to address this problem. The primary goal of the GAP is to sustain the ability to treat infectious diseases with safe medicines. The following strategic objectives were outlined in order to achieve this goal: "(1) improve awareness and understanding of antimicrobial resistance through effective communication, education and training, (2) strengthen the knowledge and evidence base through surveillance and research , (3) reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures, (4) optimize the use of antimicrobial medicines in human and animal health, (5) develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions" (World Health Organisation, 2015 (a)). The GLASS programme aims to address the objective of obtaining standardised, comparable, validated data on ABR which can be shard on a global platform in order to guide prevention and control programmes (World Health Organisation, 2015 (b)).

Differences in Antimicrobial Sensitivity Testing (AST) methods, variable quality control and differences in the choice of pathogens for surveillance are just a few of the shortfalls of existing surveillance data. Inadequate laboratory facilities to perform pathogen testing as well as limited human resourced has contributed to the lack of surveillance data in under resourced regions. The

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GLASS early implementation phase between 2015 and 2019 aims to set up basic surveillance standards and provide baseline data on ABR on a global scale based on national reports submitted by participating member states. While environmental and animal data is also needed in order to address the problem of ABR holistically, for the initial phase the focus will be on human pathogens (World Health Organisation, 2015 (b)).

The WHO has outlined priority pathogens based on specimen types, to be investigated in this phase of GLASS. Specific pathogen-drug combinations have been indicated in the GLASS manual, illustrated in Table 1. The rationale for selecting blood, urine, faeces and cervical/urethral swabs as sample types is that they represent the incidence of bloodstream infections, urinary tract infections, gastrointestinal infections and gonorrhoea respectively. The pathogens included for each specimen type are commonly encountered in both a community and hospital setting and represent infections that have important public health implications. These samples are easy processed and pathogen identification is straightforward (World Health Organisation, 2015 (b)).

Pathogen	Antibiotic Class	Antibiotic
Escherichia coli	Sulfonamides and trimethoprim	Cotrimoxazole
	Fluoroquinolones	Ciprofloxacin or levofloxacin
	Third-generation cephalosporins	Ceftriaxone or cefotaxime and
		ceftazidime
	Fourth-generation cephalosporins	Cefepime
	Carbapenems	Imipenem, meropenem, ertapenem
		or doripenem
	Polymyxins	Colistin
	Penicillins	Ampicillin
Klebsiella pneumoniae	Sulfonamides and trimethoprim	Cotrimoxazole
	Fluoroquinolones	Ciprofloxacin or levofloxacin
	Third-generation cephalosporins	Ceftriaxone or cefotaxime and
		ceftazidime
	Fourth-generation cephalosporins	Cefepime
	Carbapenems	Imipenem, meropenem, ertapenem
		or doripenem
	Polymyxins	Colistin
A. baumannii	Tetracyclines	Tigecycline or minocycline
	Aminoglycosides	Gentamicin and amikacin
	Carbapenems	Imipenem, meropenem, ertapenem
		or doripenem
	Polymyxins	Colistin
S. aureus	Penicillinase-stable $\beta$ -lactams	Cefoxitin
S. pneumoniae	Penicillins	Oxacillin
		Penicillin G
	Sulfonamides and trimethoprim	Cotrimoxazole
	Third-generation cephalosporins	Ceftriaxone or cefotaxime
Salmonella spp.	Fluoroquinolones	Ciprofloxacin or levofloxacin
	Third-generation cephalosporins	Ceftriaxone or cefotaxime and
	Carbapenem	ceftazidime
		Imipenem, meropenem, ertapenem
		or doripenem

Table 1: Pathogen-antimicrobial combinations on which GLASS will gather data

Shigella spp.	Fluoroquinolones	Ciprofloxacin or levofloxacin
	Third-generation cephalosporins	Ceftriaxone or cefotaxime and
	Macrolides	ceftazidime
		Azithromycin
N. gonorrhoeae	Third-generation cephalosporins	Cefixime
	Macrolides	Ceftriaxone
	Aminocyclitols	Azithromycin
	Fluoroquinolones	Spectinomycin
	Aminoglycosides	Ciprofloxacin
		Gentamicin

Patient data must be collected along with AST results and population data from the sample site. The surveillance data will be aggregated at a national level before reporting to the WHO annually (World Health Organisation, 2015 (b)).

Existing resources can be used in the implementation of GLASS but to facilitate proper data collection where surveillance has not yet been established, the WHO has made the WHONET software available as a data capturing and analysis tool. This software includes the capacity for core patient data as well as AST results, the analysis of which can provide trends in the distribution of resistance as well as comparable data to view the change in resistance patterns over time (World Health Organisation, 2015 (b)).

The implementation of GLASS will pave the way for the establishment of reliable surveillance systems. In the future, surveillance may be expanded to include other infections once the protocol and system for data collection and reporting has been established (World Health Organisation, 2015 (b)).

In using the GLASS methodology, the following information can be obtained:

- Population in which most AMR infections are presenting in terms of age and origin of infection (community or hospital)
- The extent of resistance based on epidemiological and laboratory data
- Changes in resistance patterns based on comparison of data year to year

Using the outlined method of data collection and analysis we can obtain an overview of trends in resistance in KwaZulu Natal which can be compared to data available from other regions, nationally and globally and may be used as baseline data for further studies.

These are also pathogens highlighted in the global priority pathogens list developed by the WHO in order to prioritise research and development into new antibiotics to treat antibiotic-resistant bacteria. Pathogens were grouped according to species and type of resistance and were classified as critical, high and medium priority. The following pathogens are classified as critical priority: carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa and Enterobacteriaceae* resistant to carbapenems and third generation cephalosporins. The following pathogens were classified as high priority: vancomycin-resistant *Enterococcus faecium*,

*Staphylococcus aureus* resistant to methicillin and vancomycin, clarithromycin-resistant *Helicobacter pylori*, fluoroquinolone-resistant *Campylobacter*, fluoroquinolone-resistant *Salmonella spp*. and *Neisseria gonorrhoea* resistant to fluoroquinolones and third generation cephalosporins. The following pathogens were classified as medium priority: penicillin-non-susceptible *Streptococcus pneumoniae*, ampicillin-resistant *Haemophilus influenzae and* fluoroquinolone-resistant *Shigella spp*. (World Health Organisation, 2017 (b)).

### **1.2.3. Existing Surveillance Programs:**

Surveillance of ABR is essential in order to determine the extent of the problem and using that information, formulate measures to curb the incidence and spread of resistance. Surveillance programmes are carried out nationally in various countries as well as by independent organisations. In addition, many studies are carried out based on data from samples routinely sent to laboratories for clinical purposes. Existing surveillance programmes implement varying methodologies and cover different pathogens, antibiotics, specimen types and settings. Outlined below is an overview of various surveillance programmes and studies with a special focus on those that have included GLASS pathogens (World Health Organisation, 2014 (b)).

#### 1.2.3.1. WHO Programmes

### African Region

The Integrated Disease Surveillance and Response (IDSR) system was adopted in the WHO Africa region in 1998, initially to monitor severe outbreaks of preventable infections. The project has since expanded to a regional surveillance network which aims to provide information on priority infections by strengthening surveillance programmes in member states and improving the use of surveillance data to guide clinical interventions. Measures include personnel training, integrating surveillance systems to promote efficient use of resources and improving the sharing of surveillance data. The contribution of data to the network is variable, depending on the resources and laboratory capacity in each participating country. The Gonococcal Antimicrobial Surveillance Programme (GASP) was initiated by the WHO in order to facilitate the collection of isolates in African countries by providing technical assistance and training (Centres for Disease Control and Prevention , 2015).

The WHO instituted pilot programmes in Durban and Brits, South Africa, as part of a global pilot study in five cities in under-resourced countries. In addition to the two South African sites, data was collected from three sites in India. The objective of the study was to investigate the feasibility and potential for ABR surveillance in resource limited settings by collecting prospective and retrospective drug usage data. The South African sites included *E. coli* isolates from urine samples and *S. pneumoniae* and *H. influenzae* isolates from sputum samples. These isolates were tested against

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ampicillin, trimethoprim/sulfamethoxazole, cefalexin/cefuroxime, chloramphenicol and erythromycin. In terms of GLASS pathogens, at the Brits surveillance site, *E. coli* isolates were found to be 50 - 65% resistant to ampicillin, trimethoprim/sulfamethoxazole and cefalexin/cefuroxime. At the Durban site, *S. pneumoniae* isolates showed the highest resistance to trimethoprim/ sulfamethoxazole (55%) followed by erythromycin (19%) and chloramphenicol (2%). The results highlighted the extensive use of antibiotics in both India and South Africa, with certain drugs more commonly used in community health centres in the public sector compared to the private sector and vice versa. In terms of the capacity for surveillance it was found that all sites were able to provide data, however methodological and logistic constraints were potential barriers to obtaining comparable data over long periods of time (Holloway, *et al.*, 2011). These sites would be ideal for the implementation of GLASS methodology, which would enhance the quality and reliability of the data obtained and address some of the shortcomings of this study.

A review of the extent to which countries in the WHO African region have implemented the WHO Policy Package on AMR showed that none of the countries had robust, representative national surveillance programmes on antimicrobial use and resistance. Pilot projects in various countries include but are not limited to (1) a study implemented in Gambia investigating the prevalence of and risk factors for the faecal carriage of resistant *Enterobacteriaceae* by food handlers in schools; a study involving the characterisation and susceptibility of *E.coli* in street food and raw beef in Tamale, Ghana; sentinel surveillance in Togo of ESBL producing *Enterobacteriaceae* in children under the age of five hospitalised for acute gastroenteritis and the correlation of antibiotic drug use and resistance found in humans, food-producing animals and retail foods in Uganda. In Rwanda, Kenya, Burundi and Tanzania a study investigating the prevalence and characterisation of ESBL producing *E. coli* in animals, humans and the environment has also been implemented. While the results of most of the abovementioned studies are not yet available, they highlight the capacity and potential for surveillance in Africa and provide useful data in terms of ABR as well as in terms of identifying limitations of surveillance methods. (Essack, *et al.*, 2016).

The 2014 WHO report on AMR noted the following resistance ranges from 2-13 countries of the 47 member countries in the Africa Region):

- *E. coli* to third generation cephalosporins: 2 70% (13 countries)
- *E. coli* to fluoroquinolones: 14 71% (14 countries)
- *K. pneumoniae* to third generation cephalosporins: 8 77%(13 countries)
- *K. pneumoniae* to carbapenems: 0 4% (4 countries)
- Incidence of methicillin-resistant *Staphylococcus aureus* (MRSA): 12 80% (9 countries)
- *S. pneumoniae* to penicillin: 3 16% (5 countries)
- Non-typhoidal *Salmonella* to fluoroquinolones: 0 35% (9 countries)

- *Shigella spp.* to fluoroquinolones: 0 3% (4 countries)
- Decreased susceptibility to fluoroquinolones in *N. gonorrhoea:* 0 12% (2 countries) (World Health Organisation (a), 2014).

# Region of the Americas

Latin American Antimicrobial Resistance Surveillance Network (ReLAVRA) is a surveillance network focussing on Latin America and was implemented by the Pan American Health Organisation (PAHO) in conjunction with the WHO. The system was implemented in 1996 and involves 21 countries, which submit surveillance data via National Reference Laboratories. There are four indicators pathogens, viz., *E. coli*, gonococci, *Klebsiella spp* and *S. aureus*. Based on the country-specific data available on the PAHO website, several countries appear to contribute to the surveillance network but to different degrees. For example, in 2013 there was data from 15 countries for *Klebsiella spp*. but only from 7 countries for gonococci. The general trend observed between the years 2000 and 2013 was an increase in ABR although the percentage of resistance fluctuated over the years as well as between countries. In 2013 resistance to third generation cephalosporins in *Klebsiella spp*. ranged from 19 - 84%, resistance to penicillin and ciprofloxacin in gonococci was more than 40% in most countries. Data on *E. coli* resistance was minimal, but data from Panama indicated that resistance to cefalotin, ciprofloxacin and trimethoprim/sulfamethoxazole ranged between 28 - 54% (World Health Organisation.(b), 2015) (Pan American Health Organisation, 2016).

The 2014 WHO report on AMR reported the following resistance ranges from 4-17 countries of the 35 member countries in the region of the Americas:

- *E. coli* to third generation cephalosporins: 0 48% (14 countries)
- *E. coli* to fluoroquinolones: 5 58% (16 countries)
- *K. pneumoniae* to third generation cephalosporins: 4-71% (17 countries)
- *K. pneumoniae* to carbapenems: 0 11% (17 countries)
- Incidence of MRSA: 21 90% (50 countries)
- *S. pneumoniae* to penicillin: 0 48% (15 countries)
- Non-typhoidal *Salmonella* to fluoroquinolones: 0 96% (13 countries)
- *Shigella spp.* to fluoroquinolones: 0 8% (14 countries)
- Decreased susceptibility to fluoroquinolones in *N. gonorrhoea*: 0 31% (4 countries) (World Health Organisation, 2014 (a))

# Eastern Mediterranean Region

Surveillance in this region so far has been largely disease-focussed and there is limited reliable data on the broader AMR situation. While the Eastern Mediterranean Regional Committee adopted resolutions to address AMR, political and economic unrest in this region makes the co-ordination of broad surveillance studies difficult. (World Health Organisation, 2014)

The 2014 WHO report on AMR reported the following resistance ranges from 2-5 countries of the 21 member countries in the Eastern Mediterranean region:

- *E. coli* to third generation cephalosporins: 22 63% (5 countries)
- *E. coli* to fluoroquinolones: 21 62% (4 countries)
- *K. pneumoniae* to third generation cephalosporins: 22 50% (4 countries)
- *K. pneumoniae* to carbapenems: 0 54% (4 countries)
- Incidence of MRSA: 10 53% (4 countries)
- *S. pneumoniae* to penicillin: 13 -34% (3 countries)
- Non-typhoidal *Salmonella* to fluoroquinolones: 2 49% (4 countries)
- *Shigella spp.* to fluoroquinolones: 3- 10% (2 countries)
- Decreased susceptibility to fluoroquinolones in *N. gonorrhoea:* 0 12% (2 countries (World Health Organisation, 2014 (a))

# European Region

Many countries within the European Union have established national surveillance programmes and all are participants in the European Antimicrobial Resistance Surveillance Network – EARS-Net. Countries outside of the European Union tend to have less well-established systems. The Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) is a WHO initiative involving countries who are not part of the European AMR Surveillance Network. The first report was published in 2014 from data submitted by five of the CAESAR participating countries while the remaining countries are in various stages of implementation of the surveillance program (World Health Organisation, 2014 (b)).

AST results are obtained from blood and cerebrospinal fluid samples on eight bacterial pathogens of particular interest in terms of public health implications. These included *E. coli*, *K. pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter spp.*, *S. aureus*, *S. pneumoniae*, *Enterococcus faecalis* and *Enterococcus faecium*. Data includes AST information on selected antimicrobial groups and resistance patterns reported as country-specific data. The data for each country is given a level of reliability based on the extent to which the data was representative of the entire population (World Health Organisation, 2014 (b)).

The WHO 2014 report on surveillance reported the following resistance ranges from 10-36 countries of the 53 member countries in the European Region:

• *E. coli* to third generation cephalosporins: 3 – 82% (35 countries)

- *E. coli* to fluoroquinolones: 8 48% (35 countries)
- *K. pneumoniae* to third generation cephalosporins: 2 82% (33 countries)
- *K. pneumoniae* to carbapenems: 0 -68% (31 countries)
- Incidence of MRSA: 0.3 60% (36 countries)
- *S. pneumoniae* to penicillin: 0 61% (31 countries)
- Non-typhoidal *Salmonella* to fluoroquinolones: 2 3% (29 countries)
- *Shigella spp.* to fluoroquinolones: 0 47% (10 countries)
- Decreased susceptibility to fluoroquinolones in *N. gonorrhoea*: 0 36% (17 countries)

(World Health Organisation, 2014 (a))

#### South-East Asia Region

AMR data in this part of the world appears to be limited aside from a few countries such as Thailand and India. In the Regional Strategy on Prevention and Containment of Antimicrobial Resistance published by the WHO in 2010 it was reported that no systematic prospective AMR studies had been conducted in the region database (World Health Organisation, 2010 (a)). In August 2012 "A Roadmap to Tackle the Challenge of Antimicrobial Resistance – A Joint meeting of Medical Societies in India" was conducted with the purpose of developing a plan for combatting ABR in Chennai, India. The Chennai Declaration, made by all delegates at the meeting, highlighted the roles of individuals in encouraging rational drug use, ABR surveillance, AST to guide treatment and improving infection control. The WHO was urged to provide technical and financial support in resource limited settings and most importantly co-ordinate initiatives on a global scale. In 2013 all 11 Member States of the region signed the Jaipur Declaration on AMR and agreed to contribute data towards a regional (Ghafur, *et al.*, 2013).

The WHO regional strategy for the period 2010-2015 aimed to increase awareness about AMR, encourage the rational use of antibiotics as well as to institute surveillance systems with inter-regional collaboration. A subsequent report on a meeting of 20 member states of the SEA region indicated that the available resistance data was mainly on HIV, tuberculosis, measles and diarrhoeal diseases. Data also commonly included extended spectrum  $\beta$ -lactamase (ESBL) producing bacteria, MRSA and *N. gonorrhoea* as well as specific antibiotics such as penicillin and ciprofloxacin. The general trend was an increase in resistance with specific concern regarding the increasing resistance to cephalosporins and carbapenems (World Health Organisation, 2013).

Various organisations have conducted AMR surveillance in the SEA region including independent laboratories, academic institutions and NGO's. The Sri Lanka College of Microbiologists conducted surveillance on AMR in Gram-negative organisms from several surveillance sites and planned to expand the program to include Gram-positive organisms as well as more surveillance sites. In the Maldives the Indira Gandhi Memorial Hospital (IGMH) Laboratory information system was able to provide limited resistance data showing the increasing patterns of resistance in the country. Other countries which reported some form of AMR data analysis included Nepal, Timor-Leste, Bangladesh, and Indonesia. (World Health Organisation, 2013) The surveillance data available in the SEA region was often as a result of activity by groups such as the International Network on Rational Use of Drugs (INRUD), ReAct- Action on Antibiotic Resistance, International Network for the Demographic Evaluation of Populations and Their Health in Under-Resourced Countries (INDEPTH), Alliance for Prudent Use of Antibiotics (APUA), Health Action International (Asia Pacific) (HAIAP) and the Global Antibiotic Resistance Partnership (GARP). Since the call for action on AMR was made, countries within the region are reported to have adopted national action plans and have made progress in implementing AST, awareness and surveillance projects. (World Health Organisation South-East Asia, 2010)

The WHO 2014 report on surveillance reported the following resistance ranges from 2-5 countries of the 11 member countries in South-East Asia region:

- *E. coli* to third generation cephalosporins: 16 68% (5 countries)
- *E. coli* to fluoroquinolones: 32 64% (5 countries)
- *K. pneumoniae* to third generation cephalosporins: 34 81% (4 countries)
- *K. pneumoniae* to carbapenems: 0 8% (4 countries)
- Incidence of MRSA: 10 26% (3 countries)
- *S. pneumoniae* to penicillin: 47 48% (2 countries)
- Non-typhoidal *Salmonella* to fluoroquinolones: 0.2 4% (2 countries)
- Decreased susceptibility to fluoroquinolones in *N. gonorrhoea*: 0 5% (5 countries) (World Health Organisation, 2014 (a))

# Western Pacific Region

In the 1980s, 14 Member States in this region agreed to collect AMR data on key pathogens, however this was disrupted due to other emergencies and co-ordination of AMR efforts between states was diminished although some countries continued surveillance on a national level. More recently, efforts have been made to re-establish AMR surveillance at a regional level (World Health Organisation (a), 2014).

The WHO 2014 report on surveillance reported the following resistance ranges from 4-16 countries of the 27 member countries in the Western Pacific region:

- *E. coli* resistance to third generation cephalosporins: 0 77% (13 countries)
- *E. coli* resistance to fluoroquinolones: 3 96% (16 countries)
- *K. pneumoniae* to third generation cephalosporins: 1 72% (14 countries)
- *K. pneumoniae* to carbapenems: 0 8% (9 countries)

- Incidence of MRSA: 4 84% (16 countries)
- S. pneumoniae to penicillin: 0 47% (10 countries)
- Non-typhoidal *Salmonella* to fluoroquinolones: 0 14% (9 countries)
- *Shigella spp.* to fluoroquinolones: 3 28% (4 countries)
- Decreased susceptibility to fluoroquinolones in *N. gonorrhoea:* 0 31% (12 countries) (World Health Organisation, 2014 (a))

#### 1.2.3.2. Global and Regional Surveillance Programmes

#### The Alexander Project and the Survey of Antibiotic Resistance (SOAR)

Initiated in 1992 by GlaxoSmithKline, the Alexander Project gathered data until 2001 and included three prominent respiratory pathogens: *H. influenza, Moraxella catarrhalis and S. pneumoniae*. Isolates from adult patients with community-acquired respiratory tract infections were obtained from surveillance sites in the USA, Mexico, Brazil, South Africa, Saudi Arabia, Hong Kong and European countries making it the first of its kind to compare standardised, quality data on an international level. MICs were established for a panel of 15 antibiotics including  $\beta$ -lactams, macrolides, fluoroquinolones and trimethoprim/sulfamethoxazole. Trends in resistance for each pathogen within and across the different classes of antibiotics were established, with the MIC values providing key information for many papers published based on the project. (Felmingham, *et al.*, 2005)

Between 1992 and 2001 there was an increase in multi-drug resistant infections with differences in resistance patterns between regions. Of specific interest is the data on *S. pneumoniae*, a GLASS pathogen, which showed high levels of penicillin-erythromycin co-resistance but a low prevalence of fluoroquinolone resistance in Europe and the USA. (Felmingham, *et al.*, 2005).

After the Alexander Project was concluded in 2001, GlaxoSmithKline initiated the Survey of Antibiotic Resistance Study (SOAR) in 2002 which also tracks ABR in respiratory infections. The latest findings for the SOAR project were published in 2016 and data for the next cycle of publications is being collated. Results from the African countries, including the Democratic Republic of Congo, Ivory Coast, Republic of Senegal and Kenya, showed that resistance to penicillin and trimethoprim/sulfamethoxazole in *S. pneumoniae* ranged from 0 - 35% and 21 - 57% respectively. Although other antibiotics were included in the panel, penicillin and trimethoprim/sulfamethoxazole are reported here as part of the GLASS panel of antibiotics for *S. pneumoniae* (Kacou-Ndouba *et al.*, 2016)

#### SENTRY

The SENTRY Antimicrobial Programme is an ongoing initiative that was started in 1997 and is funded by various pharmaceutical companies. Data on both nosocomial and community acquired infections are submitted by sentinel hospitals in the Americas, Europe and the Asia-Pacific region. The project includes the collection of surveillance data relating both to susceptibility data as well as investigation into resistance mechanisms. Reports on the data have been used as an indicator of the status of ABR in various regions of the world including South Africa (Masterton, 2008). Results cited in various studies will be discussed in more detail in the sections below.

Five major objectives of the programme were to monitor bacteraemia, outpatient respiratory tract infections, pneumonia in hospitalised patients, wound infections and urinary tract infections. The inclusion of these infections provided good insight into common infectious diseases which are of significance in terms of public health and the corresponding demographic and epidemiological data allowed for extensive comparison of resistance trends in each geographical region (Masterton, 2008).

A wide range of gram-positive and gram-negative bacteria have been investigated and numerous articles based on SENTRY data highlight trends in terms of specific pathogens, types of infections and antimicrobial agents. Of the GLASS pathogens, *S. aureus, A. baumannii, S. pneumoniae* and *E. coli* have been extensively monitored and the data shows that *S. aureus* was the most common causative pathogen of blood stream infections, pneumonia and soft tissue infections in almost all participating regions. The emergence of multi-drug resistant infections was clear, as was the distribution of resistance and variations in susceptibility patterns of pathogens across geographical regions. Between 1997 and 1999, susceptibility of *S. pneumoniae* isolates to penicillin and cefpodoxime varied from 6.8% and 9.2% in Canada to 17.8% and 22.9% in the Asia-Pacific region (Hoban, *et al.*, 2001). A study conducted by Diekema *et al.*, (2001) reported that isolates obtained from sites in Canada and the USA were generally more susceptible to all recorded drugs but that the nosocomial isolates showed higher resistance rates to  $\beta$ -lactam antibiotics than community acquired isolates. This was in contrast to Latin America where higher rates of resistance were reported with no major difference in  $\beta$ -lactam susceptibility between nosocomial and community acquired isolates. (Diekema, *et al.*, 2001)

### Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) Program

The MYSTIC programme was started in 1997 and focussed on the susceptibility of nosocomial infections to meropenem and other antibiotic agents by measuring MIC values. The study focussed on the Americas, Europe and the Middle East and the data was used together with antibiotic pharmacokinetic/pharmacodynamics data in the Optimizing Pharmacodynamic Target Attainment using the MYSTIC Antibiogram (OPTAMA) Program to provide insight into the optimal dosage to prevent the development of resistance. In addition, meropenem usage data was also collected in order to correlate usage and resistance patterns. Both Gram-positive and Gram-negative bacterial isolates were tested including *S. aureus, P. aeruginosa, A. baumannii, Enterobacteriaceae* and many others. Over the years the results of studies based on MYSTIC data have shown that meropenem is one of the more active broad-spectrum antibiotics but resistance to carbapenems is on the increase (Turner,

2000). A study published in 2008 looking at 11 years of data from a paediatric ICU found that a number of MDR isolates were susceptible to meropenem but resistant to all other agents. The study also found that the consumption of cephalosporins decreased over the study period, however the use of carbapenems increased significantly, which can be correlated with the increasing incidence of carbapenem resistance that has emerged in recent years (Patzer, *et al.*, 2008).

#### European Antimicrobial Resistance Surveillance Network (EARS-Net)

The European Antimicrobial Resistance Surveillance Network (EARS-Net) includes 30 countries and is a continuation of the European Antimicrobial Resistance Surveillance System (EARSS). Participating countries provide reports on the pathogens and antimicrobial agents under surveillance and have contributed towards a growing network of increasingly comparable AMR data. Representatives from Member States collate the AMR susceptibility data with regard to isolates from cerebrospinal fluid and blood samples from national surveillance sites. (European Centre for Disease Prevention and Control, 2015)

The standard of surveillance in the EU Member States was streamlined by the introduction of the European Committee on Antimicrobial Susceptibility Testing (EUCAST), which provides guidelines on susceptibility testing. This has allowed for greater uniformity and thus more comparable data to be collected from EARS-Net Member States. (European Centre for Disease Prevention and Control, 2015) (European Committee on Antimicrobial Susceptibility Testing, 2016)

The 2016 annual report included the AMR data for 2016 as well as a trend analysis of resistance in the region based on data from 2013 to 2016. Varying resistance patterns were noted throughout Europe between 2013 and 2016, but a general increase in resistance in E. coli to third generation cephalosporins and aminoglycosides was observed while resistance in K. pneumoniae appeared to stabilise with several countries reporting a decrease in resistance in K. pneumoniae to most antibiotic groups. For E. coli in 2016, over 50% of isolates were resistant to at least one antibiotic with the highest resistance reported to aminopenicillins (57%) while resistance to carbapenems remained low (< 0.1%). Resistance in E. coli to third generation cephalosporins remained stable at 12 - 13% while resistance to fluoroquinolones decreased from 22.5% to 21% over the 4 years. In K. pneumoniae resistance to fluoroquinolones decreased from 29.3% to 24.6%, resistance to third generation cephalosporins decreased from 30.1% to 25.7% and resistance to carbapenems decreased from 8.2% to 6.1%. Carbapenem resistance was found to be more common in Acinetobacter spp. isolates with an average of 35% resistance reported in 2016 with at least 6 countries reporting resistance greater than 70%. In S. pneumoniae isolates, resistance varied greatly between countries with non-susceptibility to penicillin ranging from 0.4% to 41.1% in 2016. Resistance to macrolides was 0 - 60% but in most countries, was higher than non-susceptibility to penicillins. The incidence of MRSA varied between countries, ranging between 1.2% and 50.5% in 2016, while the average incidence of MRSA in the

region decreased from 18.1% in 2013 to 13.7% in 2016 (European Centre for Disease Prevention and Control, 2017) (European Centre for Disease Prevention and Control, 2015).

In addition to EARS-Net which it administrates, the European Centre for Disease Control (ECDC) also funded the European Survey on Carbapenemase-Producing *Enterobacteriaceae* (EuSCAPE) which collected data between 2013 and 2014 and highlighted the increase in carbapenem resistance in *K. pneumoniae* as a cause for concern. Out of all the carbapenemase-producing isolates identified, the ratio between *K. pneumoniae* and *E. coli* was 11:1 (Grundmann *et al.*, 2017).

#### 1.2.3.3. National Surveillance Programmes

#### English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR)

In 2013, the United Kingdom published a strategy on AMR surveillance and ESPAUR was subsequently started as part of the strategy. ESPAUR collaborates with the ECDC and EARS-Net in order to enhance surveillance methods and contribute towards the broader AMR information network. Data from routine susceptibility testing is entered into a national database from hospitals across England and results are reported as pathogen-drug combinations (England Surveillance Programme for Antimicrobial Use and Resistance (ESPAUR), 2015).

Due to the increasing incidence of carbapenem resistance, an Electronic Reporting System (ERS) was implemented in 2015 for the enhanced surveillance of carbapenemase-producing Gram-negative bacteria. Between May 2015 and May 2017 there were 3 166 confirmed carbapenemase-producing organisms reported out of the 6 208 organisms submitted for testing. Sixty four percent of carbapenemase-producing *Enterobacteriaceae* (CPE) were isolated from rectal or faecal specimens (England Surveillance Programme for Antimicrobial Use and Resistance (ESPAUR), 2017).

The ESPAUR 2017 report, which included data between 2012 and 2016, highlighted the trends in resistance with respect to the different types of infection as well as by pathogen with specific focus on *E. coli, K. pneumoniae* and *P. aeruginosa*. In terms of results relevant to the GLASS methodology, bacteraemia caused by *E. coli* and *K. pneumoniae*, UTIs caused by *E. coli* and resistance in *N. gonorrhoea* was reported on. The proportion of non-susceptible *E. coli* isolates from blood samples remained stable between 2012 and 2016 although the incidence of bacteraemia caused by *E. coli* increased by 24.3% during this period with 40 272 cases reported in 2016. Isolates showed the highest resistance to amoxicillin/clavulanate (37.3% - 40.8%) followed by ciprofloxacin (18.1% - 18.7%) and third generation cephalosporins (10.8% - 12.4%) while carbapenem resistance remained low (0.07% - 0.14%). A similar trend of stable proportions of resistant isolates between 2012 and 2016 was observed in bloodstream infections caused by *K. pneumoniae* with resistance to ciprofloxacin and third generation cephalosporins fluctuating within the range of 10.0 - 12.3%. Carbapenem resistance was slightly higher than in *E. coli* isolates ranging from 0.8% to 1.15% (ESPAUR, 2017).

It was found that the underlying cause of approximately 50% of cases of bacteraemia was a UTI. Isolates were included from the community setting as well as the acute hospital setting. The majority of isolates (97%) were susceptible to first-line treatment nitrofurantoin but 34-37% of isolates were found to be resistant to trimethoprim, which is recommended where there is a low risk of resistance. Resistance to ciprofloxacin, the recommended treatment for complicated UTIs and pyelonephritis, was found to be 12% to 15% (ESPAUR, 2017).

The data regarding *N. gonorrhoea* showed that resistance to the first line drugs ceftriaxone and azithromycin was low. No isolates were found to be resistant to ceftriaxone and resistance to azithromycin showed a slight decline from 9.8% in 2015 to 4.7% in 2016 (ESPAUR, 2017).

#### India

Antimicrobial susceptibility testing is conducted by a number of public and private laboratories in India, however systematic surveillance is limited. A surveillance study supported by the WHO was carried out in Mumbai, New Delhi and Vellore between 2002 and 2005 looking at resistance in *E. coli*. There was high resistance to ampicillin (46 – 50%) and trimethoprim/sulfamethoxazole (45 – 65%) (Global Antibiotic Resistance Partnership-India National Working Group, 2011). Initiatives which have been active in India include the Indian Clinical Epidemiology Network (IndiaClen) which implemented the Invasive Bacterial Infection Surveillance (IBIS) project, the Indian Initiative for Management of Antibiotic Resistance (IIMAR) and the Indian Network for Surveillance of Antimicrobial Resistance (INSAR). These initiatives have spanned both the public and private sector and have included various pathogens (World Health Organisation South-East Asia, 2010).

Diarrhoeal and respiratory infections are responsible for 8% and 6% of deaths in India respectively and the associated resistance of the causative pathogens to antibiotics make the surveillance of antibiotic use and resistance a necessity in trying to improve public health outcomes. Studies have been carried out at various health facilities with the focus on hospital acquired infections (HAIs) by ward type as well as pathogen specific studies (Global Antibiotic Resistance Partnership-India National Working Group, 2011).

In the GARP India situational analysis published in 2011, *S. aureus* and *P. aeruginosa* were reported to be the most common causative pathogens in terms of HAIs and resistance data showed multi-drug resistance as high as 96% in a study including burn patients. *P. aeruginosa* isolates showed especially high resistance to tobramycin (83.6%) and amikacin (55.1%). The incidence of MRSA throughout India from past and present surveillance studies ranged from zero to almost 100%. A study carried out in Vellore between 1993 and 1994 found that 24% of *S. aureus* isolates were methicillin resistant and that resistance was >75% to gentamicin, ciprofloxacin and trimethoprim/sulfamethoxazole. Of the other GLASS pathogens, studies involving *A. baumannii* showed >80% resistance to third generation

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cephalosporins with the presence of ESBLs but a relatively smaller percentage of organisms were resistant to carbapenems (8%). High levels of third generation cephalosporin resistance was also found in a study on *K. pneumoniae* from urine samples (68%). Results of several studies showed that up to 60% of *E. coli* isolates obtained from various surveillance sites were resistant to at least one antibiotic. A study conducted in New Delhi found that 67% of *S. typhi* isolates from children admitted to hospital with typhoid fever were multidrug resistant. Resistance among *Salmonella* species was found to be high (>70%) against ampicillin, ciprofloxacin and chloramphenicol but relatively lower against gentamicin (>90%). The data available regarding the susceptibility of *N. gonorrhoea* was of concern as a study conducted in a community setting between 2002 and 2003 found 78% of the isolates resistant to ciprofloxacin, 51% to tetracycline and 47% to penicillin (Global Antibiotic Resistance Partnership-India National Working Group, 2011).

#### Thailand

In Thailand surveillance of AMR has been implemented on a national level with respect to both human and animal health. The National Antimicrobial Resistance Surveillance in Thailand (NARST) was started in 1997 and has since expanded to include more surveillance sites. Surveillance data available from the NARST web page indicated a general trend of increasing resistance. *Enterococcus* spp. showed 84.1% and 69.7% resistance to tetracycline and erythromycin respectively in 2015 while vancomycin and teicoplanin showed the greatest sensitivity with only 3% of isolates showing resistance. Thirty-nine percent of S. pneumoniae were found to be resistant to erythromycin in 2016 as opposed to 48% in 2009, with >30% isolates resistant to erythromycin and/or clindamycin. Resistance of S. aureus isolates to erythromycin, clindamycin, ciprofloxacin and cefoxitin was found to be high (26-36%) in 2016 with resistance to cefoxitin being the highest (36.8%). Resistance to ampicillin was found to be especially high in E. coli and K. pneumoniae isolates which showed 86% and 99% resistance in 2016 respectively. There was a sharp drop in resistance to ampicillin/sulbactam in nontyphoidal Salmonella isolated from blood, dropping from 80% in 2002 to 7% in 2016, however resistance to ampicillin remained high in 2016 at 66%. Of special concern was the trend in resistance of A. baumannii isolates to multiple antibiotic agents. In 2016 greater than 50% resistance was found to amikacin, cefepime, ciprofloxacin, piperacillin/tazobactam, ampicillin/sulbactam and imipenem (National Antimicrobial Resistance Surveillance Centre, Thailand, 2015).

An Invasive Bacterial Infection Surveillance (Thai-IBIS) was also established in 2005. The United States Centres for Disease Control (CDC) works closely with the Thailand Ministry of Public Health to improve the prevention strategies for infectious diseases (World Health Organisation South-East Asia, 2010). The CDC is also active in the rest of the Southeast Asia region and has established the Immigrant, Refugee, and Migrant Health Program (IRMHP). There are several awareness programmes aimed at encouraging the rational use of antibiotics through educational courses as well as through an initiative by the Thai Food and Drug Administration (FDA) "Antibiotics Smart Use –

ASU" Project supported by the WHO, however awareness within the general community is still limited (U.S. Centers for Disease Control and Prevention, 2009).

# National Surveillance and Reporting of Antimicrobial Resistance and Antibiotic Usage for Human Health in Australia

While Australia has a wealth of laboratories which provide antimicrobial susceptibility testing, a report published in 2013 stated that there was limited aggregation or analysis of the data at a national level and little standardisation and co-ordination occurred between surveillance sites. The Australian Group on Antimicrobial Resistance (AGAR), the National Neisseria Network (NNN) and the National Antimicrobial Utilisation Surveillance Program (NAUSP) are examples of surveillance programmes in Australia which have collected susceptibility data on several pathogens in the hospital and community setting, most commonly covering *Enterobacteriaceae* and *S. aureus*. Data from the *S. aureus* 2011 Antimicrobial Susceptibility Report noted MRSA in 29 – 36% of isolates, while the data from the Gram-negative Bacteria 2011 Hospital-onset Susceptibility Report evidenced high levels of resistance in *E. coli* to ampicillin (50.5%) while resistance in *K. pneumoniae* was highest to cefazolin (18%) and trimethoprim (18%) (Shaban, *et al.*, 2013). Resistance in *N. gonorrhoea* isolates to fluoroquinolones in 2000 was reported to be 10% (Tapsall, *et al.*, 2008). Based on existing surveillance networks such as EARS-Net, the Australian government outlined a national action plan with clear objectives to collect comparable and validated AMR (AMR) data (Shaban, *et al.*, 2013).

#### National Antimicrobial Resistance Monitoring System- Enteric Bacteria (NARMS)

The NARMS programme was started in the USA by the Centres for Disease Control (CDC), the Food and Drug Administration (FDA) and the US Department of Agriculture. NARMS collects data regarding enteric bacteria including Salmonella, Campylobacter, Shigella, E. coli from humans, retail meat and food animal sources. NARMS investigates emerging resistance trends in order to guide health policies, inform consumers about food-borne diseases and encourage rational use of antibiotics. The CDC oversees a number of other surveillance programmes including the Gonococcal Isolate Surveillance Project (GISP) and the Healthcare-Associated Infections-Community Interface. The NARMS 2014 Human Data Report showed that resistance to ciprofloxacin in non-typhoidal Salmonella and Shigella spp. was 0.4% and 2.4% respectively and resistance in E. coli was highest to tetracycline and sulfisoxazole (7%) (Centres for Disease Control, 2016). The CDC also released a report in 2013 tracking the status of resistance in all pathogens of public health concern. The data showed that carbapenem resistance especially in K. pneumoniae (2%) and E. coli (11%) was of urgent concern as it translated to increasing difficulty in treating carbapenem-resistant Enterobacteriaceae (CRE) infections. MDR gonorrhoea was also highlighted as a serious concern with 30% resistance to cephalosporins, tetracycline and azithromycin in N. gonorrhoea. Other pathogens which were highlighted were MDR Acinetobacter, ESBL producing Enterobacteriaceae, drug resistant Shigella

*spp, Salmonella spp, S. pneumoniae, P. aeruginosa* and MRSA (Centres for Disease Control and Prevention, 2014).

#### 1.2.4. ABR and ABR Surveillance in South Africa:

South Africa has a national AMR strategy framework, which is supported by antibiotic stewardship, increased surveillance and measures to prevent the spread of infection through vaccination and infection prevention and control. The framework also aims to take a comprehensive approach in dealing with AMR by implementing regulatory measures to improve the use of medicines through the Medicines Control Council (MCC) and the National Drug Policy (NDP). The national framework also highlights the need for co-operation from health professionals, members of the agricultural community as well as professionals in the veterinary field (Mendelson & Matsotso, 2015).

The surveillance indicated in the framework is specifically aimed at resistance data, drug consumption trends, drug quality as well as the occurrence of medication errors. Through the education measures suggested, the stage has already been set for the implementation of antibiotic surveillance according to WHO surveillance standards. Through the guidelines set forth in the GLASS early implementation manual, the existing AMR strategy framework can be optimised in order to provide data that is useful on both a national and international scale (Mendelson & Matsotso, 2015).

As the two infectious diseases which cause the highest numbers of deaths in South Africa, HIV and TB have been the focus of numerous studies. The National Institute for Communicable Diseases (NICD) undertakes surveillance on diarrhoeal diseases, which have a direct impact on infant mortality as well as epidemic-prone infections such as cholera, typhoid fever and meningococcal disease. An analysis of AMR in South Africa carried out in 2011 by the Global Antibiotic Resistance Partnership-South Africa (GARP-SA) found that there was an urgent need for action in establishing standardised surveillance methods. There are limitations in population representation in existing data which stems mainly from central academic sites. Existing surveillance data thus does not represent the status of AMR in the entire population. The Centre for Healthcare Associated Infections, Antimicrobial Resistance and Mycoses, a branch of the NICD, conducts laboratory based antimicrobial resistance surveillance (LARS) since 2010 and collects data from sentinel sites. Electronic surveillance was implemented in 2013 and collects data from laboratory information systems in order to generate resistance maps. Enhanced surveillance has been implemented for methicillin-resistant S. aureus (MRSA) in order to determine the prevalence and extent of nosocomial and community-acquired MRSA infections. Enhanced surveillance is also underway for carbapenem-resistant Enterobacteriaceae (CREs) (Mendelson & Matsotso, 2015).

Existing surveillance data in South Africa which include pathogens of interest recommend by GLASS will be discussed below per infection type.

#### **Blood Stream Infections**

Enhanced surveillance of *S. aureus* bacteraemia (SAB) was conducted in 3 public sector hospitals in Gauteng, South Africa between 2012 and 2013. Core patient data, treatment information as well as antimicrobial susceptibility data were included in the study which provided a comprehensive and detailed picture of the incidence of SAB in the hospitals involved. AST results showed that 36% of the isolates were MRSA and that longer hospital stays, HIV infection, frequent hospitalisation and recent antibiotic use were predictors of MRSA infection (Fortuin-de Smit, *et al.*, 2015). A wider study was conducted between 2010 and 2012 including thirteen academic hospitals around South Africa which looked at AMR trends and molecular epidemiology of SAB. *S. aureus* isolates were obtained from blood cultures over two years from academic hospitals in the public sector. There was a greater incidence of MRSA in Gauteng than in the other three provinces represented in the study and a variety of MRSA clones were present in South Africa. Methicillin resistance was found in 46% of isolates, but the incidence of MRSA decreased from 53% in 2010 to 40% in 2012 (Perovic, *et al.*, 2015). The GLASS methodology recommends cefoxitin to be included in the panel for *S. aureus* as it is an indicator for methicillin resistance (World Health Organisation (b), 2015).

A national surveillance study was carried out in 2014 based on data obtained from public laboratories conducting AST for various hospitals in different provinces. Results from laboratory data using the Vitek and disk diffusion tests were analysed according to Clinical Laboratory Standards Institute (CLSI) guidelines. The study focussed on bloodstream infections caused by eight pathogens and the susceptibility profiles obtained were analysed. A. baumannii isolates showed the greatest resistance to piperacillin/tazobactam with more than 80% resistance, while susceptibility to colistin was retained at almost 100% followed by amikacin and levofloxacin which evidenced approximately 60% susceptibility. The other antibiotics including cephalosporins and carbapenems amongst others, showed resistance ranging between 70% and 80%. S. aureus isolates showed almost 0% susceptibility to penicillin, however the susceptibility to all other agents was found to be greater than 50%. The presence of ESBL producing pathogens including E. coli and K. pneumoniae was also detected, but both pathogens were almost 100% sensitive to carbapenems and amikacin (Perovic, et al., 2014). The 2015 annual report of the Group for Enteric Respiratory and Meningeal Disease Surveillance in South Africa (GERMS-SA) published by the NICD reported national surveillance data from 36 enhanced surveillance hospital sites. Diseases under surveillance included opportunistic, nosocomial, epidemic-prone and vaccine-preventable infections throughout the 9 provinces. The GERMS-SA surveillance project includes susceptibility results from over 200 laboratories and covers a population of approximately 54.9 million. Methods such as the electronic capture on mobile phones of enhanced surveillance case report forms by surveillance officers has improved the ease of data capture and

surveillance site audits ensure that quality control is maintained (GERMS-SA, 2013) (GERMS-SA, 2015).

The GERMS-SA 2015 report included data on invasive pneumococcal disease, which in addition to blood samples, included isolates from the cerebro-spinal fluid (CSF) and other sources. The resistance data showed low levels of penicillin resistance (4%) in *S. pneumoniae*. Isolates have shown high levels of penicillin resistance in some studies, while significantly lower levels in others, leaving the overall level of penicillin resistance in the country at intermediate (GERMS-SA, 2015). Resistance to other classes of antibiotics has also been reported. Data from Johannesburg obtained as part of the Alexander Project in 1999 reported 79% of isolates to be penicillin-resistant and other data from the same year reported MDR in 37% of isolates (Crowther-Gibson, *et al.*, 2011). The GERMS-SA 2015 report found MRSA in 33% of isolates, an increase from 29% reported in 2013 and resistance to clindamycin was 29% (GERMS-SA, 2015) (GERMS-SA, 2013).

# Diarrhoeal Infections

The GERMS-SA 2015 report found that *Salmonella typhi* isolates showed a slight increase in resistance to ciprofloxacin, the first line treatment for diarrhoeal infections, from 10% in 2013 to 14% in 2015. No resistance was reported to azithromycin which could be used as alternative treatment options in cases of treatment failure with ciprofloxacin. In non-typhoidal Salmonella isolates resistance to ciprofloxacin was 21% while resistance to azithromycin was reported to be 1%. *Shigella* isolates showed low resistance (1%) to ciprofloxacin and azithromycin, although this is greater than the 0.1% resistance to ciprofloxacin reported in 2013 (GERMS-SA, 2015).

The GARP-SA situation analysis on ABR published in 2011 reported a decline in resistance to ampicillin in *Salmonella typhi* from 40% in 2006 to 10% in 2010. Resistance declined in non-typhoidal *Salmonella* isolates as well from 64% to 16% between 2003 and 2010. Resistance to ciprofloxacin was <1% in non-typhoidal *Salmonella* and *S. typhi* isolates in 2010. In *Shigella spp.*, high resistance rates to older antibiotics such as ampicillin, tetracycline and sulfamethoxazole was reported ( $\geq$ 50%), including a high prevalence of MDR isolates, while resistance to the current first-line treatment, naladixic acid, remained low (1%) (Gelband & Duse, 2011).

# Urinary Tract Infections

A study conducted in Gauteng by Lewis et.al in 2013 investigated the aetiology of UTI's in women from public and private healthcare facilities and included antibiotic prescribing data. Gram-negative bacteria, including *E. coli* and *K. pneumoniae*, were the most common causative pathogens. Resistance in Gram-negative bacilli was higher for trimethoprim/sulfamethoxazole (59%) and

amoxicillin-clavulanate (19%) than ciprofloxacin (6%). Susceptibility to cephalosporins was greater than 90% (Lewis *et.al.* 2013 (a)).

Another study was carried out between 2010 and 2012 with *K. pneumoniae* as the sentinel organism in 13 public sector healthcare sites in Gauteng, KwaZulu Natal, Limpopo, Free State and Western Cape provinces. Resistance to third generation cephalosporins was found to be greater than 70% while susceptibility to carbapenems and colistin was greater than 85% in 2012 (Perovic, *et al.*, 2014).

Coetzee et al. reported in 2016 that increasing colistin resistance in *E. coli* isolates was becoming a serious concern and that the use of colistin as a last resort was becoming more common due to resistance to other antibiotics. Resistance was thought to be spread by the presence of the mcr-1 gene in food animals such as pork and poultry, the presence of which has been confirmed by surveillance of poultry operations in South Africa. The mcr-1 gene has also been detected in colistin-resistant *E. coli* in hospitalised and outpatient-based patients in South Africa (Coetzee *et al.*, 2016).

Such studies show that there is the capacity for the collection of usable, detailed data as required for GLASS as *E. coli* and *K. pneumoniae* are the pathogens of interest for urine samples. These existing findings are useful as a means of comparing the results of this study to the existing knowledge base.

#### Gonorrhoea

Gonorrhoea is the only STI to be investigated in terms of ABR in South Africa. Isolates were found to be susceptible to ciprofloxacin until 2003, when resistance emerged in Durban. A subsequent study carried out by the STI Reference Centre in several cities including Durban, Cape Town and Johannesburg showed varying levels of quinolone resistance but a general trend of increasing resistance to ciprofloxacin. Studies in Gauteng have also found high levels of tetracycline resistance which excludes its use as well as the use of penicillin, due to the reports of penicillinase-producing gonococci. The current first line therapy was changed from ciprofloxacin to cephalosporins in 2008, which showed good activity against *N. gonorrhoea.* Treatment is recommended as either oral cefixime or intramuscular ceftriaxone but while widespread resistance to these agents has not been reported in Africa, resistance to oral cephalosporins has emerged in the Western Pacific region as well as Europe, a trend which may spread to South Africa in the near future (Crowther-Gibson, *et al.*, 2011). In 2012 the first two cases of confirmed extended-spectrum-cephalosporin-resistant *N. gonorrhoeae* were reported in Johannesburg (Lewis *et al.* 2013 (b)).

# Other Research in South Africa

Statistics from the Johannesburg Antimicrobial Resistance Laboratory and Culture Collection (AMRL-CC) of the Centre for Opportunistic, Tropical and Hospital Infections at the NICD describe CPE isolates. The majority of isolates were *K. pneumoniae*, *E. coli* and *Serratia marcescens* and the presence of these CPE isolates indicates the need for formal surveillance on a national level in order

to inform public health policy (Centre for Opportunistic, Tropical, and Hospital Infections, 2015). A study in five hospitals in the Eastern Cape, investigated carbapenem resistant *Enterobacter cloacae* and found that 72% of isolates harboured carbapenem resistance genes and strains from the same geographic location were genetically similar (Singh-Moodley, *et al.*, 2015).

Both these studies indicate a cause for concern that the incidence of carbapenem resistance is increasing and that this resistance may be conferred by mobile genetic elements. These studies also provide confidence in the capacity South Africa has to conduct systematic surveillance and provide usable data for strategy development and that the implementation of WHO recommendations, as will be discussed below, are achievable based on the resources available.

#### 1.2.5. ABR surveillance in KwaZulu Natal

A study was published in 2005 looking at data from 16 public hospitals in KwaZulu Natal including district, regional and tertiary hospitals and the resistance in isolates from the different levels of hospitals was compared. Ninety percent of isolates were found to be multi-drug resistant and the incidence of MRSA was 17 - 28% in district, regional and tertiary hospitals. Resistance to ampicillin was high (>80%) as compared to meropenem (<10%) according to the combined percentage resistance for all species included in the study (Essack *et al.*, 2005).

There are several public healthcare facilities in KZN which serve as sentinel surveillance sites including enhanced surveillance site such as Addington Hospital amongst others as mentioned above. These sites provide susceptibility data on a number of pathogens, including the ESKAPE pathogens and this information has been included in national surveillance reports (GERMS-SA, 2013) (Perovic, *et al.*, 2014).

The WHO established pilot projects in two cities in South Africa: Durban and Brits and each site implemented a protocol for collecting community-based AMR data every month for at least 12 months, using one or two indicator bacteria. In Durban *S. pneumoniae* and *H. influenzae* were the indicators and resistance was measured in terms of the MIC values (Holloway, *et al.*, 2011).

A study conducted at Inkosi Albert Luthuli Central Hospital (IALCH) in 2009 investigated the susceptibility of nosocomial infections in the Trauma Intensive Care Unit (TICU) and reviewed the accuracy of empiric antibiotics. IALCH employs antibiotic stewardship and the study found that such programmes promoted rational use of antibiotics which in turn limit the progress of AMR. Many of the GLASS pathogens of interest were isolated during the study period. *A. baumannii* isolates were most susceptible to amikacin (43%), susceptibility in *S. aureus* isolates to clindamycin, cloxacillin, erythromycin, gentamicin and vancomycin was 62 -100% while only 11% and 16% susceptibility to penicillin and ampicillin was reported respectively. *S. pneumoniae* isolates showed 7% resistance to penicillin, 33% resistance to ampicillin and 100% resistance to cloxacillin. Susceptibility in *E. coli* 

isolates was >80% for all antibiotics except amoxicillin-clavulanate (45%) while susceptibility in *K*. *pneumoniae* isolates was 58 - 92% for all antibiotics (Ramsamy, *et al.*, 2013).

Although limited surveillance has been conducted specifically in KwaZulu Natal, data from surveillance sites in the province have contributed towards national surveillance studies. Antimicrobial susceptibility data is available from public sector hospitals via data from VITEK machines which carry out automated antimicrobial susceptibility testing (GERMS-SA, 2013).

### 1.2.6. Antimicrobial Susceptibility Testing (AST)

In order to identify and quantify drug resistance in pathogens, there are various methods of carrying out susceptibility testing. The most common methods of AST are disc sensitivity testing, broth microdilution and rapid automated instrument methods. Each method has benefits and shortcomings and the accuracy of testing of certain organisms varies between methods (Barth Reller *et al.*, 2009).

Broth macrodilution includes preparing two-fold dilutions of antibiotics in a liquid growth medium and identifying the MIC after incubation. The benefit of this method is that a quantitative result is obtained, however this method is labour intensive and there is the possibility for human error. Microdilution works on the same principle, but the process in miniaturised and mechanised and multiple antibiotics can be tested on one tray. This method is that the results are reproducible, trays with prepared antibiotic panels are available and the cost of testing is relatively low (Barth Reller *et al.*, 2009).

Another method of testing is the antimicrobial gradient method whereby an antimicrobial concentration gradient in an agar medium is established. An example of this is the Etest which uses test strips impregnated with dried antibiotics of increasing concentration. After overnight incubation, MIC is determined based on the growth inhibition area. This method allows for the flexibility to choose which drugs to test, however the test strips are costly so it is not practical for testing multiple drugs. While the results from this method of testing are generally comparable with broth microdilution, there are some systematic biases to higher or lower MICs in certain antibiotic-pathogen combinations (Barth Reller *et al.*, 2009).

Disk diffusion involves applying a bacterial inoculum to a Mueller-Hinton agar plate and antibiotic disks of fixed concentration are placed on the inoculated surface. Results are determined from the diameter of the growth inhibition zone after incubation as per the interpretive criteria in CLSI/ EUCAST guidelines or as per the product insert for the disks. This method of testing produces qualitative results categorised as susceptible, intermediate or resistant instead of MIC values. The testing procedure is simple and requires no specialised equipment and it is the cheapest of all testing methods. The disadvantages are that not all bacteria can be accurately tested by this method and all preparation is manual (Barth Reller *et al.*, 2009).

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Automated microbiological testing provides pathogen identification and AST processing of specimens and is used to provide the necessary information for clinical interventions. Automated systems are a useful tool in antimicrobial surveillance and allows for easy acquisition of specimen analysis reducing the workload of the researcher. Automated instrument systems allow for rapid susceptibility testing and because computer software is used to interpret results, the reading of endpoints is standardised. The disadvantage is that there is a lessened ability to detect resistance in certain cases such as vancomycin resistance and inducible  $\beta$ -lactamases. An example of an automated testing system in the VITEK 2 machine, which is the method used for susceptibility testing in this study (Ligozzi, *et al.*, 2002) (Barth Reller *et al.*, 2009).

The VITEK 2 machine uses reagent cards with 64 wells containing a test substrate meaning that a single card can hold up to 64 organism-substrate combinations. The pure culture for analysis first needs to be prepared as a suspension before it can be inserted into the Vitek machine for inoculation and incubation. The incubator can hold up to 60 cards at a time and readings are collected by the machine at 15minute intervals. MIC results are displayed as "+" or "-" based on automatic calculations done on the raw data that are compared to test thresholds (Ligozzi, *et al.*, 2002).

The VITEK 2 system has been shown to provide accurate identification and AST results for use in hospitals where microbiological testing is in high demand and results are needed rapidly. This is especially useful in resource-limited settings where there may not be sufficient human resources to conduct manual microbiological testing for clinical use (Ligozzi, *et al.*, 2002).

#### 1.3. Conclusion

With the escalation of multi-drug resistant infections, treatment options are becoming more limited, making commonly encountered infections increasingly difficult to treat. The purpose of this study was to illustrate antibiotic resistance trends in pathogen-drug combinations stipulated in GLASS in the province of KwaZulu Natal, South Africa over a 5-year period.

It is clear from the literature that while surveillance systems do exist, there is variability in the quality and reliability of data and differences in methodology, pathogens and drugs of interest hinder the establishment of the true extent of ABR. Specifically, surveillance in Africa is less well established than in other regions such as Europe, North America and Australia and inadequate funding, human resources and infrastructure limit the capacity for surveillance in under-resourced countries. As such, there is a great need for surveillance in order to obtain information on the true extent of antibiotic resistance in the region.

The GLASS manual for early implementation provides data compilation methods, resistance markers for global reporting and a stepwise implementation plan that allows for the gradual induction into the program. By applying the GLASS methodology, simplified data collection and reporting can be established to provide baseline information on the extent of ABR which can later be expanded once

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the surveillance methodology is established. This study aims to address the gap in knowledge regarding ABR in GLASS pathogen-drug combinations to some extent. The results can be used to guide future studies and build on the existing knowledge base to provide comparable, validated data which can be shared on a global scale in order to guide future interventions against the spread of ABR.

# 1.4. Aims and objectives

# Aims:

To elucidate the extent and trends in ABR in blood stream infections, urinary tract infections (UTIs), diarrhoea and gonorrhoea in KwaZulu Natal using guidelines delineated in the Global Antimicrobial Surveillance System (GLASS) of World Health Organisation (WHO) over the period 2011-2015.

# **Objectives:**

- To create a database of blood stream infections (BSI), urinary tract infections (UTI), diarrhoeal infections and gonorrhoeal infections from extracted from the provincial database of the KwaZulu-Natal National Health Laboratory Services including but not limited to:
  - o Causative bacteria and their associated antibiotic susceptibility profiles
  - Clinical data on specimen source, diagnosis (if available), date of admission, date of specimen collection, date of discharge etc.
  - Demographic data on age, gender, co-morbidity (if available).
  - Facility data such as hospital level and ward type
- To identify the proportion of BSIs, UTIs, diarrhoeal infections and gonorrhoea caused by each pathogen of interest.
- To observe any changes/trends in the proportion of causative pathogens for each specimen type per year.
- To analyse the trends in ABR over the study period and identify changes in susceptibility profiles if evident.
- To compare the susceptibility profiles obtained with the antibiotics recommended in the Standard Treatment Guidelines published by the Department of Health with a view to informing amendments per hospital level as appropriate.
- To create a baseline for the WHO GLASS platform at provincial level

# **1.5. Dissertation Structure**

The dissertation is set out as follows:

**Chapter 1:** Introduction and Literature Review

**Chapter 2:** Manuscript entitled "A Retrospective Trend Analysis of Antibiotic Resistance in GLASS Pathogens in KwaZulu Natal: 2011- 2015" intended for submission to the Bulletin of the World Health Organisation:

Chapter 3: Conclusion, Limitations and Recommendations
# References

Aiken, A M; Nturi, N; Njuguna, P; Mohammed, S; Berkley, JA; Mwangi, I; Mwarumba, S; Kitsao, BS; Lowe, BS; C, Morpeth S; Hall, AJ; Khandawalla, I; Scott, JG; Kilifi Bacteraemia Surveillance, 2011. Risk and causes of paediatric hospital-acquired bacteraemia in Kilifi District Hospital, Kenya: a prospective cohort study. *The Lancet*, 378(9808), pp. 2021-2027.

Alliance for the Prudent Use of Antibiotics, 2008. AMROAR Scientific Meeting Report on Commensals as Reservoirs of Antibiotic Resistance, Boston: Alliance for the Prudent Use of Antibiotics.

Barth Reller, L; Weinstein, M; Jorgensen, JH; Ferraro, MJ, 2009. Antimicrobial Susceptibility Testing: A Review of General Principles and Contemporary Practices. *Clinical Infectious Diseases*, 49 (11), pp. 1749 - 17555.

Benbachir, M; Benredjeb, S; Boye, C S; Dosso, M; Bellabes, H; Kamoun, A; Kaire, O; Elmdaghri, N, 2001. Two-Year Surveillance of Antibiotic Resistance in Streptococcus pneumoniae in Four African Cities. *Antimicrobial Agents and Chemotherapy*, 45(2), pp. 627-629.

Brooks, JT; Ochieng, JB; Kumar, L; Okoth, G; Shapiro, RL; Wells, JG; Bird, M; Bopp, C; Chege, W; Beatty, ME; Chiller, T; Vulule, JM; Mintz, E; Slursker, L, 2006. Surveillance for Bacterial Diarrhea and Antimicrobial Resistance in Rural Western Kenya, 1997–2003. *Clinical Infectious Diseases*, 43(4), pp. 393-401.

Centre for Opportunistic, Tropical, and Hospital Infections, 2015. Update on carbapenemaseproducing Enterobacteriaceae. *Communicable Diseases Communiqué*, 14(12), pp. 1-2.

Centres for Disease Control and Prevention, 2015. *Integrated Disease Surveillance and Response*. [Online] Available at: http://www.cdc.gov/globalhealth/healthprotection/idsr/what/objectives.html [Accessed 22 May 2016].

Centres for Disease Control and Prevention, 2014. *Antibiotic Resistance Threat in the United States*, 2013. [Online] Available at: http://www.cdc.gov/drugresistance/threat-report-2013/ [Accessed 26 May 2016].

Centres for Disease Control, 2015. *National Antimicrobial Resistance Monitoring System*. [Online] Available at: http://www.cdc.gov/narms/about/index.html [Accessed 18 April 2016].

Coetzee, J; Corcoran, C; Prentice, E; Moodley, M; Mendelson, M; Poirel, L; Nordmann, P; Brink, AJ, 2016. Emergence of plasmid-mediated colistin resistance (MCR-1) among Escherichia coli isolated from South African patients. *South African Medical Journal*, 106(5): 449 – 450.

Crowther-Gibson, P; Govender, N; Lewis, DA; Bamford, C; Brink, A, 2011. Part IV: Human Infections and Antibiotic Resistance. *South African Medical Journal*, 101(8), pp. 567-578.

Diekema, DJ; Pfaller, MA; Schmitz, FJ; Smayevski, J; Bell, J; Jones, RN; Beach, M, 2001. Survey of Infections Due to Staphylococcus Species: Frequency of Occurrence and Antimicrobial Susceptibility of Isolates Collected in the United States, Canada, Latin America, Europe and the Western Pacific Region for the SENTRY Antimicrobial Surveillance. *Clinical Infectious Diseases*, 32(S2), pp. 114-132.

England Surveillance Programme for Antimicrobial Use and Resistance (ESPAUR), 2015. England Surveillance Programme for Antimicrobial Use and Resistance (ESPAUR) 2010 - 2014 Report, London: Public Health England. Available from:

https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobialutilisation-and-resistance-espaur-report

England Surveillance Programme for Antimicrobial Use and Resistance (ESPAUR), 2017. England Surveillance Programme for Antimicrobial Use and Resistance (ESPAUR) Report 2017, London: Public Health England. Available from: https://www.gov.uk/government/publications/englishsurveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report

Essack, S; Connolly, C; Sturm, AW. Antibiotic Use and Resistance in Public Sector Hospitals in KwaZulu Natal. *South African Medical Journal*, 95(11), pp 865- 870.

Essack, S., Abotsi, R., Desta, A. & Agoba, E., 2016. Antimicrobial Resistance in Africa – Roadmap for Action, 2016. *Journal of Public Health*, 39(1), pp. 8-13. Available at: http://jpubhealth.oxfordjournals.org/content/early/2016/03/03/pubmed.fdw015.full.pdf+html [Accessed 6 April 2016].

European Centre for Disease Prevention and Control, 2015. Antimicrobial Resistance Surveillance in Europe. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) 2014, Stockholm: ECDC. Available from: https://ecdc.europa.eu/en/publications-data/antimicrobial-resistance-surveillance-europe-2014

European Centre for Disease Prevention and Control, 2017. Antimicrobial Resistance Surveillance in Europe. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net) 2016, Stockholm: ECDC. Available from: https://ecdc.europa.eu/en/publications-data/antimicrobial-resistance-surveillance-europe-2016

European Committee on Antimicrobial Susceptibility Testing, 2016. EUCAST Organization. [Online] Available at: http://www.eucast.org/organization/eucaststatutes/ [Accessed 17 April 2016]. Felmingham, D; White, AR; Jacobs, MR; Appelbaum, PC; Poupard, J; Miller, LA; Gruneberg, RN, 2005. The Alexander Project: the benefits from a decade of surveillance. *Journal of Antimicrobial Chemotherapy*, 56(Suppliment 2), pp. ii3-ii21.

Fortuin-de Smit, MC; Singh-Moodley, A; Badat, R; Quan, V; Kularatne, R; Nana, T; Lekalakala, R; Govender, NP; Perovic, O, 2015. Staphylococcus aureus bacteraemia in Gauteng academic hospitals, South Africa. *International Journal of Infectious Diseases*, 30, pp. 41-48.

GERMS-SA, 2013. GERMS South Africa Anual Report 2013, Johannesburg: National Institute for Communicable Diseases. Available from: http://www.nicd.ac.za/index.php/publications/germs-annual-reports/

GERMS-SA, 2015. GERMS South Africa Anual Report 2015, Johannesburg: National Institute for Communicable Diseases. Available from: h8p://www.nicd.ac.za/assets/files/2015%20GERMS-SA% 20AR.pdf

Global Antibiotic Resistance Partnership-India National Working Group, 2011. Situation Analysis: Antibiotic Use and Resistance in India, New Delhi: The Centre for Disease Dynamics, Economics and Policy. Available from:

https://www.cddep.org/publications/situation\_analysis\_antibiotic\_use\_and\_resistance\_india/

Gelband, H. & Duse, A., 2011. The Global Antibiotic Resistance Partnership (GARP). *South African Medical Journal*, 101(8), pp. 552-555.

Grundmann, H; Glasner, C; Albiger, B; Aanensen, DM; Tomlinson, CT; Tambic Andrasevic, A;
Canton, R; Carmeli, Y; Friedrich, AW; Giske, CG; Glupczynski, Y; Gniadkowski, M; Livermore,
DM; Nordmann, P; Poirel, L; Rossolini, GM; Seifert, H; Vatopoulos, A; Walsh, T; Woodford, N;
Monnet, DL; European Survey of Carbapenemase-Producing Enterobacteriaceae (EuSCAPE)
Working Group, 2017. Occurrence of carbapenemase-producing *Klebsiella pneumoniae* and *Escherichia coli* in the European survey of carbapenemase-producing *Enterobacteriaceae* (EuSCAPE): a prospective, multinational study. *The Lancet. Infectious Diseases*, 17 (2), pp. 153 - 163.

Hoban, DJ; Doern, GV; Fluit, AC; Roussel-Delvalles, M; Jones, RN, 2001. Worldwide Prevalence of Antimicrobial Resistance in Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis in the SENTRY Antimicrobial Resistance Programme, 1997-1999. *Clinical Infectious Diseases*, 32(S2), pp. 81-93.

Hoffman, SJ; Caleo, GM; Daulaire, N; Elbe, S; Matsoso, P; Mossialos, E: Rizvi, Z; Røttingen, JA, 2015. Strategies for achieving global collective action on antimicrobial resistance. *Bulletin of the World Health Organisation*, 93(12), pp. 867-876.

Holloway, K., Mathai, E. & Gray, A., 2011. Surveillance of antimicrobial resistance in resourceconstrained settings – experience from five pilot projects. *Tropical Medicine and International Health*, 16(3), pp. 368-374.

Kacou-Ndouba, A., Revathi, G., Mwathi, P., Seck, A., Diop, A., Kabedi-Bajani, MJ., Mwiti , W., Anguibi-Pokou, MJ., Morrissey, I., Torumkuney, D., 2016. Results from the Survey of Antibiotic Resistance (SOAR) 2011-14 in the Democratic Republic of Congo, Ivory Coast, Republic of Senegal and Kenya. *Journal of Antimicrobial Chemotherapy*, 71(S1) i21-i31. Available from: https://academic.oup.com/jac/article/71/suppl\_1/i21/2488613. doi:10.1093/jac/dkw070

Leopold, S., van Leth, F., Tarekegn, H. & Schultz, C., 2014. Antimicrobial drug resistance among clinically relevant bacterial isolates in sub-Saharan Africa: a systematic review. *Journal of Antimicrobial Chemotherapy*, 69(9), pp. 2337-2353.

Lewis, DA; Gumede, LYE; van der Hoven, LA; de Gita, GN; EJE, de Kock; de Lange, T; C, Maseko; Kekana, V; Smuts, FP; Perovic, O, 2013 (a). Antimicrobial susceptibility of organisms causing community-acquired urinary tract infections in Gauteng Province, South Africa. *South African Medical Journal*, 103(6), pp. 377-381.

Lewis, DA; Sriruttan, C; Müller, EM; Golparian, D; Gumede, L; Fick, D; de Wet, J; Maseko, V; Coetzee, JJ; Unemo, M, 2013(b). Phenotypic and genetic characterisation of the first two cases of extended-spectrum cephalosporin resistant Neisseria gonorrhoeae infection in South Africa and association with cefixime treatment failure. *Journal of Antimicrobial Chemotherapy*, 68 (6), pp 1267 -1270. Available at: http://jac.oxfordjournals.org/content/early/2013/02/14/jac.dkt034.full.pdf+html [Accessed 4 June 2016].

Ligozzi, M; Bernini, C; Bonora, MG; de Fatima, M; Zuliani, J; Fontana, R, 2002. Evaluation of the Vitek 2 System for Identification and Antimicrobial Susceptibility Testing of Medically Relevant Gram-positive Cocci. *Journal of Clnical Microbiology*, 40(5), pp. 1681-1686.

Masterton, R., 2000. Surveillance studies: How can they help the management of infection?. *Journal of Antimicrobial Chemotherapy*, 46(S2), pp. 53-58.

Masterton, R., 2008. The Importance and Future of Antimicrobial Surveillance Studies. *Clinical Infectious Diseases*, 47(S1), pp. 21-31.

Mendelson, M. & Matsotso, M., 2015. The South African Antimicrobial Resistance Strategy Framework. *Antimicrobial Resistance Control 2015*, Issue Monitoring, Surveillance And National Plans, pp. 54-61.

National Institute for Communicable Diseases, 2015. Publications: NICD Monthly Surveillance Report. [Online] Available at: http://www.nicd.ac.za/?page=surveillance\_report&id=15 [Accessed 6 June 2016]. Opintan, JA; Newman, MJ; Arhen, RE; Donkor, ES; Gyansa-Lutterdt, M; Mills-Pappoe, W, 2015. Laboratory-based nationwide surveillance of antimicrobial resistance in Ghana. *Infection and Drug Resistance*, 18(8), pp. 379-389.

Pan American Health Organisation, 2016. *Topics: Antimicrobial Resistance*. [Online] Available at: http://www.paho.org/data/index.php/en/mnu-topics/antimicrobial-resistance.html [Accessed 21 April 2016].

Patzer, J., Dzierzanowska, D. & Turner, P., 2008. Trends in Antimicrobial Susceptibility of Gramnegative Isolates from a Paediatric Intensive Care Unit in Warsaw: Results from the MYSTIC Programme 1997-2007. *Clinical Infectious Diseases*, 62(2), pp. 369-375.

Perovic, O., Chetty, V. & Iyaloo, S., 2014. Antimicrobial Resistance Surveillance from Sentinel Public Hospitals, South Africa, 2014 (a). *Communicable Diseases Surveillance Bulletin*, 13(1), pp. 1-12.

Perovic, O; Duse, A; Elliot, G; Swe Swe-Han, K; Kularatne, R; Lowman, W; Nana, T; Lekalakala, R; Marais, E, 2014(b). National sentinel site surveillance for antimicrobial resistance in Klebsiella pneumoniae isolates in South Africa, 2010 - 2012. *South African Medical Journal*, 104(8), pp. 563-568.

Perovic, O; Iyaloo, S; Kularatne, R; Lowman, W; Bosman, N; Wadula, J; Seetharam, S; Duse, A; Mbelle, N; Bamford, C; Dawood, H; Mahaber, Y; Bhola, P; Abrahams, S; Singh-Moodley, A, 2015. Prevalence and Trends of Staphylococcus aureus Bacteraemia in Hospitalized Patients in South Africa, 2010 to 2012: Laboratory-Based Surveillance Mapping of Antimicrobial Resistance and Molecular Epidemiology. *PLoS ONE*, 10(12), pp. 1-14.

Ramsamy, Y., Muckart, D. J. J. & Swe Swe-Han, K., 2013. Microbiological surveillance and antimicrobial stewardship minimise the need for ultrabroad-spectrum combination therapy for treatment of nosocomial infections in a trauma intensive care unit: An audit of an evidence-based empiric antimicrobial policy. *South African Medical Journal*, 103(6), pp. 371-376.

ReAct, 2009. Summary report: INDEPTH-ReAct workshop on Antibiotic Resistance, Pune: ReAct.

Shaban, R., Cruickshank, M., Christiansen, K. & Antimicrobial Resistance Standing Committee, 2013. National Surveillance and Reporting of Antimicrobial Resistance and Antibiotic Usage for Human Health in Australia. Canberra: Antimicrobial Resistance Standing Committee.

Singh-Moodley, A., Ekermans, P. & Perovic, O., 2015. Emerging Carbapenem-Resistant Enterobacter cloacae Producing OXA-48-, VIM- and IMP-Type-β-Lactamases in Eastern Cape Hospitals in South Africa. *Open Journal of Medical Microbiology*, 5(4), pp. 246-253.

Swe Swe-Han, K. & Coovadia, Y., 2010. Prevalence of Antimicrobial Resistant Bacteria from Adult ICUs and the Burns Unit at a Large Tertiary Hospital in Durban. *International Journal of Infection Control*, 6(2), pp 1 - 8.

Tapsall, J., Limnios, E. & Murphy, D., 2008. Analysis of trends in antimicrobial resistance in Neisseria gonorrhoeae isolated in Australia, 1997–2006. *Journal of Antimicrobial Chemotherapy*, 62(1), pp. 150-155.

Turner, P., 2000. MYSTIC (Meropenem Yearly Susceptibility Test Information Collection): a global overview. *Journal of Antimicrobial Chemotherapy*, 46(S2), pp. 9-23.

U.S. Centers for Disease Control and Prevention, 2009. CDC Southeast Asia Regional Office Annual Report, Nonthaburi: U.S. Centers for Disease Control and Prevention.

Vernet, G; Mary, C; Altman, DM; Doumbo, O; Morpeth, S; Bhutta, ZA; Klugman, KP, 2014. Surveillance for Antimicrobial Drug Resistance in Under-Resourced Countries. *Emerging Infectious Diseases*, 20(3), pp. 434-441.

World Health Organisation South-East Asia, 2010 (a). Regional Strategy on Prevention and Containment of Antimicrobial Resistance. [Online] Available at: http://www.searo.who.int/entity/antimicrobial\_resistance/documents/en/ [Accessed 3 March 2016].

World Health Organisation, 2010 (b). Asia Pacific Strategy for Strengthening Health Laboratory Services 2010-2015, Geneva: World Health Organisation. Available from: http://apps.searo.who.int/PDS\_DOCS/B4531.pdf

World Health Organisation, 2011. Laboratory-based surveillance of Antimicrobial Resistance: Report of Regional Workshop, Chennai, Chennai: World Health Organisation. Available from: http://apps.who.int/medicinedocs/en/d/Js20134en/

World Health Organisation, 2014(a). Antimicrobial Resistance Global Report on Surveillance, France: World Health Organisation. Available from: http://www.who.int/drugresistance/documents/surveillancereport/en/

World Health Organisation, 2014(b). Central Asian and Eastern European Surveillance of Antimicrobial Resistance Annual Report 2014, Geneva: World Health Organisation. Available from: http://www.euro.who.int/\_\_data/assets/pdf\_file/0006/285405/CAESAR-Surveillance-Antimicrobial-Resistance2014.pdf

World Health Organisation, 2014 (c). WHO global platform for collaborative surveillance of antimicrobial resistance: Standards for Antibacterial resistance, Geneva.: World Health Organisation.

World Health Organisation, 2015 (a). Global Action Plan on Antimicrobial Resistance. [Online] Available at: http://www.who.int/drugresistance/global\_action\_plan/en/ [Accessed 12 June 2016].

World Health Organisation, 2015 (b). Global Antimicrobial Surveillance System: Manual for Early Implementation. [Online] Available at: http://www.who.int/drugresistance/surveillance/en/ [Accessed 26 February 2016].

World Health Organisation, 2015 (c). Media Centre: Fact Sheets: Antimicrobial resistance. [Online] Available at: http://www.who.int/mediacentre/factsheets/fs194/en/ [Accessed 21 April 2016].

World Health Organisation, 2016. Immunisation, Vaccines and Biologicals. [Online] Available at:

http://www.who.int/immunization/monitoring\_surveillance/burden/vpd/surveillance\_type/sentinel/en/ [Accessed 21 April 2016].

World Health Organisation, 2016. Implementation of the Global Action Plan on Antimicrobial Resistance. *WHO GAP AMR Newsletter*, Issue 7. Available from: http://www.who.int/antimicrobial-resistance/news/newsletter/en/

World Health Organisation, 2017 (a). Public health surveillance. [Online] Available at: http://www.who.int/topics/public\_health\_surveillance/en/

[Accessed 14 December 2017]

World Health Organisation, 2017 (b). Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. [Online] Available at: http://www.who.int/medicines/publications/WHO-PPL-Short\_Summary\_25Feb-ET\_NM\_WHO.pdf

# **CHAPTER 2. MANUSCRIPT**

The findings are reported in the following manuscript intended for submission to the Bulletin of the World Health Organisation:

A Retrospective Trend Analysis of Antibiotic Resistance in GLASS Pathogens in KwaZulu Natal: 2011-2015

Patel, M, Mlisana, KP, Ramsamy, Y, Sartorius B and Essack, SY.

- Miriam Patel, as the principal investigator, co-conceptualized the study, undertook data cleaning, alignment and calculations, compilation of tables and figures and drafted the manuscript
- Koleka Mlisana, as co-supervisor, co-conceptualised the study and undertook a critical review of the manuscript.
- Yogandree Ramsamy, undertook data extraction, cleaning and alignment, assisted in review of results and undertook a critical review of the manuscript
- Ben Sartorius, undertook statistical analysis and critical review of the manuscript
- Sabiha Yusuf Essack, as principal supervisor, co-conceptualised the study, reviewed data analysis and undertook a critical review of the manuscript.

# A Retrospective Trend Analysis of Antimicrobial Resistance in GLASS pathogens in KwaZulu Natal: 2011- 2015

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#### Abstract

**Objective:** Antibiotic resistance trends in pathogen-drug combinations stipulated in the Global Antimicrobial Surveillance System (GLASS) of the World Health Organization were investigated for the period 2011-2015 in KwaZulu-Natal, South Africa.

**Methods:** Antibiotic susceptibility data from blood, urine, faecal and urethral/cervical samples was retrospectively analyzed from six public hospitals. Pathogens included *Escherichia coli*, *Streptococcus pneumoniae, Klebsiella pneumoniae, Salmonella spp., Acinetobacter baumannii, Staphylococcus aureus, Shigella spp. and N. gonorrhoea.* Results included MIC50, MIC90, percentage resistance, incidence of infections in the population and proportion of non-susceptible infections. Results were also evaluated against South African treatment guidelines. Significant differences in resistance proportions by year were identified using the Pearson  $\chi^2$  test. Comparison of MIC50 were analysed using the equality-of-medians test.

**Findings:** Urine samples were most abundant (61.22%, n= 33 018) and *E. coli* (52%) was the most common pathogen. Most isolates were multi-drug resistant and resistance to cephalosporins and fluoroquinolones increased in *K. pneumoniae*, *E. coli* and *Shigella spp*. Notable changes in resistance were: *K. pneumoniae* from blood samples to carbapenems (1 - 26%, p< 0.001) and *A. baumannii* to carbapenems (69% - 50%, no p-value). Susceptibility to antibiotics recommended in treatment guidelines was >50% for most pathogen-drug combinations.

**Conclusion:** Although resistance in some pathogen-drug combinations plateaued or declined, antibiotic resistance in hospitals in KwaZulu-Natal increased from 2011 to 2015, necessitating a review of the existing treatment guidelines. To our knowledge, this is the first South African report on ABR using GLASS metrics. There is a need for more extensive research in order to build an accurate picture of ABR in South Africa.

# Introduction

Antibiotics are essential for treating bacterial infections however antibiotic resistance (ABR) has become a fast spreading phenomenon which is limiting treatment options for common infections. A key strategic objective of the Global Action Plan (GAP) on Antimicrobial Resistance (AMR), adopted by member states of the World Health Organisation (WHO) in 2015, is to strengthen the knowledge and evidence base through surveillance and research. Surveillance was highlighted as an important tool in mapping out the prevalence, trends and mechanisms of ABR to understand the extent of the problem on a global scale <sup>(1)</sup>. The 2014 surveillance report on antimicrobial resistance published by the WHO highlighted the scarcity of reliable data on ABR in Africa as not many countries in the region carry out surveillance compared to the relatively well-established surveillance systems found in the European region. Inadequate funding, human resources and infrastructure limit the capacity for surveillance in under-resourced countries <sup>(2)</sup>. As such, there is a great need for surveillance in order to obtain information on the true extent of antibiotic resistance in the region.

ABR surveillance is more extensive in South Africa compared to other countries in the WHO Africa region. Existing literature from both public and private sector facilities indicate a decline in efficacy of older antibiotics such as ampicillin and tetracycline and more recently, cephalosporins and fluoroquinolones. This has necessitated the increased use of carbapenems to treat resistant infections.<sup>(3)</sup> In addition, methicillin resistant *Staphylococcus aureus* (MRSA) as well as extended spectrum  $\beta$ -lactamase (ESBL) producing pathogens are prevalent. With the escalation of multi-drug resistant infections, treatment options are becoming more limited, making commonly encountered infections increasingly difficult to treat. <sup>(4)</sup>

While many countries are already conducting surveillance, there is a lack in uniformity in surveillance methods as well as the pathogens and antibiotics investigated. In order for data to be meaningful and comparable on a global scale, the WHO published the Global Antimicrobial Surveillance System (GLASS) manual which aimed to standardise surveillance methods to yield validated data reported in a uniform manner. Specific pathogen-drug combination for four specimen types namely blood, urine, stool and cervical/urethral swabs, were outlined and WHO member states are encouraged to implement GLASS as far as possible in order to provide a baseline database of ABR on a global scale that can be built on as surveillance methods become more firmly established <sup>(2)</sup>.

The purpose of this study was to illustrate antibiotic resistance trends in pathogen-drug combinations stipulated in GLASS for the period 2011-2015 in six public hospitals in the province of KwaZulu Natal, South Africa from blood, urine, stool and cervical/urethral samples indicative of blood stream infections (BSIs), urinary tract infections (UTIs), diarrhoeal infections and gonorrhoeal infections respectively. To our knowledge, this is the first South African report on ABR using GLASS metrics.

# Methods

# Study Design

Antibiotic susceptibility data from 2011 to 2015 was retrospectively extracted from the KwaZulu-Natal National Health Laboratory Services (NHLS) computerized database from six public sector hospitals in KwaZulu Natal, South Africa and included all levels of care from the first point of contact at district level o the centralized, specialized care at tertiary and quaternary levels.

The extracted de-duplicated data included specimen type, bacterial identity and antibiotic susceptibility results in the form of minimum inhibitory concentrations (MICs). The data was analysed to determine the trends in MICs and resistance in selected isolates during the study period. Only blood, urine and faecal samples positive for the pathogens of interest highlighted in the GLASS manual were included in the study. In terms of gonorrhoea, the data collected did not define urethral or cervical swabs as a specimen type and thus all *Neisseria gonorrhoea* specimens classified as "other" or with the specimen type missing were included. Priority pathogens for blood specimens included *Escherichia coli*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Salmonella spp.*, *Acinetobacter baumannii* and *Staphylococcus aureus*. Priority pathogens for urine samples were *E. coli* and *K. pneumoniae*. Priority pathogens for faecal samples were *Salmonella spp.* and *Shigella spp.* 

The population data for KwaZulu Natal required for the calculation of GLASS metrics was obtained from the results of the 2011 national census.<sup>(5)</sup>

# Ethical Considerations

The study was approved by the Biomedical Research Ethics Committee (BREC) (REF: BE085/12). All data was anonymized in order to maintain patient confidentiality.

### Antimicrobial Susceptibility Testing

Pathogen identification and susceptibility testing was carried out at each participating hospital on the VITEK 2 system (bioMerieux) according to the Clinical Laboratory Standards Institute (CLSI) guidelines and isolates were classified as sensitive or resistant using CLSI-approved breakpoints. Antibiotic panels per pathogen appear in Supplementary Table 1 as recommended by GLASS.

#### External Quality Assurance

The participating hospital laboratories subscribe to the NHLS Proficiency Testing Scheme (PTS) coordinated by the PTS Managers(Microbiology) at the NHLS Academic Affairs, Research and Quality Assurance(AARQA) Unit. The scheme entails quarterly evaluations for, amongst others, bacteriology. Microscopy, culture and identification methods and manual and automated antimicrobial susceptibility testing (AST) methods are evaluated based on samples prepared with the

assistance of the National Institute for Communicable Diseases (NICD) – Centre for Opportunistic, Tropical and Hospital Infections, a division of the NHLS.

# Statistical Analysis

All data processing and analyses were performed using Stata 13.0 software SE (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.). Categorical GLASS pathogen data were presented using stratified frequency tables (n and %). Differences in MIC50 levels over the period of 2011-2015 were assessed using a non-parametric equality-of-medians test. Differences or trends or association for resistance types and year for example was assessed using the standard Pearson's chi-square ( $\chi$ 2) test. If expected cell count in the cross tabulation contained fewer than 5 observations (sparse numbers) then the Fishers exact test was utilized instead. A p-value of <0.05 was considered statistically significant.

## Results

Table 1 illustrates the number of isolates per specimen type and pathogen between 2011 and 2015. Isolate numbers for 2014 are not accurate as six months of data from one of the participating hospitals was missing from the NHLS database. The number of samples positive for any of the GLASS pathogens increased more than two-fold from 4 737 collected in 2011 to 10 289 collected in 2015. Blood (n=11 722) and urine (n=20 212) samples formed the vast majority of specimens. The most frequently isolated pathogen was *E. coli* from urine specimens constituting 56.08% (n=33018) of the isolates over the five-year study period.

Specimen Type	2011	2012	2013	2014	2015	Total	P-value*
Blood	1792 (37.83)	2391 (37.26)	2823 (37.42)	1353 (33.56)	3363 (32.69)	11722 (35.50)	< 0.001
E. coli	397 (8.38)	441 (6.87)	417 (5.53)	221 (5.48)	609 (5.92)	2085 (6.31)	< 0.001
K. pneumoniae	373 (7.87)	577 (8.99)	698 (9.25)	358 (8.88)	1053 (10.23)	3059 (9.26)	< 0.001
A. baumanii	248 (5.24)	341 (5.31)	483 (6.4)	147 (3.65)	353 (3.43)	1572 (4.76)	< 0.001
S. aureus	543 (11.46)	773 (12.05)	890 (11.8)	471 (11.68)	1110 (10.79)	3787 (11.47)	< 0.001
S. pneumoniae	188 (3.97)	179 (2.79)	238 (3.15)	118 (2.93)	170 (1.65)	893 (2.7)	< 0.001
Salmonella spp.	43 (0.91)	80 (1.25)	97 (1.29)	38 (0.94)	68 (0.66)	326 (0.99)	< 0.001
Urine	2808 (59.28)	3859 (60.15)	4451 (58.99)	2494 (61.87)	6600 (64.15)	20212 (61.22)	< 0.001
E. coli	2202 (46.49)	2936 (45.76)	3257 (43.17)	1907 (47.31)	4913 (47.75)	15215 (46.08)	< 0.001
K. pneumoniae	606 (12.79)	923 (14.39)	1194 (15.83)	587 (14.56)	1687 (16.40)	4997 (15.13)	< 0.001
Faeces	102 (2.15)	142 (2.22)	237 (3.14)	163 (4.04)	272 (2.64)	916 (2.77)	< 0.001
Salmonella spp.	47 (0.99)	46 (0.72)	78 (1.03)	46 (1.14)	82 (0.80)	299 (0.91)	< 0.001
Shigella spp.	55 (1.16)	96 (1.50)	159 (2.11)	117 (2.90)	190 (1.85)	617 (1.87)	< 0.001
Urethral/cervical	35 (0.74)	24 (0.37)	34 (0.45)	21 (0.52)	54 (0.52)	168 (0.51)	< 0.001
N. gonorrhoea	35 (0.74)	24 (0.37)	34 (0.45)	21 (0.52)	54 (0.52)	168 (0.51)	< 0.001
Total	4737 (100)	6416 (100)	7545 (100)	4031 (100)	10289 (100)	33018 (100)	

Table 1: Number of isolates per specimen type and pathogen between 2011 and 2015(percentage indicated in parenthesis)

\*Pearson's chi2p-value

### Antibiotic Resistance

The antibiotic resistance data was stratified by year and analysed on 3 levels: (1) a trend analysis of resistance including MIC50, MIC90, MIC range and percentage resistance over 5 years was conducted; (2) metrics recommended in the GLASS manual were calculated and (3) susceptibility data was compared with existing standard treatment guidelines. Table 2 illustrates the AST results over the study period for each specimen type (See Supplementary Table 2 for overall AST results for the study period).

The trends in resistance observed over the five years varied between the different pathogen-drug combinations. While the percentage resistance across most pathogen-drug combinations increased from 2011 to 2015, the MIC50 and MIC90 remained stable, with changes observed in only a few pathogen-drug combinations. *K. pneumoniae* isolates showed the most changes in MIC50 with statistically significant increases in MIC50 in isolates from urine samples for ceftazidime ( $\leq 1 \mu g/ml - 8 \mu g/ml$ , p= < 0.001), cefotaxime ( $\leq 1 \mu g/ml - 2 64 \mu g/ml$ , p < 0.001) and cefepime ( $\leq 1 \mu g/ml - 2 \mu g/ml$ , p< 0.001). Other pathogen-drug combinations that showed fluctuations in MIC50 were *A. baumannii* for - amikacin ( $4 \mu g/ml - 8 \mu g/ml$ , p= 0.001), gentamicin ( $\geq 16 \mu g/ml - 8 \mu g/ml$ , p-value not available) and imipenem ( $\geq 16 \mu g/ml - \leq 1 \mu g/ml$ , p-value not available); *E. coli* from urine samples for imipenem ( $\leq 1 \mu g/ml - \leq 1 \mu g/ml$ , p-( $\leq 0.001$ ); *Salmonella spp*. from faeces for ceftazime ( $4 \mu g/ml - \leq 1 \mu g/ml$ , p-( $\leq 1 \mu g/ml$ ).

p < 0.001). These changes in MIC50 corroborated the changes in percentage resistance observed. The majority of pathogens showed an increase in percentage resistance from 2011 to 2015, with the exception of A. baumannii isolates from blood samples as well as Salmonella spp. isolates from both blood and faecal samples. All A. baumannii isolates showed a decrease in resistance to all the antibiotics tested while Salmonella spp. isolates showed a decrease or plateau in resistance to all antibiotics tested except for ciprofloxacin in isolates from blood samples which only showed a 0.33% increase in resistance. A statistically significant ( $p \le 0.05$ ) increase in percentage resistance between 2011 and 2015 was observed in the following pathogen-drug combinations: E. coli isolates from blood samples for ceftazidime, cefotaxime, ciprofloxacin, imipenem; K. pneumoniae isolates from blood samples for ciprofloxacin, cefepime, ertapenem, imipenem, meropenem; E. coli isolates from urine samples for ceftazidime, cefotaxime, ertapenem, cefepime; K. pneumoniae isolates from urine samples for ceftazidime, ceftazidime, cefepime, ertapenem, imipenem, meropenem; and, Salmonella *spp.* isolates from faecal samples for ciprofloxacin. The escalating resistance to the broad spectrum cephalosporins, carbapenems and fluoroquinolones was evident. A statistically significant ( $p \le 0.05$ ) decrease in resistance between 2011 and 2015 was observed in the following pathogen-drug combinations: Salmonella spp. isolates from blood samples - ciprofloxacin, cefotaxime, ertapenem; Salmonella spp. isolates from faecal samples - cefotaxime, ceftazidime, ertapenem.

Table 2: AST Results by Year 2011 – 2015

| 235         26.81         <0.001         0.004           237         37.97         0.001         0.004           235         37.97         0.001         0.01           235         39.57         <0.001         0.001           235         39.57         <0.001         0.001           235         0.64         <0.001         0.001           235         0.64         <0.001         0.091           235         0.64         <0.001         0.091           234         1.71         <0.001         0.044*           216         0.93         0.563         0.591*           237         67.93         0.563         0.591*  
   
   
   | 235         2.6.81         <0.001         0.004           237         37.97         <0.001         0.01           237         37.97         <0.001         0.01           233         39.57         <0.001         0.001           232         0.64         <0.001         0.01           233         0.64         <0.001         0.092           234         1.71         <0.001         0.042           234         1.71         <0.001         0.042           234         1.71         <0.001         0.042           235         0.54         <0.0101         0.042           234         1.71         <0.001         0.044           20         9.33         0.563         0.591*           234         1.71         <0.01         0.44*           235         67.93         0.563         0.581*           237         67.93         0.563         0.581*           238         0.563         0.564         0.587*           231         9.74         0.563         0.581*   
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  | 235         2.6.81         <0.001         0.004           237         37.97         <0.001         0.01           237         37.97         <0.001         0.01           235         39.57         <0.001         0.01           235         0.64         <0.001         0.01           235         0.64         <0.001         0.04*           235         0.64         <0.001         0.04*           235         0.64         <0.001         0.04*           235         0.543         <0.001         0.04*           216         0.93         0.549*         0.567           216         0.93         0.540*         0.587           237         67.93         0.549*         0.68           84         MIC50         9.*R         0.60           84         MIC50         0.69         0.63           35.45         <0.001         0.03         0.59           35.45         <0.001         0.03         0.59           856         53.93         <0.001         0.03           35.45         <0.001         0.043         -  | 235         2.6.11         <0.001         0.004           237         37.97         <0.001         0.014           233         39.57         <0.001         0.011           233         39.57         <0.001         0.011           233         10.64         <0.001         0.012           233         10.64         <0.001         0.043           234         1.71         <0.001         0.043           235         10.64         <0.001         0.044           216         0.336         0.533         0.591*           235         1.71         <0.001         0.044*           216         0.33         0.543         0.591*           234         47.001         0.060         0.68           349         7.5.4         40.001         0.080           356         8.19         <0.001         0.043           *         4.001         0.043         -           354         8.109         .         0.043           *         4.001         0.043         -   
   
   
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   | 235         2.6.81         -0.001         0.004           27         3°.97         -0.001         -           235         39.57         -0.001         0.001           235         39.57         -0.001         0.001           235         0.64         -0.01         0.014           235         0.64         -0.01         0.044*           235         0.64         -0.01         0.044*           235         0.753         0.53*         0.573**           236         0.773**         0.59*         0.573**           236         0.73         0.59*         0.573**           236         0.793         0.59*         0.573**           234         171         -0.01         0.04*           37         67.93         -0.59*         0.573**           37         67.93         -0.50*         0.57*           37         67.93         -0.50*         0.67*           36         0.75*         0.01         0.00           36         37.64         -0.01         -0.01*           37         49         9.83         -0.01         -0.01*           36         26.93   
   
   | 235         2.6.81         -0.001         0.004           27         3°.97         -0.001         0.004           23         39.57         -0.001         0.011           235         39.57         -0.001         0.014           233         0.66         -0.3001         0.014           233         0.66         -0.301         0.044*           234         1.71         -0.001         0.044*           216         0.33         -0.563         0.591*           217         67.93         -0.591         0.44*           218         0.753         0.563         0.591*           218         0.753         0.563         0.591*           216         0.93         0.563         0.591*           217         67.93         -0.501         0.004           319         57.93         -0.001         0.001           324         25.07         -0.001         -0.001           324         25.07         -0.001         -0.001*           324         25.07         -0.001         -0.001*           335         3.41         -0.001         -0.001* <tr td="">         -0.001         -0.001*</tr>  
   
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  | 235         5.6.1         -0.001         0.004           23         3'.9.7         -0.001         0.001           23         3'.5.7         -0.001         0.001           235         3'.5.7         -0.001         0.001           235         0.64         -0.01         0.014           235         0.66         -0.001         0.044*           235         0.56         -0.573**         0.573**           235         0.93         0.591*         0.567           235         0.93         0.591*         0.587           235         57.93         0.591*         0.587           236         73.64         -0.01         0.000           355         53.93         0.510         0.030           356         53.93         -0.01         0.010           356         53.93         -0.01         0.01           356         53.93         -0.01         0.01           357         54.91         -0.01         -0.01           353         26.25         -0.01         -0.01           353         25.25         -0.01         -0.01           353         26.01         -0.01 <th>235         2.6.81         -0.001         0.004           237         37.97         -0.001         0.001           233         39.57         -0.001         0.001           233         39.57         -0.001         0.001           233         0.86         0.336         0.373 ***           232         0.86         0.301         0.044*           233         0.543         0.591*         0.587           234         171         -0.001         0.044*           216         0.33         0.563         0.591*           235         57.93          0.587           235         57.93          0.587           335         57.36         0.576         0.591*           349         26.07          0.01           349         26.07          0.01           349         26.07          0.01           349         26.07          0.01           349         26.07          0.01           349         26.07          0.01           349         26.07          0.01</th> <th></th> <th>235         2.6.81         -0.001         0.004           23         3°.9.57         -0.001         0.001           23         39.57         -0.001         0.001           235         39.57         -0.001         0.013           233         0.58         0.390         0.373 ssc.           234         1.71         -0.001         0.044*           234         1.71         -0.001         0.044*           234         77.93          0.587           234         77.93          0.587           349         75.64         -0.001         0.080           349        
2.001         0.0101            349         2.001         -0.011            349         2.001          0.001           349         2.001          0.001           349         2.001          0.001           349         2.001          0.001           349         2.001          0.001           349         2.010          0.001           349         2.010        </th> <th></th> <th></th> <th>235         2.6.81         -0.001         0.004           23         3°.57         -0.001         0.001           23         3°.57         -0.001         0.001           235         3°.57         -0.001         0.014           233         0.68         -0.001         0.044*           233         0.64         -0.01         0.044*           234         171         -0.001         0.044*           234         171         -0.001         0.044*           234         77.93          0.587           234         77.64         -0.001         0.080           349         75.64         -0.01         0.016*           349         26.07         -0.01         -0.01*           349         26.33         -0.001         -0.01*           349         26.37         -0.001         -0.01*           349         26.37         -0.001         -0.01*           349         26.37         -0.001         -0.01*           349         26.37         -0.001         -0.01*           349         26.37         -0.001         -0.01*           349         26.37         <td< th=""><th>235         2.6.81         -0.001         0.004           23         3°.57         -0.001         0.001           23         3°.57         -0.001         0.001           233         0.86         0.396         0.373           233         0.64         -0.001         0.014           233         0.64         -0.001         0.044*           234         1.71         -0.001         0.044*           216         0.93         0.553         0.591*           234         173.04         -0.001         0.080           349         75.04         -0.001         0.001*           349         26.07         -0.01         -0.01*           349         26.33         -0.001         -0.01**           349         26.35         -0.001         -0.01**           349         26.37         -0.001         -0.01**           349         26.35         -0.001         -0.01**           349         26.37         -0.001         -0.01**           349         26.37         -0.001         -0.01**           349         26.37         -0.001         -0.01**           349         26.37</th><th>233         2.6.81         -0.001         0.004           231         5.7.97         -0.001         0.001           232         0.86         -0.396         0.373           233         0.64         -0.001         0.014           233         0.66         0.376         0.573           233         0.66         0.376         0.573           234         171         -0.001         0.044*           235         0.563         0.591*         0.587           234         171         -0.001         0.044*           235         5.33         0.563         0.591*           335         57.361         -0.001         0.001           349         25.03         -0.01         0.010           343         25.33         -0.001         -0.01*           343         25.35         -0.001         -0.01*           343         25.35         -0.001         -0.01*           343         25.35         -0.001         -0.01*           343         25.35         -0.001         -0.01*           343         25.35         1.41         -         0.01*           343         25.35&lt;</th><th><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></th><th><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></th><th><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></th><th></th></td<></th>  | 235         2.6.81         -0.001         0.004           237         37.97         -0.001         0.001           233         39.57         -0.001         0.001           233         39.57         -0.001         0.001           233         0.86         0.336         0.373 ***           232         0.86         0.301         0.044*           233         0.543         0.591*         0.587           234         171         -0.001         0.044*           216         0.33         0.563         0.591*           235        
57.93          0.587           235         57.93          0.587           335         57.36         0.576         0.591*           349         26.07          0.01           349         26.07          0.01           349         26.07          0.01           349         26.07          0.01           349         26.07          0.01           349         26.07          0.01           349         26.07          0.01   |   
   | 235         2.6.81         -0.001         0.004           23         3°.9.57         -0.001         0.001           23         39.57         -0.001         0.001           235         39.57         -0.001         0.013           233         0.58         0.390         0.373 ssc.           234         1.71         -0.001         0.044*           234         1.71         -0.001         0.044*           234         77.93          0.587           234         77.93          0.587           349         75.64         -0.001         0.080           349         2.001         0.0101            349         2.001         -0.011            349         2.001          0.001           349         2.001          0.001           349         2.001          0.001           349         2.001          0.001           349         2.001          0.001           349         2.010          0.001           349         2.010   
   |   |   
   | 235         2.6.81         -0.001         0.004           23         3°.57         -0.001         0.001           23         3°.57         -0.001         0.001           235         3°.57         -0.001         0.014           233         0.68         -0.001         0.044*           233         0.64         -0.01         0.044*           234         171         -0.001         0.044*           234         171         -0.001         0.044*           234         77.93          0.587           234         77.64         -0.001         0.080           349         75.64         -0.01         0.016*           349         26.07         -0.01         -0.01*           349         26.33         -0.001         -0.01*           349         26.37         -0.001         -0.01*           349         26.37         -0.001         -0.01*           349         26.37         -0.001         -0.01*           349         26.37         -0.001         -0.01*           349         26.37         -0.001         -0.01*           349         26.37 <td< th=""><th>235         2.6.81         -0.001         0.004           23         3°.57         -0.001         0.001           23         3°.57         -0.001         0.001           233         0.86         0.396         0.373           233         0.64         -0.001         0.014           233         0.64         -0.001         0.044*           234         1.71         -0.001         0.044*           216         0.93         0.553         0.591*           234         173.04         -0.001         0.080           349         75.04         -0.001         0.001*           349         26.07         -0.01         -0.01*           349         26.33         -0.001         -0.01**           349         26.35         -0.001         -0.01**           349         26.37         -0.001         -0.01**           349         26.35         -0.001         -0.01**           349         26.37         -0.001         -0.01**           349         26.37         -0.001         -0.01**           349         26.37         -0.001         -0.01**           349         26.37</th><th>233         2.6.81         -0.001         0.004           231         5.7.97         -0.001         0.001           232         0.86         -0.396         0.373           233         0.64         -0.001         0.014           233         0.66         0.376         0.573           233         0.66         0.376         0.573           234         171         -0.001         0.044*           235         0.563         0.591*         0.587           234         171         -0.001         0.044*           235         5.33         0.563         0.591*           335         57.361         -0.001         0.001           349         25.03         -0.01         0.010           343         25.33         -0.001         -0.01*           343         25.35         -0.001         -0.01*           343         25.35         -0.001         -0.01*           343         25.35         -0.001         -0.01*           343         25.35         -0.001         -0.01*           343         25.35         1.41         -         0.01*           343         25.35&lt;</th><th><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></th><th><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></th><th><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></th><th></th></td<>  | 235         2.6.81         -0.001         0.004           23         3°.57         -0.001         0.001           23         3°.57         -0.001         0.001           233         0.86         0.396         0.373           233         0.64         -0.001         0.014           233         0.64         -0.001         0.044*           234         1.71         -0.001         0.044*           216         0.93         0.553         0.591*           234         173.04         -0.001         0.080           349         75.04         -0.001         0.001*           349         26.07         -0.01         -0.01*           349         26.33         -0.001         -0.01**           349         26.35         -0.001         -0.01**           349         26.37         -0.001         -0.01**           349         26.35         -0.001         -0.01**           349         26.37         -0.001         -0.01**           349         26.37         -0.001         -0.01**           349         26.37         -0.001         -0.01**           349         26.37  
  | 233         2.6.81         -0.001         0.004           231         5.7.97         -0.001         0.001           232         0.86         -0.396         0.373           233         0.64         -0.001         0.014           233         0.66         0.376         0.573           233         0.66         0.376         0.573           234         171         -0.001         0.044*           235         0.563         0.591*         0.587           234         171         -0.001         0.044*           235         5.33         0.563         0.591*           335         57.361         -0.001         0.001           349         25.03         -0.01         0.010           343         25.33         -0.001         -0.01*           343         25.35         -0.001         -0.01*           343         25.35         -0.001         -0.01*           343         25.35         -0.001         -0.01*           343         25.35         -0.001         -0.01*           343         25.35         1.41         -         0.01*           343         25.35<  | $ \begin{array}{c c c c c c c c c c c c c c c c c c c $   | $ \begin{array}{c c c c c c c c c c c c c c c c c c c $  
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| 1         16         s1-264         235           25         24         20.25-24         237           1         26.5         30.56         24         236           5         50.5         30.56         24         237           1         26.5         30.56         24         235           5         30.5         30.56         24         235           5         50.5         50.56         235         235           5         50.26         50.26         236         235           26         50.26         50.26         216         234           27         30.56         50.26         206         237           28         50.26         50.26         216         216           28         50.26         50.26         216         216           29         20.23         50.0<         200         237   
   
   
   | 1         16         s1-264         235           25         24         3025-24         237           1         26.5         30.56-84         235           5         30.5         30.56-84         235           5         50.5         50.56-44         235           5         50.5         50.56-46         235           25         50.55         50.52-266         246           25         50.25         50.52-266         216           26         2325         20.52-261         234           20         2320         510-2200         237           20         2320         810.92         81.86         n   
  | I         16         s1-264         235           25         s0.5         s0.25         s4         237           1         26.5         s0.5         s4         237           5         s0.5         s0.5         s0.5         s37           5         s0.5         s0.5         s4         235           5         s0.5         s0.5         s1.5         4           5         s0.5         s0.5         s1.5         4         235           25         s0.5         s0.5         s2.5         235         235           26         s0.25         s0.55         s16         246         237           26         s0.25         s0.25         s16         246         237           27         s0.25         s0.25         s16         216         216           20         s20         s10.25         s10         237         216           20         s20         s10.6         s16         316         316           20         s24         s1.84         s1.84         317         317           20         s4         s1.84         s1.85         316         316   
   
   
  | I         16         s1-264         235           25         24         20.25-24         237           1         26.5         30.25-24         237           5         30.5         30.5-24         235           1         26.5         30.5-4         235           5         30.5         30.5-4         235           16         51.5         30.5-26         216           25         50.25         30.5-26         216           26         30.25-26         216         216           20         230.5         30.25-26         216           26         32.5         30.25-26         316           27         20.15         215         216           28         40.25-28         316         316           20         230         317         2015           26         4         50.25         316         316           5         4         50.25         316         316           5         4         316         316         316           5         4         310.55         316         316  | I         16         s1-264         235           25         24         0.25-24         237           1         26.5         50.5         24         237           5         50.5         50.5         50.5         235           5         50.5         50.5         24         235           5         50.5         50.5         44         235           15         50.5         50.25-246         235           25         50.25         50.25-246         216           25         50.25         50.25-246         216           26         2325         50.25-246         316           26         2325         50.25-246         316           20         2320         510-2320         237           2015         2015         2015         2015           5         4         50.25-86         349           5         4         50.5-246         349           5         4         50.5-246         349           5         4         50.5-266         349           5         4         50.5-266         349           5         4         5  
   
   
   | 1         16         s1-264         235           25         24         3025-241         237           1         26.5         30.55         24         235           5         30.5         30.56         24         235           5         50.5         30.5-4         235         235           5         50.5         30.5-4         235         235           26         50.25-26         236         236         235           25         50.25-26         236         236         237           26         30.25-26         236         237         236           27         20.25         20.5-26         236         237           28         20.25         20.25-26         349         349           50         MC09         Range         n         349           50         20.5-266         349         349         349           55         24         50.5-266         349         349           56         4         51-264         349         349           56         25         25         25         25         349           56         26   
   | 1         16         s1-264         235           25         24         30.25-24         237           1         26.5         30.55-24         237           5         30.5         30.55-24         235           5         50.5         30.55-44         235           5         50.5         30.55-42         235           25         50.55         50.25-266         216           26         50.25         20.55-266         216           26         20.55         20.55-266         316           20         2320         510.25-286         349           5         0.MC09         Range         n           5         4         50.57-286         349           5         4         50.57-864         349           5         20         80.5-864         349           5         26         4         51-264         349           5         26         4         51-264         349           5         26         21-264         349           5         26         21-264         349           5         26         51-264         349     <   
   
   | i         i6         s1-264         235           25         s0.25         s4         237           5         s0.55         s0.25         s4         237           5         s0.55         s0.55         s0.55         s35           5         s0.55         s0.55         s235         s35           5         s0.55         s0.55         s234         234           5         s0.55         s0.25         s26         234           26         s0.25         s0.25         s26         234           20         s320         s010         s232         s16         249           20         s320         s010         s205         s16         349           5         MIC90         Runge         n         366         349           5         add         s15-s6d         319         36           6         add         s15-s6d         319         36   
   
  | I         16         s1-264         235           25         50,5         43         20,25-24         237           5         50,5         50,5         45,2         235           5         50,5         50,5         50,5         235           5         50,5         50,5         50,5         234           5         50,5         50,5         234         233           6         30,25         50,5         20,5         24         234           26         30,25         50,25         26,5         216         216           20         2320         510         231         216         216           27         2015         50,25         26         349         349           5         204         3-20,25         339         356         356           5         24         50,25         30,5         366         349         356         356         356         356         356         356         356         356         356         356         356         356         356         356         356         356         356         356         366         349         366   
   
  | i         i6         s1-264         235           25         s0.25         s4         237           5         s0.55         s0.55         s4         235           5         s0.55         s0.55         s0.55         s35           5         s0.55         s0.55         s0.55         s35           5         s0.55         s0.55         s26         s24           55         s0.25         s0.25         s6         234           26         s0.25         s0.25         s0.55         s34           26         MIC90         Range         n         s6           56         MIC90         Range         n         s6           57         s0         s0.25-s6         349         s6           56         S0.25-s6         313         s6         s6           56         MIC90         Range         n         s6           56         s0         s6         s6         s6           57         s6         s0         s5-s6         s6           56         s0         s6         s6         s6           57         s6         s6         s6  
   
   | i         i6         s1-264         235           25         50,5         30,5-4         237           5         50,5         30,5-4         235           5         50,5         30,5-4         233           5         50,5         30,5-4         233           5         50,5         30,5-4         233           5         50,5         50,5-246         234           20         2320         517-8         234           20         2320         517-8         234           20         2320         517-84         349           20         2320         517-84         349           5         84         51-864         349           5         84         52-86         349           5         84         51-864         349           5         84         51-864         349           5         84         51-864         349           5         84         51-864         349           5         84         51-864         349           5         86         80,5-86         349           5         86         60  
   | I         I6         s1-264         235           25         50,5         30,25         -84         237           5         50,5         30,55         -84         235           5         50,5         30,55         -4         235           5         50,5         50,55         -4         233           5         50,5         50,55         -26         234           26         80,25         50,25         26         234           26         80,25         80,25         26         234           26         80,25         80,25         26         234           26         80,25         20,25         26         237           27         2015         30,0         237         2616           28         80,5-26         319         9         9           5         26         4         319         9           5         28         80,5-28         319         9           5         28         80,5-28         319         9           5         28         80,5-28         319         9
          5         28         80,5-28   | I         16         s1-264         235           25         50.5         30.25-34         237           5         50.5         30.55-34         237           5         50.5         30.55-34         235           5         50.5         30.55-34         237           26         30.55         265-246         234           26         50.25         30.55-246         237           26         50.25         50.25-246         246           20         2320         517-232         237           26         50.25         50.25-246         349           26         50.25         50.25-246         349           27         2015         2015-248         349           26         4         50.25-28         346           5         2015-246         349         349           5         2015-246         349         349           5         24         51.56         349         349           26         266         50.52-286         349         349           27         284         50.52-286         349         349           26         286  
   | I         I6         s1-264         235           25         50.5         30.25-34         237           5         50.5         30.25-34         237           5         50.5         30.5-4         233           5         50.5         30.5-4         233           6         50.5         30.5-4         233           26         30.5         30.5-4         233           26         30.5         30.5-4         234           26         30.25         20.5-246         216           27         20.15         30.25-246         319           27         20.5         50.25-246         319           27         20.5         50.25-246         319           28         4        
50.5-246         319           5         20.5-246         319         316           5         20.5-246         319         319           5         24         50.5-246         319           5         26         20.5-246         319           26         21         21         20         221           27         28         20.5-246         319      2   
   | I         16         s1-264         235           25         50,5         43,5         20,5         -34           5         50,5         50,5         50,5         -35           6         50,5         50,5         40,5         -23           7         16         50,5         50,5         23           6         50,5         50,5         40,2         23           76         50,5         50,5         26,5         26           76         50,5         50,25         26         26           70         2320         517         23         26           70         2320         517         23         26           70         2320         517         23         35           70         2015         50,5         35         35           86         80,5-28         339         35         35           87         20,5         80,5-28         33         35           8         80,5-28         30,5         36         36           8         80,5-28         319         39         36           8         80,5-28         30,5  
  | I         I6         s1-264         233           25         50.5         30.25-34         237           5         50.5         30.55-34         237           5         50.5         30.55-34         233           5         50.5         50.55-34         233           5         50.5         50.55-246         234           26         50.25         20.25-246         234           26         50.25         50.25-246         216           26         50.25         50.25-246         319           26         50.25         50.25-246         319           27         2015         310-2320         237           28         50.25-246         319           29         50.25-246         319           26         51.5-26  
      319           27         2015         319           26         20.5-26         319           26         216         20.5-26         319           26         216         20.5-26         319           27         28         50.5-26         319           26         216         20.5-26         319 <tr< th=""><th>i         i6         s1-264         235           25         s0.5         s0.5         s0.5         335           5         s0.5         s0.5         s0.5         335           5         s0.5         s0.5         s0.5         335           5         s0.5         s0.5         s0.5         s0.5         335           5         s0.5         s0.5         s0.5         s0.5         349           26         s0.25         s0.25         s0.25         s0.49         349           26         s0.25         s0.25         s0.25         s0         s0         s0           50         MIC90         Runge         n         s0         s0         s0         s0           5         s0.25         s0.25         s0         s0         s0         s0         s0           5         a         s0.25         s0         s</th><th>i         ic         stst</th><th><math display="block"> \begin{array}{ c c c c c c c c c c c c c c c c c c c</math></th><th>i         i         si-ads         233           2         30.5         -34         20.25         -34         237           5         50.5         50.5         50.5         30.5         4         233           5         50.5         50.5         50.5         45         234         234           6         50.5         50.5         45         234         234         234           26         80.25         50.25         20.5         26         234         234           26         80.25         50.25         20.55         20.5         234         234           27         20.15         20.55         80.5         20.55         339         4           27         20.15         20.52         20.52         24         349         349           26         MC90         Range         339         4         4         349         4           25         26         60.52         20.52         26         281         349           26         28         20.52         26         284         349         4           26         28         20.52         20.52         <t< th=""><th>I         I6         s1-264         233           5         265         30.5         -84         237           5         50.5         30.5         -84         233           6         30.5         40.5         -84         233           75         30.5         40.5         -84         233           75         30.25         20.5         -24         234           76         30.25         30.25         216         216           20         20.25         30.25         216         216           20         20.25         40.25         356         356           20         20         20.5         20.5         36         356           56         MC9         Range         n         356         356           57         20         20.5         20.5         36         356           56         MC9         Range         n         356         356           56         20.5         20.5         20.5         36         36           56         20.5         20.5         20.5         36         36           56         20.5         20.5</th><th>I         I6         s1-264         233           5         265         3025         -34         237           5         50.5         30.55         -35         355           5         50.5         50.55         -35         355           5         50.5         50.55         -23         35           5         50.25         50.25         -216         216           20         20.25         20.25         216         216           20         20.25         50.25         216         216           20         20.25         50.25         216         319           21         20         20.52         216         319           26         MC90         Range         n         339           26         20         20.52         216         319           26         26         216         217         339           26         26         20.52         216         319           26         216         20.52         216         319           26         26         20.52         216         319           27         26         216</th><th>i         i         stradd         233           5         34         51add         237           5         30.5         30.5ad         237           5         30.5         30.5ad         233           5         30.5         30.5ad         233           5         30.5         30.5ad         233           5         30.25         30.5ad         234           26         30.25         30.5ad         234           26         30.25         30.5-2d         234           27         20.5-2d         339         356           27         20.5-2d         339         356           27         20.5-2d         339         356           26         20.5-2d         339         356           25         26         30.5-2d         339           25         26         30.5-2d         339           25         26         30.5-2d         339           26         30.5-2d         339         349           26         30.5-2d         339         349           26         30.5-2d         349         349           26</th></t<><th>i         i         si-add         233           5         50.5         50.5-         237           5         50.5         50.5-         237           5         50.5         50.5-         237           5         50.5         50.5-         237           5         50.5         50.5-         234           5         50.55         50.25-         246         234           20         2320         50.7-         2015         234           20         2320         50.25-         246         349           5         4         50.55-         36         349           5         4         50.55-         349         349           5         24         50.55-         349         349           5         4         50.55-         349         349           5         4         50.55-         349         349           5         2         2         2         349         349           5         2         2         2         349         349           5         2         2         2         2         349</th><th>I         I6         s1-264         233           5         80.5         80.25-24         235           5         80.5         80.5-24         233           5         80.5         80.5-24         233           5         80.5         80.5-24         234           5         80.5         80.5-24         234           5         80.5         80.55-246         234           20         80.25         80.55-246         234           20         20.25-246         249         349           5         80.25         80.25-246         349           5         80.25         80.25-246         349           5         80.4         81.5-84         349           5         80.5-266         349         349           5         80         80.25-246         349           5         80         80.25-246         349           5         80         80.25-246         349           5         80         80.25-246         349           5         80         80.25-246         349           5         80         80.25-846         39           <t< th=""><th>I         I6         s1-264         233           5         50.5         50.5-24         237           5         50.5         50.5-24         233           5         50.5         50.5-24         233           5         50.5         50.5-24         234           5         50.5         50.25-246         234           25         50.25         50.25-246         216           20         2320         517-26         216           20         2320         517-26         231           26         MC90         Range         849           5         20.5-266         349           5         20.5-266         349           5         20.5-266         349           5         20.5-266         349           5         20.5-266         349           5         20.5         20.25-266         349           5         20.5         20.5-266         39           5         20.5         20.5-266         39           5         20.5         20.5-266         19           5         20.5         20.5-266         19           5</th></t<><th><math display="block"> \begin{array}{ c c c c c c c c c c c c c c c c c c c</math></th></th></th></tr<> | i         i6         s1-264         235           25         s0.5         s0.5         s0.5         335           5         s0.5         s0.5         s0.5         335           5         s0.5         s0.5         s0.5         335           5         s0.5         s0.5         s0.5         s0.5         335           5         s0.5         s0.5         s0.5         s0.5         349           26         s0.25         s0.25         s0.25         s0.49         349           26         s0.25         s0.25         s0.25         s0         s0         s0           50         MIC90         Runge         n         s0         s0         s0         s0           5         s0.25         s0.25         s0         s0         s0         s0         s0           5         a         s0.25         s0         s   | i         ic         stst  
   
  | $ \begin{array}{ c c c c c c c c c c c c c c c c c c c$   | i         i         si-ads         233           2         30.5         -34         20.25         -34         237           5         50.5         50.5         50.5         30.5         4         233           5         50.5         50.5         50.5         45         234         234           6         50.5         50.5         45         234         234         234           26         80.25         50.25         20.5         26         234         234           26         80.25         50.25         20.55         20.5         234         234           27         20.15         20.55         80.5         20.55         339         4           27         20.15         20.52         20.52         24         349         349           26         MC90         Range         339         4         4         349         4           25         26         60.52         20.52         26         281         349           26         28         20.52         26         284         349         4           26         28         20.52         20.52 <t< th=""><th>I         I6         s1-264         233           5         265         30.5         -84         237           5         50.5         30.5         -84         233           6         30.5         40.5         -84         233           75         30.5         40.5         -84         233           75         30.25         20.5         -24         234           76         30.25         30.25         216         216           20         20.25         30.25         216         216           20         20.25         40.25         356         356           20         20         20.5         20.5         36         356           56         MC9         Range         n         356         356           57         20         20.5         20.5         36         356           56         MC9         Range         n         356         356           56         20.5         20.5         20.5         36         36           56         20.5         20.5         20.5         36         36           56         20.5         20.5</th><th>I         I6         s1-264         233           5         265         3025         -34         237           5         50.5         30.55         -35         355           5         50.5         50.55         -35         355           5         50.5         50.55         -23         35           5         50.25         50.25         -216         216           20         20.25         20.25         216         216           20         20.25         50.25         216         216           20         20.25         50.25         216         319           21         20         20.52         216         319           26         MC90         Range         n         339           26         20         20.52         216         319           26         26         216         217         339           26         26         20.52         216         319           26         216         20.52         216         319           26         26         20.52         216         319           27         26         216</th><th>i         i         stradd         233           5         34         51add         237           5         30.5         30.5ad         237           5         30.5         30.5ad         233           5         30.5         30.5ad         233           5         30.5         30.5ad         233           5         30.25         30.5ad         234           26         30.25         30.5ad         234           26         30.25         30.5-2d         234           27         20.5-2d         339         356           27         20.5-2d         339         356           27         20.5-2d         339         356           26         20.5-2d         339         356           25         26         30.5-2d         339           25         26         30.5-2d         339           25         26         30.5-2d         339           26         30.5-2d         339         349           26         30.5-2d         339         349           26         30.5-2d         349         349           26</th></t<> <th>i         i         si-add         233           5         50.5         50.5-         237           5         50.5         50.5-         237           5         50.5         50.5-         237           5         50.5         50.5-         237           5         50.5         50.5-         234           5         50.55         50.25-         246         234           20         2320         50.7-         2015         234           20         2320         50.25-         246         349           5         4         50.55-         36         349           5         4         50.55-         349         349           5         24         50.55-         349         349           5         4         50.55-         349         349           5         4         50.55-         349         349           5         2         2         2         349         349           5         2         2         2         349         349           5         2         2         2         2         349</th> <th>I         I6         s1-264         233           5         80.5         80.25-24         235           5         80.5         80.5-24         233           5         80.5         80.5-24         233           5         80.5         80.5-24         234           5         80.5         80.5-24         234           5         80.5         80.55-246         234           20         80.25         80.55-246         234           20         20.25-246
        249         349           5         80.25         80.25-246         349           5         80.25         80.25-246         349           5         80.4         81.5-84         349           5         80.5-266         349         349           5         80         80.25-246         349           5         80         80.25-246         349           5         80         80.25-246         349           5         80         80.25-246         349           5         80         80.25-246         349           5         80         80.25-846         39           <t< th=""><th>I         I6         s1-264         233           5         50.5         50.5-24         237           5         50.5         50.5-24         233           5         50.5         50.5-24         233           5         50.5         50.5-24         234           5         50.5         50.25-246         234           25         50.25         50.25-246         216           20         2320         517-26         216           20         2320         517-26         231           26         MC90         Range         849           5         20.5-266         349           5         20.5-266         349           5         20.5-266         349           5         20.5-266         349           5         20.5-266         349           5         20.5         20.25-266         349           5         20.5         20.5-266         39           5         20.5         20.5-266         39           5         20.5         20.5-266         19           5         20.5         20.5-266         19           5</th></t<><th><math display="block"> \begin{array}{ c c c c c c c c c c c c c c c c c c c</math></th></th>  | I         I6         s1-264         233           5         265         30.5         -84         237           5         50.5         30.5         -84         233           6         30.5         40.5         -84         233           75         30.5         40.5         -84         233           75         30.25         20.5         -24         234           76         30.25         30.25         216         216           20         20.25         30.25         216         216           20         20.25         40.25         356         356           20         20         20.5         20.5         36         356           56         MC9         Range         n         356         356           57         20         20.5         20.5         36         356           56         MC9         Range         n         356         356           56         20.5         20.5         20.5         36         36           56         20.5         20.5         20.5         36         36           56         20.5         20.5   | I         I6         s1-264         233           5         265         3025         -34         237           5         50.5         30.55         -35         355           5         50.5         50.55         -35         355           5         50.5         50.55         -23         35           5         50.25         50.25         -216         216           20         20.25         20.25         216         216           20         20.25         50.25         216         216           20         20.25         50.25         216         319           21         20         20.52         216         319           26         MC90         Range         n         339           26         20         20.52         216         319           26         26         216         217         339           26         26         20.52         216         319           26         216         20.52         216         319           26         26         20.52         216         319           27         26         216  
   | i         i         stradd         233           5         34         51add         237           5         30.5         30.5ad         237           5         30.5         30.5ad         233           5         30.5         30.5ad         233           5         30.5         30.5ad         233           5         30.25         30.5ad         234           26         30.25         30.5ad         234           26         30.25         30.5-2d         234           27         20.5-2d         339         356           27         20.5-2d         339         356           27         20.5-2d         339         356           26         20.5-2d         339         356           25         26         30.5-2d         339           25         26         30.5-2d         339           25         26         30.5-2d         339           26         30.5-2d         339         349           26         30.5-2d         339         349           26         30.5-2d         349         349           26   | i         i         si-add         233           5         50.5         50.5-         237           5         50.5         50.5-         237           5         50.5         50.5-         237           5         50.5         50.5-         237           5         50.5         50.5-         234           5         50.55         50.25-         246         234           20         2320         50.7-         2015         234           20         2320         50.25-         246         349           5         4         50.55-         36         349           5         4         50.55-         349         349           5         24         50.55-         349         349           5         4         50.55-         349         349           5         4         50.55-         349         349           5         2         2         2         349         349           5         2         2         2         349         349           5         2         2         2         2         349   | I         I6         s1-264         233           5         80.5         80.25-24         235           5         80.5         80.5-24         233           5         80.5         80.5-24         233           5         80.5         80.5-24         234           5         80.5         80.5-24         234           5         80.5         80.55-246         234           20         80.25         80.55-246         234           20         20.25-246         249         349           5         80.25         80.25-246         349           5         80.25         80.25-246         349           5         80.4         81.5-84         349           5         80.5-266         349         349           5         80         80.25-246         349           5         80         80.25-246         349           5         80         80.25-246         349           5         80         80.25-246         349           5         80         80.25-246         349           5         80         80.25-846         39 <t< th=""><th>I         I6         s1-264         233           5         50.5         50.5-24         237           5         50.5         50.5-24         233           5         50.5        
50.5-24         233           5         50.5         50.5-24         234           5         50.5         50.25-246         234           25         50.25         50.25-246         216           20         2320         517-26         216           20         2320         517-26         231           26         MC90         Range         849           5         20.5-266         349           5         20.5-266         349           5         20.5-266         349           5         20.5-266         349           5         20.5-266         349           5         20.5         20.25-266         349           5         20.5         20.5-266         39           5         20.5         20.5-266         39           5         20.5         20.5-266         19           5         20.5         20.5-266         19           5</th></t<> <th><math display="block"> \begin{array}{ c c c c c c c c c c c c c c c c c c c</math></th>   | I         I6         s1-264         233           5         50.5         50.5-24         237           5         50.5         50.5-24         233           5         50.5         50.5-24         233           5         50.5         50.5-24         234           5         50.5         50.25-246         234           25         50.25         50.25-246         216           20         2320         517-26         216           20         2320         517-26         231           26         MC90         Range         849           5         20.5-266         349           5         20.5-266         349           5         20.5-266         349           5         20.5-266         349           5         20.5-266         349           5         20.5         20.25-266         349           5         20.5         20.5-266         39           5         20.5         20.5-266         39           5         20.5         20.5-266         19           5         20.5         20.5-266         19           5   | $ \begin{array}{ c c c c c c c c c c c c c c c c c c c$   |
| 10         10         21         10           3         161         21/35         30.5         30.5         30.5           3         4         20.5         30.5         30.5         30.5         30.5           156         28.83         31         26.4         30.5         30.5         30.5           155         129         30.5         30.5         30.5         30.5         30.5           17         157         8.28         31         16         16.5         30.25         30.25           18         155         0.00         30.25         30.25         30.25         30.25           155         0.00         30.25         30.25         30.25         30.25           155         0.00         30.25         30.25         30.25         30.25           160         76.88         2320         3320         3320         3320   
   
   
   | 3         10         21         10           5         16         27.95         50.5         24           5         *         *         50.5         50.5         24           5         *         *         50.5         50.5         50.5         50.5           15         1         28         50.5         50.5         50.5         50.5         50.5           155         1.57         8.28         50.5         50.5         50.5         50.6         50.25         50.25         50.25         50.25         50.25         50.25         50.25         50.25         50.25         50.25         50.25         50.25         50.26 </td <td>3         10         21         10           5         4         2         5         24           5         4         5         5         5         24           5         4         5         5         5         25         24           5         4         5&lt;</td> <td>3         161         27.05         35         10           5         *         *         *         50.5         24           5         *         *         *         50.5         50.5         24           5         *         *         *         50.5         50.5         50.5         50.5           157         127         \$         20.5         50.5         50.5         50.6           157         \$         128         \$         20.5         50.25         50.25         50.25           1         156         0.00         \$         20.25         \$         20.25         \$         20.6         \$         20.25         \$         20.4</td> <td>3         161         27.05         35.1         10           5         *         *         \$0.5         \$0.5         \$10           5         *         *         \$0.5         \$0.5         \$24           5         *         \$0.5         \$0.5         \$24         \$0.5           155         129         \$0.5         \$0.5         \$0.5         \$0.6           157         82.8         \$21         \$0.5         \$0.5         \$0.6           157         82.8         \$0.0         \$0.25         \$0.25         \$0.26           156         0.00         \$0.25         \$0.25         \$0.25         \$0.25         \$0.26           155         0.00         \$0.25         \$0.25         \$0.25         \$0.25         \$0.25           155         0.00         \$0.25         \$0.25         \$0.25         \$0.25         \$0.25           16         76.88         \$2320         \$2320         \$2320         \$2025         \$2320           1         24         64.10         16         \$64         \$4         \$4           1         24.1         36.03         2         \$24         \$4         \$4</td> <td>10         10         21         10           5         *         *         50.5         50.5         24           5         *         *         50.5         50.25         50.5<!--</td--><td>8         10         2         10           5         *         *         \$         5         5         2           5         *         *         \$         50.5         \$         40.5         \$         50.5         \$         40.5         \$         50.5         \$         50.5         \$         50.5         \$         50.5         \$         50.5         \$         50.5         \$         50.5         \$         50.5         \$         50.5         \$         50.5         \$<!--</td--><td>1         0         10</td><td>I         I         I         2         1           3         161         27.55         50.55         24           3         4         ×         30.5         50.55         24           155         12.9         50.5         50.5         50.5         50.5           155         12.9         50.5         50.5         50.5         50.5           155         12.9         50.5         50.25         50.25         50.25           1         156         0.00         50.25         50.25         50.25         50.25           1         155         0.00         50.25         50.25         50.25         50.25           1         16         76.88         220         50.25         50.25         50.25           1         155         0.00         50.25         50.25         50.25         50.25           234         64.10         16         264         264         264           234         64.10         16         264         264         264         264         264         264         264         264         264         264         264         264         264         264</td><td>1         0   
     0         10         10</td><td><math display="block"> \begin{array}{c ccccccccccccccccccccccccccccccccccc</math></td><td>3         161         27.95         50.5         51.6           5         *         *         *         50.5         50.5         50.5           5         1.5         1.28.5         51.28.5         50.5         50.5         50.5           155         1.55         1.28.8         50.5         50.5         50.5         50.5           155         1.55         0.00         50.25         50.5         50.5         50.5           155         1.55         0.00         50.25         50.25         50.25         50.25           155         0.00         50.25         50.25         50.25         50.25         50.25           155         0.00         50.25         50.25         50.25         50.25         50.25           1         0.60         76.88         20.25         26.4         4         4         4         4         20.5         26.4         54         26.4         54         26.4         54         26.4         54         26.4         54         26.4         54         26.4         54         26.4         54         26.4         53.2         25.2         26.6         26.6         26.6         26.6</td><td>3         161         27.95         6.3         10         <th< td=""><td>3         161         27.95         50.5         54           5         *         *         *         50.5         50.5         50.5           5         1.55         1.28.85         50.5         50.5         50.5         50.5           155         1.55         1.28         50.5         50.5         50.5         50.5           155         1.55         1.50         50.25         50.5         50.5         50.5           155         1.50         50.26         50.25         50.25         50.25         50.25           155         0.00         50.25         50.25         50.25         50.25         50.25           155         0.00         50.25         50.25         50.25         50.25         50.25           160         76.88         20.21         20.25         20.25         264         264           231         2.01         1.6         1.6         26.4         264         264           232         2.198         2.4         264         264         264         264         264         264         264         264         264         264         264         264         264         264</td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td>1         0</td><td>I         0</td><td></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td></td><td>8         10         23         21         23<!--</td--><td>3         10         0.03         3         10           3         161         27.95         20.5         24           3         4         23.85         21.5         24         26.5         24           155         1.29         50.5         24         24         54.0         50.5         24         24         24         24         24         24         24         24         24         24         24         24         264         26         26         26         26         26         26         26         26         26         26         26         26         26         26         26         26         26         26</td><td></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td></td></th<></td></td></td> | 3         10         21         10           5         4         2         5         24           5         4         5         5         5         24           5         4         5         5         5         25         24           5         4         5<  
   
   
  | 3         161         27.05         35         10           5         *         *         *         50.5         24           5         *         *         *         50.5         50.5         24           5         *         *         *         50.5         50.5         50.5         50.5           157         127         \$         20.5         50.5         50.5         50.6           157         \$         128         \$         20.5         50.25         50.25         50.25           1         156         0.00         \$         20.25         \$         20.25         \$         20.6         \$         20.25         \$         20.4 | 3         161         27.05         35.1         10           5         *         *         \$0.5         \$0.5         \$10           5         *         *         \$0.5         \$0.5         \$24           5         *         \$0.5         \$0.5         \$24         \$0.5           155         129         \$0.5         \$0.5         \$0.5         \$0.6           157         82.8         \$21         \$0.5         \$0.5         \$0.6           157         82.8         \$0.0         \$0.25         \$0.25         \$0.26           156         0.00         \$0.25         \$0.25         \$0.25         \$0.25         \$0.26           155         0.00         \$0.25         \$0.25         \$0.25         \$0.25         \$0.25           155         0.00         \$0.25         \$0.25         \$0.25         \$0.25         \$0.25           16         76.88         \$2320         \$2320         \$2320         \$2025         \$2320           1         24         64.10         16         \$64         \$4         \$4           1         24.1         36.03         2         \$24         \$4         \$4  
   
   
   | 10         10         21         10           5         *         *         50.5         50.5         24           5         *         *         50.5         50.25         50.5 </td <td>8         10         2         10           5         *         *         \$         5         5         2           5         *         *         \$         50.5         \$         40.5         \$         50.5         \$         40.5         \$         50.5         \$         50.5         \$         50.5         \$         50.5         \$         50.5         \$         50.5         \$         50.5         \$         50.5         \$         50.5         \$         50.5         \$<!--</td--><td>1         0         10</td><td>I         I         I         2         1           3         161         27.55         50.55         24           3         4         ×         30.5         50.55         24           155         12.9         50.5         50.5         50.5         50.5           155         12.9         50.5         50.5         50.5         50.5           155         12.9         50.5         50.25         50.25         50.25           1         156         0.00         50.25         50.25         50.25         50.25           1         155         0.00         50.25         50.25         50.25         50.25           1         16         76.88         220         50.25         50.25         50.25           1         155         0.00         50.25         50.25         50.25         50.25           234         64.10         16         264         264         264           234         64.10         16         264         264         264         264         264         264         264         264         264         264         264         264         264         264</td><td>1         0         10</td><td><math display="block"> \begin{array}{c ccccccccccccccccccccccccccccccccccc</math></td><td>3         161         27.95         50.5         51.6           5         *         *         *         50.5         50.5         50.5           5         1.5         1.28.5         51.28.5         50.5         50.5         50.5           155         1.55         1.28.8         50.5         50.5         50.5         50.5           155         1.55         0.00         50.25         50.5         50.5         50.5           155         1.55         0.00         50.25         50.25         50.25         50.25           155         0.00         50.25         50.25    
    50.25         50.25         50.25           155         0.00         50.25         50.25         50.25         50.25         50.25           1         0.60         76.88         20.25         26.4         4         4         4         4         20.5         26.4         54         26.4         54         26.4         54         26.4         54         26.4         54         26.4         54         26.4         54         26.4         54         26.4         53.2         25.2         26.6         26.6         26.6         26.6</td><td>3         161         27.95         6.3         10         <th< td=""><td>3         161         27.95         50.5         54           5         *         *         *         50.5         50.5         50.5           5         1.55         1.28.85         50.5         50.5         50.5         50.5           155         1.55         1.28         50.5         50.5         50.5         50.5           155         1.55         1.50         50.25         50.5         50.5         50.5           155         1.50         50.26         50.25         50.25         50.25         50.25           155         0.00         50.25         50.25         50.25         50.25         50.25           155         0.00         50.25         50.25         50.25         50.25         50.25           160         76.88         20.21         20.25         20.25         264         264           231         2.01         1.6         1.6         26.4         264         264           232         2.198         2.4         264         264         264         264         264         264         264         264         264         264         264         264         264         264</td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td>1         0</td><td>I         0</td><td></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td></td><td>8         10         23         21         23<!--</td--><td>3         10         0.03         3         10           3         161         27.95         20.5         24           3         4         23.85         21.5         24         26.5         24           155         1.29         50.5         24         24         54.0         50.5         24         24         24         24         24         24         24         24         24         24         24         24         264         26         26         26         26         26         26         26         26         26         26         26         26         26         26         26         26         26         26</td><td></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td></td></th<></td></td> | 8         10         2         10           5         *         *         \$         5         5         2           5         *         *         \$         50.5         \$         40.5         \$         50.5         \$         40.5         \$         50.5         \$         50.5         \$         50.5         \$         50.5         \$         50.5         \$         50.5         \$         50.5         \$         50.5         \$         50.5         \$         50.5         \$ </td <td>1         0         10</td> <td>I         I         I         2         1           3         161     
   27.55         50.55         24           3         4         ×         30.5         50.55         24           155         12.9         50.5         50.5         50.5         50.5           155         12.9         50.5         50.5         50.5         50.5           155         12.9         50.5         50.25         50.25         50.25           1         156         0.00         50.25         50.25         50.25         50.25           1         155         0.00         50.25         50.25         50.25         50.25           1         16         76.88         220         50.25         50.25         50.25           1         155         0.00         50.25         50.25         50.25         50.25           234         64.10         16         264         264         264           234         64.10         16         264         264         264         264         264         264         264         264         264         264         264         264         264         264</td> <td>1         0         10</td> <td><math display="block"> \begin{array}{c ccccccccccccccccccccccccccccccccccc</math></td> <td>3         161         27.95         50.5         51.6           5         *         *         *         50.5         50.5         50.5           5         1.5         1.28.5         51.28.5         50.5         50.5         50.5           155         1.55         1.28.8         50.5         50.5         50.5         50.5           155         1.55         0.00         50.25         50.5         50.5         50.5           155         1.55         0.00         50.25         50.25         50.25         50.25           155         0.00         50.25         50.25         50.25         50.25         50.25           155         0.00         50.25         50.25         50.25         50.25         50.25           1         0.60         76.88         20.25         26.4         4         4         4         4         20.5         26.4         54         26.4         54         26.4         54         26.4         54         26.4         54         26.4         54         26.4         54         26.4         54         26.4         53.2         25.2         26.6         26.6         26.6         26.6</td> <td>3         161         27.95         6.3         10         <th< td=""><td>3         161         27.95         50.5         54           5         *         *         *         50.5         50.5         50.5           5         1.55         1.28.85         50.5         50.5         50.5         50.5           155         1.55         1.28         50.5         50.5         50.5         50.5           155         1.55         1.50         50.25         50.5         50.5         50.5           155         1.50         50.26         50.25         50.25         50.25         50.25           155         0.00         50.25         50.25         50.25         50.25         50.25           155         0.00         50.25         50.25         50.25         50.25         50.25           160         76.88         20.21         20.25         20.25         264         264           231         2.01         1.6         1.6         26.4         264         264           232         2.198         2.4         264         264         264         264         264         264         264         264         264         264         264         264         264         264</td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td>1         0</td><td>I         0</td><td></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td></td><td>8         10         23         21         23<!--</td--><td>3         10         0.03         3         10           3         161         27.95         20.5         24           3         4         23.85         21.5         24         26.5         24           155         1.29         50.5         24         24         54.0         50.5         24         24         24         24         24         24         24         24         24         24         24         24         264         26         26         26         26         26         26        
26         26         26         26         26         26         26         26         26         26         26         26</td><td></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td></td></th<></td> | 1         0         10  
   
  | I         I         I         2         1           3         161         27.55         50.55         24           3         4         ×         30.5         50.55         24           155         12.9         50.5         50.5         50.5         50.5           155         12.9         50.5         50.5         50.5         50.5           155         12.9         50.5         50.25         50.25         50.25           1         156         0.00         50.25         50.25         50.25         50.25           1         155         0.00         50.25         50.25         50.25         50.25           1         16         76.88         220         50.25         50.25         50.25           1         155         0.00         50.25         50.25         50.25         50.25           234         64.10         16         264         264         264           234         64.10         16         264         264         264         264         264         264         264         264         264         264         264         264         264         264   
   
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   | 3         161         27.95         50.5         51.6           5         *         *         *         50.5         50.5         50.5           5         1.5         1.28.5         51.28.5         50.5         50.5         50.5           155         1.55         1.28.8         50.5         50.5         50.5         50.5           155         1.55         0.00         50.25         50.5         50.5         50.5           155         1.55         0.00         50.25         50.25         50.25         50.25           155         0.00         50.25         50.25         50.25         50.25         50.25           155         0.00         50.25         50.25         50.25         50.25         50.25           1         0.60         76.88         20.25         26.4         4 
       4         4         4         20.5         26.4         54         26.4         54         26.4         54         26.4         54         26.4         54         26.4         54         26.4         54         26.4         54         26.4         53.2         25.2         26.6         26.6         26.6         26.6   | 3         161         27.95         6.3         10 <th< td=""><td>3         161         27.95         50.5         54           5         *         *         *         50.5         50.5         50.5           5         1.55         1.28.85         50.5         50.5         50.5         50.5           155         1.55         1.28         50.5         50.5         50.5         50.5           155         1.55         1.50         50.25         50.5         50.5         50.5           155         1.50         50.26         50.25         50.25         50.25         50.25           155         0.00         50.25         50.25         50.25         50.25         50.25           155         0.00         50.25         50.25         50.25         50.25         50.25           160         76.88         20.21         20.25         20.25         264         264           231         2.01         1.6         1.6         26.4         264         264           232         2.198         2.4         264         264         264         264         264         264         264         264         264         264         264         264         264         264</td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td>1         0</td><td>I         0</td><td></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td></td><td>8         10         23         21         23<!--</td--><td>3         10         0.03         3         10           3         161         27.95         20.5         24           3         4         23.85         21.5         24         26.5         24           155         1.29         50.5         24         24         54.0         50.5         24         24         24         24         24         24         24         24         24         24         24         24         264         26         26         26         26         26         26         26         26         26         26         26         26         26         26         26         26         26         26</td><td></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td></td></th<>   
   | 3         161         27.95         50.5         54           5         *         *         *         50.5         50.5         50.5           5         1.55         1.28.85         50.5         50.5         50.5         50.5           155         1.55         1.28         50.5         50.5         50.5         50.5           155         1.55         1.50         50.25         50.5         50.5         50.5           155         1.50         50.26         50.25         50.25 
       50.25         50.25           155         0.00         50.25         50.25         50.25         50.25         50.25           155         0.00         50.25         50.25         50.25         50.25         50.25           160         76.88         20.21         20.25         20.25         264         264           231         2.01         1.6         1.6         26.4         264         264           232         2.198         2.4         264         264         264         264         264         264         264         264         264         264         264         264         264         264   
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  | 8         10         23         21         23 </td <td>3         10         0.03         3         10           3         161         27.95         20.5         24           3         4         23.85         21.5         24         26.5         24           155         1.29         50.5         24         24         54.0         50.5         24         24         24         24         24         24         24         24         24         24         24         24         264         26         26         26         26         26         26         26         26         26         26         26         26         26         26         26         26         26         26</td> <td></td> <td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td> <td></td> <td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td> <td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td>  | 3         10         0.03         3         10           3         161         27.95         20.5         24           3         4         23.85         21.5         24         26.5         24           155         1.29         50.5         24         24         54.0         50.5         24         24         24         24         24         24         24         24         24         24         24         24         264         26         26         26         26         26         26         26         26         26         26         26         26         26         26         26         26         26         26  
   |   | $ \begin{array}{c c c c c c c c c c c c c c c c c c c $   |   
   | $ \begin{array}{c c c c c c c c c c c c c c c c c c c $   | $ \begin{array}{c c c c c c c c c c c c c c c c c c c $   |
| \$0.5         \$0.5         \$0.5         \$20.5         \$26         *           \$1         \$26         \$1.5         \$20.4         \$15         \$1.5 <td>40.5         90.5         20.5         26.6         *           40.5         90.5         30.5         26.4         15.6         *           40.5         30.5         30.5         4         15.6         *         *           40.5         30.5         40.5         30.5         4         15.7         *</td> <td>40.5         90.5         20.5         264         5         30.5         264         156         15           40.5         30.5         30.5         30.5         4         157         4         157           21         264         31.5         30.5         41.5         16         17         16         16         16         16         16         16         16         16         16         16         16         16         16         16         16         16         <td< td=""><td>40.5         90.5         20.5         26.6         *           20.5         26.4         21-26         15         16</td><td>90.5         90.5.         20.5.         264         51.         54.         156.         156.         156.         156.         156.         156.         156.         156.         156.         156.         157.         167.         157.         167.         157.         157.         157.         157.         167.         157.         <td< td=""><td>30.5         30.5. 20.5. 246         *           26.4         26.4         15.6           30.5         30.5.         30.5.         4           31.6         30.5.         30.5.         4         15.7           31.7         30.5         30.5.         4         15.7           32.0.5         30.25         30.25.         4         15.7           30.25         30.25         30.25.         1         15.6           30.25         30.25         30.25.         1         15.7           30.25         30.25         30.25.         1         15.7           30.25         30.25         30.25         1         15.7           30.44         31.7         30.14         1         15.7           30.44         31.7         30.4         31.4           30.5         30.25         21.4         1         31.4           30.5         30.4         8.4         21.4         21.4           30.5         30.4         30.25         21.4         31.7           30.5         30.4         30.25         30.4         31.4           30.5         30.4         30.25         31.2</td><td>90.5         90.5.         20.5.         26.4         50.5.         26.4         150.5           90.5         90.5         90.5.         30.5.         41.55         41.57           90.5         90.5         90.5         90.5.         41.57         41.57           90.5         90.5         90.5         50.25         41         157           90.25         80.25         80.25         41         155           90.25         80.25         41         155           90.25         80.25         41         155           90.25         80.25         20.44         21.44           16         86         47.84         21.44           16         86         21.92         101           16         86         21.92         101           16         86         21.84         21.84         21.84           80.5         1         80.55         21.84         21.84           80.5         1         80.55         21.84         23.84           80.5         90.5         90.55         23.84         23.84           80.55         80.25         80.25         23.86         23.86</td><td>\$0.5         <t< td=""><td>≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.6         ≤0           ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5           ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5           ≤0.25         ≤0.25         ≤0.25         ≤0.25         ≤0.20         ≤0           ≤0.25         ≤0.25         ≤0.25         ≤0.20         ≤0         ≤0           ≤0.25         ≤0.25         ≤0.25         ≤0.20         ≤0         ≤0           ≥20         ≥0.25         ≤0.25         ≤0.24         ≥0.4         ≤0           ×0.05         ≈20.5         ≤0.1         ≤0.4         ≥0.4         ≤0         ≤0           ×0.15         ≈0.25         ≥0.4         ≤0.5         ≤0         ≥0         ≤0         ≤0        
≤0         <td< td=""><td>\$0.5         \$0.5         \$0.5         \$0.5         \$2.64         \$15.6         \$1.84         \$15.6         \$1.84         \$15.7         \$1.85         \$1.85         \$1.85         \$1.85         \$15.7         \$15.6         \$2.65         \$15.25         \$10.25         \$20.10         \$10.7         \$2.01         \$10.7         \$2.01         \$10.7         \$2.01</td><td>40.5         90.5         20.5         2.64         150           261         263         20.5         21.264         157           261         263         20.5         21.26         151         151           261         263         20.5         20.5         21.26         151         155           261.5         20.25         20.25         21.26         151         155           202.5         20.25         20.25         20.1         151         155           202.5         20.0         20.0         20.4         21.4         21.4           MIC50         MIC90         Range         n         16         26.4         23.4           201.4         20.5         24         21.4         23.4         23.4         23.4           MIC50         MIC90         Range         21.4         23.6         23.4         23.4           20.5         24.4         23.5         20.5         24.2         23.4         23.4           20.5         24.5         25.5         24.5         23.4         23.4         23.4         23.4           20.5         20.55         20.25         20.16         23.4</td><td>90.5         90.5.         26.6.         ≥ 80.5.         26.6         15           90.5         90.5         30.5.         ≥ 84         157         157           21         36         30.5         30.5.         4157         157         151           21         36         30.5.         4157         157         151         156           20.25         30.25         20.25         1         150         152         151         150           20.25         30.25         30.25         20         1         150         1         157         1         157         1         157         1         157         1         157         1         157         1         155         1         156         2         1         156         2         1         156         2         1         156         2         1         157         1         157         2         1         157         2         1         157         2         1         2         2         2         2         2         2         2         2         2         2         2         2         2         2         2         2         2</td><td>90.5         90.5.         260.5         260.5         30.5.         260.4         150           90.5         90.5         30.5.         26.4         150         150           20.5         30.5         30.5.         41.55         150         151         150           20.5         30.5         30.5.         26.5         21.4         155         151         150           20.25         30.25         30.25         210         155         20.25         1         150           20.25         21.0         20.25         21.0         1         150         20.4           MIC50         MIC90         Range         n         20.25         20.4         10.4         20.4         20.4         20.4         20.4         20.4         20.4         20.4         20.4         20.4</td><td>90.5         90.5.         26.4         30.5.         26.4         15.6           90.5         90.5         30.5.         26.4         15.6         15.7           91.5         90.5         30.5.         4         15.7         15.7         15.7           91.5         50.5.5         50.25.5         51.25.5         15.1         150         150           92.0.5         50.25.5         51.0.25.7         150         20.4         157         150           92.0.5         50.25.5         50.25.5         10.4         150         20.4         21.4           MIC50         MIC90         Range         1         20.25.2         2.1         20.25           20.14         50.25         21.4         20.25.2         2.1         20.25         2.1           MIC50         MIC90         Range         2.1         <t< td=""><td>90.5         90.5.         264         315.         264         156           90.5         90.5         30.5.         264         157         315.         41         157           21         36         30.5.         30.5.         30.5.         41         157           20.5         50.55         50.25         51         250         41         157           20.55         50.25         50.25         20         1         157         21           20.25         30.25         30.25         1         150         21         450           20.25         30.25         30.25         20         41         21         460         21           20.55         21         4         20.25         21         40         21         40         21           20.5         21         4         20.25         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21</td><td>90.5         90.5.         26.6.         5         90.5.         26.4         15.6           90.5         90.5         90.5         90.5         90.5         15.6         15.7         15.1         15.7         16.7         15.7         16.7         15.7         16.7         17.6         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         17.7         17.7         17.7         1</td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td>90.5         90.5.         260.5         260.5         260.5         260.4         150.5           20.5         20.5         20.5         20.5         20.5         21.4         157.5           20.5         20.5         20.5         20.5         21.4         157.5         21.4         157.5           20.5         20.5         20.5         20.5         21.4         155.5         20.5         1         150.5           20.5         20.5         20.5         20.5         20.5         1         150.5         20.4         20.5         20.5         20.5         20.5         20.4         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.4         20.5         20.5         20.4         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.4         20.5         20.5         20.4&lt;</td><td>90.5         90.5.         264         30.5.         264         315           90.5         90.5         30.5.         26.4         315         315           91.5         80.5         30.5.         41.57         315         315         315         315         315         315         315         315         315         315 
       315         315         315         315         315         315         315         315         315         315         315         315         315         315         315         315         315         316         317         316</td><td>90.5         90.5.         264         30.5.         264         156           90.5         90.5         90.5.         20.5.         4         157           91.5         80.5         90.5.         20.5.         4         157           91.5         80.5         80.5.         80.25.         41         157           91.5         80.5         80.25.         41         157           92.5         80.25         80.25.         41         157           90.5         80.25         1         50.25         8         214           MIC50         MIC90         Range         1         232         241           90.5         21         30.5.25         8         233         241           90.5         31         90.25-26         241         233         241           90.5         30.5         50.25         20.25         241         233         241           90.5         30.5         50.25         241         233         241         241           90.5         30.25         20.25         214         233         241         241           90.5         20.25         20.25</td><td>90.5         90.5.         264         30.5.         264         156           90.5         90.5         30.5.         4         157         44         157           90.5         90.5         80.5         40.5         41         157         44         157           90.5         80.5         80.55         80.25         41         157         41         157           90.5         80.25         80.25         10         323         104         11         157         114         157         114         157         114         157         114         157         114         157         11</td><td>90.5         90.5.         26.4         30.5.         26.4         15.6           90.5         90.5         30.5.         26.4         15.6         15.7           91.5         90.5         90.5         30.5.         41         15.7           91.5         90.5         90.5         30.5.         41         15.7           91.5         90.5         90.5         30.5.         41         15.7           90.5         90.5         90.25         41         15.7         15.7           90.5         20.25         1         50.25         2.4         15.2           90.5         20.4         21.4         23.2         20.4         23.2           90.5         20.5         20.5         20.5         2.4         23.2           90.5         30.5         30.5         20.25         2.4         23.2           90.5         30.5         30.5         20.25         2.4         23.2           90.5         30.5         30.5         20.25         2.4         114           90.5         30.5         30.25         2.4         114         2.7           90.5         20.5         20.5         2</td><td>90.5         90.5         26.4         30.5.         26.4         15.6           90.5         90.5         30.5.         26.4         15.6           90.5         80.5         30.5.         4         15.7           90.5         80.5         50.5.         21.4         15.7           90.5         80.5         50.25         4         15.7           90.5         80.25         1         15.6         21.4           90.5         80.25         1         15.2         21.4           90.5         20.25         1         50.25         21.4           90.5         21.4         21.7         20.4         21.4           90.5         21.4         21.7         21.4         21.7           90.5         21.4         21.7         21.4         21.7           90.5         21.5         20.25-2.8         21.4         21.7           90.5         30.5         20.25-2.46         11.7         21.4           216         21.7         20.12         21.4         11.7           216         21.7         20.12         21.4         11.7           216         21.7         21.7</td><td>90.5         90.5         <math>20.5</math> <math>20.5</math><td>90.5         <t< td=""><td>90.5         90.5         29.6         30.5         29.6         30.5         20.5         20.5         30.5         <th< td=""><td>90.5         <th< td=""></th<></td></th<></td></t<></td></td></t<></td></td<></td></t<></td></td<></td></td<></td> | 40.5         90.5         20.5         26.6         *           40.5         90.5         30.5         26.4         15.6         *           40.5         30.5         30.5         4         15.6         *         *           40.5         30.5         40.5         30.5         4         15.7         *        
*         *  
   | 40.5         90.5         20.5         264         5         30.5         264         156         15           40.5         30.5         30.5         30.5         4         157         4         157           21         264         31.5         30.5         41.5         16         17         16         16         16         16         16         16         16         16         16         16         16         16         16         16         16         16 <td< td=""><td>40.5         90.5         20.5         26.6         *           20.5         26.4         21-26         15         16</td><td>90.5         90.5.         20.5.         264         51.         54.         156.         156.         156.         156.         156.         156.         156.         156.         156.         156.         157.         157.         157.         157.         157.         157.         157.         157.         157.         157.         157.         157.         157.         157.         157.         157.         157. 
       157.         167.         157.         167.         157.         157.         157.         157.         167.         157.         <td< td=""><td>30.5         30.5. 20.5. 246         *           26.4         26.4         15.6           30.5         30.5.         30.5.         4           31.6         30.5.         30.5.         4         15.7           31.7         30.5         30.5.         4         15.7           32.0.5         30.25         30.25.         4         15.7           30.25         30.25         30.25.         1         15.6           30.25         30.25         30.25.         1         15.7           30.25         30.25         30.25.         1         15.7           30.25         30.25         30.25         1         15.7           30.44         31.7         30.14         1         15.7           30.44         31.7         30.4         31.4           30.5         30.25         21.4         1         31.4           30.5         30.4         8.4         21.4         21.4           30.5         30.4         30.25         21.4         31.7           30.5         30.4         30.25         30.4         31.4           30.5         30.4         30.25         31.2</td><td>90.5         90.5.         20.5.         26.4         50.5.         26.4         150.5           90.5         90.5         90.5.         30.5.         41.55         41.57           90.5         90.5         90.5         90.5.         41.57         41.57           90.5         90.5         90.5         50.25         41         157           90.25         80.25         80.25         41         155           90.25         80.25         41         155           90.25         80.25         41         155           90.25         80.25         20.44         21.44           16         86         47.84         21.44           16         86         21.92         101           16         86         21.92         101           16         86         21.84         21.84         21.84           80.5         1         80.55         21.84         21.84           80.5         1         80.55         21.84         23.84           80.5         90.5         90.55         23.84         23.84           80.55         80.25         80.25         23.86         23.86</td><td>\$0.5         <t< td=""><td>≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.6         ≤0           ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5           ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5           ≤0.25         ≤0.25         ≤0.25         ≤0.25         ≤0.20         ≤0           ≤0.25         ≤0.25         ≤0.25         ≤0.20         ≤0         ≤0           ≤0.25         ≤0.25         ≤0.25         ≤0.20         ≤0         ≤0           ≥20         ≥0.25         ≤0.25         ≤0.24         ≥0.4         ≤0           ×0.05         ≈20.5         ≤0.1         ≤0.4         ≥0.4         ≤0         ≤0           ×0.15         ≈0.25         ≥0.4         ≤0.5         ≤0         ≥0         ≤0         <td< td=""><td>\$0.5         \$0.5         \$0.5         \$0.5         \$2.64         \$15.6         \$1.84         \$15.6         \$1.84         \$15.7         \$1.85         \$1.85         \$1.85         \$1.85         \$15.7         \$15.6         \$2.65         \$15.25         \$10.25         \$20.10         \$10.7         \$2.01         \$10.7         \$2.01         \$10.7         \$2.01</td><td>40.5         90.5         20.5         2.64         150           261         263         20.5         21.264         157           261         263         20.5         21.26         151         151           261         263         20.5         20.5         21.26         151         155           261.5         20.25         20.25         21.26         151         155           202.5         20.25         20.25         20.1         151         155           202.5         20.0         20.0         20.4         21.4         21.4           MIC50         MIC90         Range         n         16         26.4         23.4           201.4         20.5         24         21.4         23.4         23.4         23.4           MIC50         MIC90         Range         21.4         23.6         23.4         23.4           20.5         24.4         23.5         20.5         24.2         23.4         23.4           20.5         24.5         25.5         24.5         23.4         23.4         23.4         23.4           20.5         20.55         20.25         20.16         23.4</td><td>90.5         90.5.         26.6.         ≥ 80.5.         26.6         15           90.5         90.5         30.5.         ≥ 84         157         157           21         36         30.5         30.5.         4157         157         151           21         36         30.5.         4157         157         151         156           20.25         30.25         20.25         1         150         152         151         150           20.25         30.25         30.25         20         1         150         1         157         1         157         1         157         1         157         1         157         1         157         1         155         1         156         2         1         156         2         1         156         2         1         156         2         1         157         1         157         2         1         157         2         1         157         2         1         2         2         2         2         2         2         2         2         2         2         2         2         2         2         2         2         2</td><td>90.5         90.5.         260.5         260.5         30.5.         260.4         150           90.5         90.5         30.5.         26.4         150         150           20.5         30.5         30.5.         41.55         150         151         150           20.5         30.5         30.5.         26.5         21.4         155         151         150           20.25         30.25         30.25         210         155         20.25         1         150           20.25         21.0         20.25         21.0         1         150         20.4           MIC50         MIC90         Range         n         20.25         20.4         10.4         20.4         20.4         20.4         20.4         20.4         20.4         20.4         20.4         20.4</td><td>90.5         90.5.    
    26.4         30.5.         26.4         15.6           90.5         90.5         30.5.         26.4         15.6         15.7           91.5         90.5         30.5.         4         15.7         15.7         15.7           91.5         50.5.5         50.25.5         51.25.5         15.1         150         150           92.0.5         50.25.5         51.0.25.7         150         20.4         157         150           92.0.5         50.25.5         50.25.5         10.4         150         20.4         21.4           MIC50         MIC90         Range         1         20.25.2         2.1         20.25           20.14         50.25         21.4         20.25.2         2.1         20.25         2.1           MIC50         MIC90         Range         2.1         <t< td=""><td>90.5         90.5.         264         315.         264         156           90.5         90.5         30.5.         264         157         315.         41         157           21         36         30.5.         30.5.         30.5.         41         157           20.5         50.55         50.25         51         250         41         157           20.55         50.25         50.25         20         1         157         21           20.25         30.25         30.25         1         150         21         450           20.25         30.25         30.25         20         41         21         460         21           20.55         21         4         20.25         21         40         21         40         21           20.5         21         4         20.25         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21</td><td>90.5         90.5.         26.6.         5         90.5.         26.4         15.6           90.5         90.5         90.5         90.5         90.5         15.6         15.7         15.1         15.7         16.7         15.7         16.7         15.7         16.7         17.6         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         17.7         17.7         17.7         1</td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td>90.5         90.5.         260.5         260.5         260.5         260.4         150.5           20.5         20.5         20.5         20.5         20.5         21.4         157.5           20.5         20.5         20.5         20.5         21.4         157.5         21.4         157.5           20.5         20.5         20.5         20.5         21.4         155.5         20.5         1         150.5           20.5         20.5         20.5         20.5         20.5         1         150.5         20.4         20.5         20.5         20.5         20.5         20.4         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.4         20.5         20.5         20.4         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.4         20.5         20.5         20.4&lt;</td><td>90.5         90.5.         264         30.5.         264         315           90.5         90.5         30.5.         26.4         315         315           91.5         80.5         30.5.         41.57         315         316         317         316</td><td>90.5         90.5.         264         30.5.         264         156           90.5         90.5         90.5.         20.5.         4         157           91.5         80.5         90.5.         20.5.         4         157           91.5         80.5         80.5.         80.25.         41         157           91.5         80.5         80.25.         41         157           92.5         80.25         80.25.         41         157           90.5         80.25         1         50.25         8         214           MIC50         MIC90         Range         1         232         241           90.5         21         30.5.25         8         233         241           90.5         31         90.25-26         241         233         241           90.5         30.5         50.25         20.25         241         233         241           90.5         30.5         50.25         241         233         241         241           90.5         30.25         20.25         214         233         241         241           90.5         20.25         20.25</td><td>90.5         90.5.         264         30.5.         264         156           90.5         90.5         30.5.         4         157         44         157           90.5         90.5         80.5         40.5         41         157         44         157           90.5         80.5         80.55         80.25         41         157         41         157           90.5         80.25         80.25         10         323         104         11         157         114         157         114         157         114         157         114         157         114         157         11</td><td>90.5         90.5.         26.4         30.5.         26.4         15.6           90.5         90.5         30.5.         26.4         15.6         15.7           91.5         90.5         90.5         30.5.         41         15.7           91.5         90.5         90.5         30.5.         41         15.7           91.5         90.5         90.5         30.5.         41         15.7           90.5         90.5         90.25         41         15.7         15.7           90.5         20.25         1         50.25         2.4         15.2           90.5         20.4         21.4         23.2         20.4         23.2           90.5         20.5         20.5         20.5         2.4         23.2           90.5         30.5         30.5         20.25         2.4         23.2           90.5         30.5         30.5         20.25         2.4         23.2           90.5         30.5         30.5         20.25         2.4         114           90.5         30.5         30.25         2.4         114         2.7           90.5         20.5         20.5         2</td><td>90.5         90.5         26.4         30.5.         26.4         15.6           90.5         90.5         30.5.         26.4         15.6           90.5         80.5         30.5.         4         15.7           90.5         80.5         50.5.         21.4         15.7           90.5         80.5         50.25         4         15.7           90.5         80.25         1         15.6         21.4           90.5         80.25         1         15.2         21.4           90.5         20.25         1         50.25         21.4           90.5         21.4         21.7         20.4         21.4           90.5         21.4         21.7         21.4         21.7           90.5         21.4         21.7         21.4         21.7           90.5         21.5         20.25-2.8         21.4         21.7           90.5         30.5         20.25-2.46         11.7         21.4           216         21.7     
   20.12         21.4         11.7           216         21.7         20.12         21.4         11.7           216         21.7         21.7</td><td>90.5         90.5         <math>20.5</math> <math>20.5</math><td>90.5         <t< td=""><td>90.5         90.5         29.6         30.5         29.6         30.5         20.5         20.5         30.5         <th< td=""><td>90.5         <th< td=""></th<></td></th<></td></t<></td></td></t<></td></td<></td></t<></td></td<></td></td<> | 40.5         90.5         20.5         26.6         *           20.5         26.4         21-26         15         16         | 90.5         90.5.         20.5.         264         51.         54.         156.         156.         156.         156.         156.         156.         156.         156.         156.         156.         157.         167.         157.         167.         157.         157.         157.         157.         167.         157. <td< td=""><td>30.5         30.5. 20.5. 246         *           26.4         26.4         15.6           30.5         30.5.         30.5.         4           31.6         30.5.         30.5.         4         15.7           31.7         30.5         30.5.         4         15.7           32.0.5         30.25         30.25.         4         15.7           30.25         30.25         30.25.         1         15.6           30.25         30.25         30.25.         1         15.7           30.25         30.25         30.25.         1         15.7           30.25         30.25         30.25         1         15.7           30.44         31.7         30.14         1         15.7           30.44         31.7         30.4         31.4           30.5         30.25         21.4         1         31.4           30.5         30.4         8.4         21.4         21.4           30.5         30.4         30.25         21.4         31.7           30.5         30.4         30.25         30.4         31.4           30.5         30.4         30.25         31.2</td><td>90.5         90.5.         20.5.         26.4         50.5.         26.4         150.5           90.5         90.5         90.5.         30.5.         41.55         41.57           90.5         90.5         90.5         90.5.         41.57         41.57           90.5         90.5         90.5         50.25         41         157           90.25         80.25         80.25         41         155           90.25         80.25         41         155           90.25         80.25         41         155           90.25         80.25         20.44         21.44           16         86         47.84         21.44           16         86         21.92         101           16         86         21.92         101           16         86         21.84         21.84         21.84           80.5         1         80.55         21.84         21.84           80.5         1         80.55         21.84         23.84           80.5         90.5         90.55         23.84         23.84           80.55         80.25         80.25         23.86         23.86</td><td>\$0.5         <t< td=""><td>≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.6         ≤0           ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5           ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5           ≤0.25         ≤0.25         ≤0.25         ≤0.25         ≤0.20 
       ≤0           ≤0.25         ≤0.25         ≤0.25         ≤0.20         ≤0         ≤0           ≤0.25         ≤0.25         ≤0.25         ≤0.20         ≤0         ≤0           ≥20         ≥0.25         ≤0.25         ≤0.24         ≥0.4         ≤0           ×0.05         ≈20.5         ≤0.1         ≤0.4         ≥0.4         ≤0         ≤0           ×0.15         ≈0.25         ≥0.4         ≤0.5         ≤0         ≥0         ≤0         <td< td=""><td>\$0.5         \$0.5         \$0.5         \$0.5         \$2.64         \$15.6         \$1.84         \$15.6         \$1.84         \$15.7         \$1.85         \$1.85         \$1.85         \$1.85         \$15.7         \$15.6         \$2.65         \$15.25         \$10.25         \$20.10         \$10.7         \$2.01         \$10.7         \$2.01         \$10.7         \$2.01</td><td>40.5         90.5         20.5         2.64         150           261         263         20.5         21.264         157           261         263         20.5         21.26         151         151           261         263         20.5         20.5         21.26         151         155           261.5         20.25         20.25         21.26         151         155           202.5         20.25         20.25         20.1         151         155           202.5         20.0         20.0         20.4         21.4         21.4           MIC50         MIC90         Range         n         16         26.4         23.4           201.4         20.5         24         21.4         23.4         23.4         23.4           MIC50         MIC90         Range         21.4         23.6         23.4         23.4           20.5         24.4         23.5         20.5         24.2         23.4         23.4           20.5         24.5         25.5         24.5         23.4         23.4         23.4         23.4           20.5         20.55         20.25         20.16         23.4</td><td>90.5         90.5.         26.6.         ≥ 80.5.         26.6         15           90.5         90.5         30.5.         ≥ 84         157         157           21         36         30.5         30.5.         4157         157         151           21         36         30.5.         4157         157         151         156           20.25         30.25         20.25         1         150         152         151         150           20.25         30.25         30.25         20         1         150         1         157         1         157         1         157         1         157         1         157         1         157         1         155         1         156         2         1         156         2         1         156         2         1         156         2         1         157         1         157         2         1         157         2         1         157         2         1         2         2         2         2         2         2         2         2         2         2         2         2         2         2         2         2         2</td><td>90.5         90.5.         260.5         260.5         30.5.         260.4         150           90.5         90.5         30.5.         26.4         150         150           20.5         30.5         30.5.         41.55         150         151         150           20.5         30.5         30.5.         26.5         21.4         155         151         150           20.25         30.25         30.25         210         155         20.25         1         150           20.25         21.0         20.25         21.0         1         150         20.4           MIC50         MIC90         Range         n         20.25         20.4         10.4         20.4         20.4         20.4         20.4         20.4         20.4         20.4         20.4         20.4</td><td>90.5         90.5.         26.4         30.5.         26.4         15.6           90.5         90.5         30.5.         26.4         15.6         15.7           91.5         90.5         30.5.         4         15.7         15.7         15.7           91.5         50.5.5         50.25.5         51.25.5         15.1         150         150           92.0.5         50.25.5         51.0.25.7         150         20.4         157         150           92.0.5         50.25.5         50.25.5         10.4         150         20.4         21.4           MIC50         MIC90         Range         1         20.25.2         2.1         20.25           20.14         50.25         21.4         20.25.2         2.1         20.25         2.1           MIC50         MIC90         Range         2.1         <t< td=""><td>90.5         90.5.         264         315.         264         156           90.5         90.5         30.5.         264         157         315.         41         157           21         36         30.5.         30.5.         30.5.         41         157           20.5         50.55         50.25         51         250         41         157           20.55         50.25         50.25         20         1         157         21           20.25         30.25         30.25         1         150         21         450           20.25         30.25         30.25         20         41         21         460         21           20.55         21         4         20.25         21         40         21         40         21           20.5         21         4         20.25         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21</td><td>90.5         90.5.         26.6.         5         90.5.         26.4         15.6           90.5         90.5         90.5         90.5         90.5         15.6         15.7         15.1         15.7         16.7         15.7         16.7         15.7         16.7         17.6         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         17.7         17.7         17.7         1</td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td>90.5         90.5.         260.5         260.5         260.5         260.4         150.5           20.5         20.5         20.5         20.5         20.5         21.4         157.5           20.5         20.5         20.5         20.5         21.4         157.5         21.4         157.5           20.5         20.5         20.5         20.5         21.4         155.5         20.5         1         150.5           20.5         20.5         20.5         20.5         20.5         1         150.5         20.4         20.5         20.5         20.5         20.5         20.4         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.4         20.5         20.5         20.4         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5     
   20.4         20.5         20.4         20.5         20.4         20.4         20.5         20.5         20.4&lt;</td><td>90.5         90.5.         264         30.5.         264         315           90.5         90.5         30.5.         26.4         315         315           91.5         80.5         30.5.         41.57         315         316         317         316</td><td>90.5         90.5.         264         30.5.         264         156           90.5         90.5         90.5.         20.5.         4         157           91.5         80.5         90.5.         20.5.         4         157           91.5         80.5         80.5.         80.25.         41         157           91.5         80.5         80.25.         41         157           92.5         80.25         80.25.         41         157           90.5         80.25         1         50.25         8         214           MIC50         MIC90         Range         1         232         241           90.5         21         30.5.25         8         233         241           90.5         31         90.25-26         241         233         241           90.5         30.5         50.25         20.25         241         233         241           90.5         30.5         50.25         241         233         241         241           90.5         30.25         20.25         214         233         241         241           90.5         20.25         20.25</td><td>90.5         90.5.         264         30.5.         264         156           90.5         90.5         30.5.         4         157         44         157           90.5         90.5         80.5         40.5         41         157         44         157           90.5         80.5         80.55         80.25         41         157         41         157           90.5         80.25         80.25         10         323         104         11         157         114         157         114         157         114         157         114         157         114         157         11</td><td>90.5         90.5.         26.4         30.5.         26.4         15.6           90.5         90.5         30.5.         26.4         15.6         15.7           91.5         90.5         90.5         30.5.         41         15.7           91.5         90.5         90.5         30.5.         41         15.7           91.5         90.5         90.5         30.5.         41         15.7           90.5         90.5         90.25         41         15.7         15.7           90.5         20.25         1         50.25         2.4         15.2           90.5         20.4         21.4         23.2         20.4         23.2           90.5         20.5         20.5         20.5         2.4         23.2           90.5         30.5         30.5         20.25         2.4         23.2           90.5         30.5         30.5         20.25         2.4         23.2           90.5         30.5         30.5         20.25         2.4         114           90.5         30.5         30.25         2.4         114         2.7           90.5         20.5         20.5         2</td><td>90.5         90.5         26.4         30.5.         26.4         15.6           90.5         90.5         30.5.         26.4         15.6           90.5         80.5         30.5.         4         15.7           90.5         80.5         50.5.         21.4         15.7           90.5         80.5         50.25         4         15.7           90.5         80.25         1         15.6         21.4           90.5         80.25         1         15.2         21.4           90.5         20.25         1         50.25         21.4           90.5         21.4         21.7         20.4         21.4           90.5         21.4         21.7         21.4         21.7           90.5         21.4         21.7         21.4         21.7           90.5         21.5         20.25-2.8         21.4         21.7           90.5         30.5         20.25-2.46         11.7         21.4           216         21.7         20.12         21.4         11.7           216         21.7         20.12         21.4         11.7           216         21.7         21.7</td><td>90.5         90.5         <math>20.5</math> <math>20.5</math><td>90.5         <t< td=""><td>90.5         90.5         29.6         30.5         29.6         30.5         20.5         20.5         30.5         <th< td=""><td>90.5         <th< td=""></th<></td></th<></td></t<></td></td></t<></td></td<></td></t<></td></td<> | 30.5         30.5. 20.5. 246         *           26.4         26.4         15.6           30.5         30.5.         30.5.         4           31.6         30.5.         30.5.         4         15.7           31.7         30.5         30.5.         4         15.7           32.0.5         30.25         30.25.         4         15.7           30.25         30.25         30.25.         1         15.6           30.25         30.25         30.25.         1         15.7           30.25         30.25         30.25.         1         15.7           30.25         30.25         30.25         1         15.7          
30.44         31.7         30.14         1         15.7           30.44         31.7         30.4         31.4           30.5         30.25         21.4         1         31.4           30.5         30.4         8.4         21.4         21.4           30.5         30.4         30.25         21.4         31.7           30.5         30.4         30.25         30.4         31.4           30.5         30.4         30.25         31.2   
  | 90.5         90.5.         20.5.         26.4         50.5.         26.4         150.5           90.5         90.5         90.5.         30.5.         41.55         41.57           90.5         90.5         90.5         90.5.         41.57         41.57           90.5         90.5         90.5         50.25         41         157           90.25         80.25         80.25         41         155           90.25         80.25         41         155           90.25         80.25         41         155           90.25         80.25         20.44         21.44           16         86         47.84         21.44           16         86         21.92         101           16         86         21.92         101           16         86         21.84         21.84         21.84           80.5         1         80.55         21.84         21.84           80.5         1         80.55         21.84         23.84           80.5         90.5         90.55         23.84         23.84           80.55         80.25         80.25         23.86         23.86   
  | \$0.5         \$0.5 <t< td=""><td>≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.6         ≤0           ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5           ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5           ≤0.25         ≤0.25         ≤0.25         ≤0.25         ≤0.20         ≤0           ≤0.25         ≤0.25         ≤0.25         ≤0.20         ≤0         ≤0           ≤0.25         ≤0.25         ≤0.25         ≤0.20         ≤0         ≤0           ≥20         ≥0.25         ≤0.25         ≤0.24         ≥0.4         ≤0           ×0.05         ≈20.5         ≤0.1         ≤0.4         ≥0.4         ≤0         ≤0           ×0.15         ≈0.25         ≥0.4         ≤0.5         ≤0         ≥0         ≤0         <td< td=""><td>\$0.5         \$0.5         \$0.5         \$0.5         \$2.64         \$15.6         \$1.84         \$15.6         \$1.84         \$15.7         \$1.85         \$1.85         \$1.85         \$1.85         \$15.7         \$15.6         \$2.65         \$15.25         \$10.25         \$20.10         \$10.7         \$2.01         \$10.7         \$2.01         \$10.7         \$2.01</td><td>40.5         90.5         20.5         2.64         150           261         263         20.5         21.264         157           261         263         20.5         21.26         151         151        
  261         263         20.5         20.5         21.26         151         155           261.5         20.25         20.25         21.26         151         155           202.5         20.25         20.25         20.1         151         155           202.5         20.0         20.0         20.4         21.4         21.4           MIC50         MIC90         Range         n         16         26.4         23.4           201.4         20.5         24         21.4         23.4         23.4         23.4           MIC50         MIC90         Range         21.4         23.6         23.4         23.4           20.5         24.4         23.5         20.5         24.2         23.4         23.4           20.5         24.5         25.5         24.5         23.4         23.4         23.4         23.4           20.5         20.55         20.25         20.16         23.4</td><td>90.5         90.5.         26.6.         ≥ 80.5.         26.6         15           90.5         90.5         30.5.         ≥ 84         157         157           21         36         30.5         30.5.         4157         157         151           21         36         30.5.         4157         157         151         156           20.25         30.25         20.25         1         150         152         151         150           20.25         30.25         30.25         20         1         150         1         157         1         157         1         157         1         157         1         157         1         157         1         155         1         156         2         1         156         2         1         156         2         1         156         2         1         157         1         157         2         1         157         2         1         157         2         1         2         2         2         2         2         2         2         2         2         2         2         2         2         2         2         2         2</td><td>90.5         90.5.         260.5         260.5         30.5.         260.4         150           90.5         90.5         30.5.         26.4         150         150           20.5         30.5         30.5.         41.55         150         151         150           20.5         30.5         30.5.         26.5         21.4         155         151         150           20.25         30.25         30.25         210         155         20.25         1         150           20.25         21.0         20.25         21.0         1         150         20.4           MIC50         MIC90         Range         n         20.25         20.4         10.4         20.4         20.4         20.4         20.4         20.4         20.4         20.4         20.4         20.4</td><td>90.5         90.5.         26.4         30.5.         26.4         15.6           90.5         90.5         30.5.         26.4         15.6         15.7           91.5         90.5         30.5.         4         15.7         15.7         15.7           91.5         50.5.5         50.25.5         51.25.5         15.1         150         150           92.0.5         50.25.5         51.0.25.7         150         20.4         157         150           92.0.5         50.25.5         50.25.5         10.4         150         20.4         21.4           MIC50         MIC90         Range         1         20.25.2         2.1         20.25           20.14         50.25         21.4         20.25.2         2.1         20.25         2.1           MIC50         MIC90         Range         2.1         <t< td=""><td>90.5         90.5.         264         315.         264         156           90.5         90.5         30.5.         264         157         315.         41         157           21         36         30.5.         30.5.         30.5.         41         157           20.5         50.55         50.25         51         250         41         157           20.55         50.25         50.25         20         1         157         21           20.25         30.25         30.25         1         150         21         450           20.25         30.25         30.25         20         41         21         460         21           20.55         21         4         20.25         21         40         21         40         21           20.5         21         4         20.25         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21</td><td>90.5         90.5.         26.6.         5         90.5.         26.4         15.6           90.5         90.5         90.5         90.5         90.5         15.6         15.7         15.1         15.7         16.7         15.7         16.7         15.7         16.7         17.6         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         17.7         17.7         17.7         1</td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td>90.5         90.5.         260.5         260.5         260.5         260.4         150.5           20.5         20.5         20.5         20.5         20.5         21.4         157.5           20.5         20.5         20.5         20.5         21.4         157.5         21.4         157.5           20.5         20.5         20.5         20.5         21.4         155.5         20.5         1         150.5           20.5         20.5         20.5         20.5         20.5         1         150.5         20.4         20.5         20.5         20.5         20.5         20.4         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.4         20.5         20.5         20.4         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.4         20.5         20.5         20.4&lt;</td><td>90.5         90.5.         264         30.5.         264         315           90.5         90.5         30.5.         26.4         315         315           91.5         80.5         30.5.         41.57         315         316         317         316</td><td>90.5         90.5.         264         30.5.         264         156           90.5         90.5         90.5.         20.5.         4         157           91.5         80.5         90.5.         20.5.         4         157           91.5         80.5         80.5.         80.25.         41         157           91.5         80.5         80.25.         41         157           92.5         80.25         80.25.         41         157           90.5         80.25         1         50.25         8         214           MIC50         MIC90         Range         1         232         241           90.5         21         30.5.25         8         233         241           90.5         31         90.25-26         241         233         241           90.5         30.5         50.25         20.25         241         233         241           90.5         30.5         50.25         241         233         241         241           90.5         30.25         20.25         214         233         241         241           90.5   
     20.25         20.25</td><td>90.5         90.5.         264         30.5.         264         156           90.5         90.5         30.5.         4         157         44         157           90.5         90.5         80.5         40.5         41         157         44         157           90.5         80.5         80.55         80.25         41         157         41         157           90.5         80.25         80.25         10         323         104         11         157         114         157         114         157         114         157         114         157         114         157         11</td><td>90.5         90.5.         26.4         30.5.         26.4         15.6           90.5         90.5         30.5.         26.4         15.6         15.7           91.5         90.5         90.5         30.5.         41         15.7           91.5         90.5         90.5         30.5.         41         15.7           91.5         90.5         90.5         30.5.         41         15.7           90.5         90.5         90.25         41         15.7         15.7           90.5         20.25         1         50.25         2.4         15.2           90.5         20.4         21.4         23.2         20.4         23.2           90.5         20.5         20.5         20.5         2.4         23.2           90.5         30.5         30.5         20.25         2.4         23.2           90.5         30.5         30.5         20.25         2.4         23.2           90.5         30.5         30.5         20.25         2.4         114           90.5         30.5         30.25         2.4         114         2.7           90.5         20.5         20.5         2</td><td>90.5         90.5         26.4         30.5.         26.4         15.6           90.5         90.5         30.5.         26.4         15.6           90.5         80.5         30.5.         4         15.7           90.5         80.5         50.5.         21.4         15.7           90.5         80.5         50.25         4         15.7           90.5         80.25         1         15.6         21.4           90.5         80.25         1         15.2         21.4           90.5         20.25         1         50.25         21.4           90.5         21.4         21.7         20.4         21.4           90.5         21.4         21.7         21.4         21.7           90.5         21.4         21.7         21.4         21.7           90.5         21.5         20.25-2.8         21.4         21.7           90.5         30.5         20.25-2.46         11.7         21.4           216         21.7         20.12         21.4         11.7           216         21.7         20.12         21.4         11.7           216         21.7         21.7</td><td>90.5         90.5         <math>20.5</math> <math>20.5</math><td>90.5         <t< td=""><td>90.5         90.5         29.6         30.5         29.6         30.5         20.5         20.5         30.5         <th< td=""><td>90.5         <th< td=""></th<></td></th<></td></t<></td></td></t<></td></td<></td></t<> | ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.6         ≤0           ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5           ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5         ≤0.5           ≤0.25         ≤0.25         ≤0.25         ≤0.25         ≤0.20         ≤0           ≤0.25         ≤0.25         ≤0.25         ≤0.20         ≤0         ≤0           ≤0.25         ≤0.25         ≤0.25         ≤0.20         ≤0         ≤0           ≥20         ≥0.25         ≤0.25         ≤0.24         ≥0.4         ≤0           ×0.05         ≈20.5         ≤0.1         ≤0.4         ≥0.4         ≤0         ≤0           ×0.15         ≈0.25         ≥0.4         ≤0.5         ≤0         ≥0         ≤0 <td< td=""><td>\$0.5         \$0.5         \$0.5         \$0.5         \$2.64         \$15.6         \$1.84         \$15.6         \$1.84         \$15.7         \$1.85         \$1.85         \$1.85         \$1.85         \$15.7         \$15.6         \$2.65         \$15.25         \$10.25         \$20.10         \$10.7         \$2.01         \$10.7         \$2.01         \$10.7         \$2.01</td><td>40.5         90.5         20.5         2.64         150           261         263         20.5         21.264         157           261         263         20.5         21.26         151         151           261         263         20.5         20.5         21.26         151         155           261.5         20.25         20.25         21.26         151         155           202.5         20.25         20.25         20.1         151         155           202.5         20.0         20.0         20.4        
21.4         21.4           MIC50         MIC90         Range         n         16         26.4         23.4           201.4         20.5         24         21.4         23.4         23.4         23.4           MIC50         MIC90         Range         21.4         23.6         23.4         23.4           20.5         24.4         23.5         20.5         24.2         23.4         23.4           20.5         24.5         25.5         24.5         23.4         23.4         23.4         23.4           20.5         20.55         20.25         20.16         23.4</td><td>90.5         90.5.         26.6.         ≥ 80.5.         26.6         15           90.5         90.5         30.5.         ≥ 84         157         157           21         36         30.5         30.5.         4157         157         151           21         36         30.5.         4157         157         151         156           20.25         30.25         20.25         1         150         152         151         150           20.25         30.25         30.25         20         1         150         1         157         1         157         1         157         1         157         1         157         1         157         1         155         1         156         2         1         156         2         1         156         2         1         156         2         1         157         1         157         2         1         157         2         1         157         2         1         2         2         2         2         2         2         2         2         2         2         2         2         2         2         2         2         2</td><td>90.5         90.5.         260.5         260.5         30.5.         260.4         150           90.5         90.5         30.5.         26.4         150         150           20.5         30.5         30.5.         41.55         150         151         150           20.5         30.5         30.5.         26.5         21.4         155         151         150           20.25         30.25         30.25         210         155         20.25         1         150           20.25         21.0         20.25         21.0         1         150         20.4           MIC50         MIC90         Range         n         20.25         20.4         10.4         20.4         20.4         20.4         20.4         20.4         20.4         20.4         20.4         20.4</td><td>90.5         90.5.         26.4         30.5.         26.4         15.6           90.5         90.5         30.5.         26.4         15.6         15.7           91.5         90.5         30.5.         4         15.7         15.7         15.7           91.5         50.5.5         50.25.5         51.25.5         15.1         150         150           92.0.5         50.25.5         51.0.25.7         150         20.4         157         150           92.0.5         50.25.5         50.25.5         10.4         150         20.4         21.4           MIC50         MIC90         Range         1         20.25.2         2.1         20.25           20.14         50.25         21.4         20.25.2         2.1         20.25         2.1           MIC50         MIC90         Range         2.1         <t< td=""><td>90.5         90.5.         264         315.         264         156           90.5         90.5         30.5.         264         157         315.         41         157           21         36         30.5.         30.5.         30.5.         41         157           20.5         50.55         50.25         51         250         41         157           20.55         50.25         50.25         20         1         157         21           20.25         30.25         30.25         1         150         21         450           20.25         30.25         30.25         20         41         21         460         21           20.55         21         4         20.25         21         40         21         40         21           20.5         21         4         20.25         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21</td><td>90.5         90.5.         26.6.         5         90.5.         26.4         15.6           90.5         90.5         90.5         90.5         90.5         15.6         15.7         15.1         15.7         16.7         15.7         16.7         15.7         16.7         17.6         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         17.7         17.7         17.7         1</td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td>90.5         90.5.         260.5         260.5         260.5         260.4         150.5           20.5         20.5         20.5         20.5         20.5         21.4         157.5           20.5         20.5         20.5         20.5         21.4         157.5         21.4         157.5           20.5         20.5         20.5         20.5         21.4         155.5         20.5         1         150.5           20.5         20.5         20.5         20.5         20.5         1         150.5         20.4         20.5         20.5         20.5         20.5         20.4         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.4         20.5         20.5         20.4         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.4         20.5         20.5         20.4&lt;</td><td>90.5         90.5.         264         30.5.         264         315           90.5         90.5         30.5.         26.4         315         315           91.5         80.5         30.5.         41.57         315         316         317         316</td><td>90.5         90.5.         264         30.5.         264         156           90.5         90.5         90.5.         20.5.         4         157           91.5         80.5         90.5.         20.5.         4         157           91.5         80.5         80.5.         80.25.         41         157           91.5         80.5         80.25.         41         157           92.5         80.25         80.25.         41         157           90.5         80.25         1         50.25         8         214           MIC50         MIC90         Range         1         232         241           90.5         21         30.5.25         8         233         241           90.5         31         90.25-26         241         233         241           90.5         30.5         50.25         20.25         241         233         241           90.5         30.5         50.25         241         233         241         241           90.5         30.25         20.25         214         233         241         241           90.5         20.25         20.25</td><td>90.5         90.5.         264         30.5.         264         156           90.5         90.5         30.5.         4         157         44         157           90.5         90.5         80.5         40.5         41         157         44         157           90.5    
    80.5         80.55         80.25         41         157         41         157           90.5         80.25         80.25         10         323         104         11         157         114         157         114         157         114         157         114         157         114         157         11</td><td>90.5         90.5.         26.4         30.5.         26.4         15.6           90.5         90.5         30.5.         26.4         15.6         15.7           91.5         90.5         90.5         30.5.         41         15.7           91.5         90.5         90.5         30.5.         41         15.7           91.5         90.5         90.5         30.5.         41         15.7           90.5         90.5         90.25         41         15.7         15.7           90.5         20.25         1         50.25         2.4         15.2           90.5         20.4         21.4         23.2         20.4         23.2           90.5         20.5         20.5         20.5         2.4         23.2           90.5         30.5         30.5         20.25         2.4         23.2           90.5         30.5         30.5         20.25         2.4         23.2           90.5         30.5         30.5         20.25         2.4         114           90.5         30.5         30.25         2.4         114         2.7           90.5         20.5         20.5         2</td><td>90.5         90.5         26.4         30.5.         26.4         15.6           90.5         90.5         30.5.         26.4         15.6           90.5         80.5         30.5.         4         15.7           90.5         80.5         50.5.         21.4         15.7           90.5         80.5         50.25         4         15.7           90.5         80.25         1         15.6         21.4           90.5         80.25         1         15.2         21.4           90.5         20.25         1         50.25         21.4           90.5         21.4         21.7         20.4         21.4           90.5         21.4         21.7         21.4         21.7           90.5         21.4         21.7         21.4         21.7           90.5         21.5         20.25-2.8         21.4         21.7           90.5         30.5         20.25-2.46         11.7         21.4           216         21.7         20.12         21.4         11.7           216         21.7         20.12         21.4         11.7           216         21.7         21.7</td><td>90.5         90.5         <math>20.5</math> <math>20.5</math><td>90.5         <t< td=""><td>90.5         90.5         29.6         30.5         29.6         30.5         20.5         20.5         30.5         <th< td=""><td>90.5         <th< td=""></th<></td></th<></td></t<></td></td></t<></td></td<> | \$0.5         \$0.5         \$0.5         \$0.5         \$2.64         \$15.6         \$1.84         \$15.6         \$1.84         \$15.7         \$1.85         \$1.85         \$1.85         \$1.85         \$15.7         \$15.6         \$2.65         \$15.25         \$10.25         \$20.10         \$10.7         \$2.01         \$10.7         \$2.01         \$10.7         \$2.01   
   
   | 40.5         90.5         20.5         2.64         150           261         263         20.5         21.264         157           261         263         20.5         21.26         151         151           261         263         20.5         20.5         21.26         151         155           261.5         20.25         20.25         21.26         151         155           202.5         20.25         20.25         20.1         151         155           202.5         20.0         20.0         20.4         21.4         21.4           MIC50         MIC90         Range         n         16         26.4         23.4           201.4         20.5         24         21.4         23.4         23.4         23.4           MIC50         MIC90         Range         21.4         23.6         23.4         23.4           20.5         24.4         23.5         20.5         24.2         23.4         23.4           20.5         24.5         25.5         24.5         23.4         23.4         23.4         23.4           20.5         20.55         20.25         20.16         23.4  
   
   | 90.5         90.5.         26.6.         ≥ 80.5.         26.6         15           90.5         90.5         30.5.         ≥ 84         157         157           21         36         30.5         30.5.         4157         157         151           21         36         30.5.         4157         157         151         156           20.25         30.25         20.25         1         150         152         151         150           20.25         30.25         30.25         20         1         150         1         157         1         157         1         157         1         157         1         157         1         157         1         155         1         156         2         1         156         2         1         156         2         1         156         2         1         157         1         157         2         1         157         2         1         157         2         1         2         2         2         2         2         2         2         2         2         2         2         2         2         2         2         2         2   | 90.5         90.5.         260.5         260.5         30.5.         260.4         150           90.5         90.5         30.5.         26.4         150         150           20.5         30.5         30.5.         41.55         150         151         150           20.5         30.5         30.5.         26.5         21.4         155         151         150           20.25         30.25         30.25         210         155         20.25         1         150           20.25         21.0         20.25         21.0         1         150         20.4           MIC50         MIC90         Range         n         20.25         20.4         10.4         20.4         20.4         20.4         20.4         20.4         20.4         20.4         20.4         20.4   
   
   | 90.5         90.5.         26.4         30.5.         26.4         15.6           90.5         90.5         30.5.         26.4         15.6         15.7           91.5         90.5         30.5.         4         15.7         15.7         15.7           91.5         50.5.5         50.25.5         51.25.5         15.1         150         150           92.0.5         50.25.5         51.0.25.7         150         20.4         157         150           92.0.5         50.25.5         50.25.5         10.4         150         20.4         21.4           MIC50         MIC90         Range         1         20.25.2         2.1         20.25           20.14         50.25         21.4         20.25.2         2.1         20.25         2.1           MIC50         MIC90         Range         2.1 <t< td=""><td>90.5         90.5.         264         315.         264         156           90.5         90.5         30.5.         264         157         315.         41         157           21         36         30.5.         30.5.         30.5.         41         157           20.5         50.55         50.25         51         250         41         157           20.55         50.25         50.25         20         1         157         21           20.25         30.25         30.25         1         150         21         450           20.25         30.25         30.25         20         41         21         460         21           20.55         21         4         20.25         21         40         21         40         21           20.5         21         4         20.25         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21</td><td>90.5         90.5.         26.6.         5         90.5.         26.4         15.6           90.5         90.5         90.5         90.5         90.5         15.6         15.7         15.1         15.7         16.7         15.7         16.7         15.7         16.7         17.6         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         17.7         17.7         17.7         1</td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td>90.5         90.5.         260.5         260.5         260.5         260.4         150.5           20.5         20.5         20.5         20.5         20.5         21.4         157.5           20.5         20.5         20.5         20.5         21.4         157.5         21.4         157.5           20.5         20.5         20.5         20.5         21.4         155.5         20.5         1         150.5           20.5         20.5         20.5         20.5         20.5         1         150.5         20.4         20.5         20.5         20.5         20.5         20.4         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.4         20.5         20.5         20.4         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.4         20.5         20.5         20.4&lt;</td><td>90.5         90.5.         264         30.5.         264         315           90.5         90.5         30.5.         26.4         315         315           91.5         80.5         30.5.         41.57         315         316         317         316</td><td>90.5         90.5.         264         30.5.         264         156           90.5         90.5         90.5.         20.5.         4         157           91.5         80.5         90.5.         20.5.         4         157           91.5         80.5         80.5.         80.25.         41         157           91.5         80.5         80.25.         41         157           92.5         80.25         80.25.         41         157           90.5         80.25         1         50.25         8         214           MIC50         MIC90         Range         1         232         241           90.5         21         30.5.25         8         233         241           90.5         31         90.25-26         241         233         241           90.5         30.5         50.25         20.25         241         233         241           90.5         30.5         50.25         241         233         241         241           90.5         30.25         20.25         214         233         241         241           90.5         20.25         20.25</td><td>90.5         90.5.         264         30.5.         264         156           90.5         90.5         30.5.         4         157         44         157           90.5         90.5         80.5         40.5         41         157         44         157           90.5         80.5         80.55         80.25         41         157         41         157           90.5         80.25         80.25         10         323         104         11         157         11         157         11         157         11         157         11         157         11         157         11         157         11         157         11         157         11         157         11         157         11         157         11         157         11         157         11         157         11         157         11         157         11         157         11       
 157         11         157         11         157         11         157         11         157         11         157         114         157         114         157         114         157         114         157         114         157         11</td><td>90.5         90.5.         26.4         30.5.         26.4         15.6           90.5         90.5         30.5.         26.4         15.6         15.7           91.5         90.5         90.5         30.5.         41         15.7           91.5         90.5         90.5         30.5.         41         15.7           91.5         90.5         90.5         30.5.         41         15.7           90.5         90.5         90.25         41         15.7         15.7           90.5         20.25         1         50.25         2.4         15.2           90.5         20.4         21.4         23.2         20.4         23.2           90.5         20.5         20.5         20.5         2.4         23.2           90.5         30.5         30.5         20.25         2.4         23.2           90.5         30.5         30.5         20.25         2.4         23.2           90.5         30.5         30.5         20.25         2.4         114           90.5         30.5         30.25         2.4         114         2.7           90.5         20.5         20.5         2</td><td>90.5         90.5         26.4         30.5.         26.4         15.6           90.5         90.5         30.5.         26.4         15.6           90.5         80.5         30.5.         4         15.7           90.5         80.5         50.5.         21.4         15.7           90.5         80.5         50.25         4         15.7           90.5         80.25         1         15.6         21.4           90.5         80.25         1         15.2         21.4           90.5         20.25         1         50.25         21.4           90.5         21.4         21.7         20.4         21.4           90.5         21.4         21.7         21.4         21.7           90.5         21.4         21.7         21.4         21.7           90.5         21.5         20.25-2.8         21.4         21.7           90.5         30.5         20.25-2.46         11.7         21.4           216         21.7         20.12         21.4         11.7           216         21.7         20.12         21.4         11.7           216         21.7         21.7</td><td>90.5         90.5         <math>20.5</math> <math>20.5</math><td>90.5         <t< td=""><td>90.5         90.5         29.6         30.5         29.6         30.5         20.5         20.5         30.5         <th< td=""><td>90.5         <th< td=""></th<></td></th<></td></t<></td></td></t<>  | 90.5         90.5.         264         315.         264         156           90.5         90.5         30.5.         264         157         315.         41         157           21         36         30.5.         30.5.         30.5.         41         157           20.5         50.55         50.25         51         250         41         157           20.55         50.25         50.25         20         1         157         21           20.25         30.25         30.25         1         150         21         450           20.25         30.25         30.25         20         41         21         460         21           20.55         21         4         20.25         21         40         21         40         21           20.5         21         4         20.25         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21         40         21   
   
  | 90.5         90.5.         26.6.         5         90.5.         26.4         15.6           90.5         90.5         90.5         90.5         90.5         15.6         15.7         15.1         15.7         16.7         15.7         16.7         15.7         16.7         17.6         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         16.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         15.7         17.7         17.7         17.7         17.7         1   
  | $ \begin{array}{c c c c c c c c c c c c c c c c c c c $   | 90.5         90.5.         260.5         260.5         260.5         260.4         150.5           20.5         20.5         20.5         20.5         20.5         21.4         157.5           20.5         20.5         20.5         20.5         21.4         157.5         21.4         157.5           20.5         20.5         20.5         20.5         21.4         155.5         20.5         1         150.5           20.5         20.5         20.5         20.5         20.5         1         150.5         20.4         20.5         20.5         20.5         20.5         20.4         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.4         20.5         20.5         20.4         20.5         20.5         20.5         20.5         20.5         20.5         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.5         20.4         20.4         20.5         20.5         20.4<  
  | 90.5         90.5.         264         30.5.         264         315           90.5         90.5         30.5.         26.4         315         315           91.5         80.5         30.5.         41.57         315         316         317         316   | 90.5         90.5.         264         30.5.         264         156           90.5         90.5         90.5.         20.5.         4         157           91.5         80.5         90.5.         20.5.         4         157           91.5         80.5         80.5.         80.25.         41         157           91.5         80.5         80.25.         41         157           92.5         80.25         80.25.         41         157           90.5         80.25         1         50.25         8         214           MIC50         MIC90         Range         1         232         241           90.5         21         30.5.25         8         233         241           90.5         31         90.25-26         241         233         241           90.5         30.5         50.25         20.25         241         233         241           90.5         30.5         50.25         241         233         241         241           90.5         30.25         20.25         214         233         241         241           90.5         20.25         20.25  
  | 90.5         90.5.         264         30.5.         264         156           90.5         90.5         30.5.         4         157         44         157           90.5         90.5         80.5         40.5         41         157         44         157           90.5         80.5         80.55         80.25         41         157         41         157           90.5         80.25         80.25         10         323         104         11         157         114         157         114         157         114         157         114         157         114         157         11  | 90.5         90.5.         26.4         30.5.      
  26.4         15.6           90.5         90.5         30.5.         26.4         15.6         15.7           91.5         90.5         90.5         30.5.         41         15.7           91.5         90.5         90.5         30.5.         41         15.7           91.5         90.5         90.5         30.5.         41         15.7           90.5         90.5         90.25         41         15.7         15.7           90.5         20.25         1         50.25         2.4         15.2           90.5         20.4         21.4         23.2         20.4         23.2           90.5         20.5         20.5         20.5         2.4         23.2           90.5         30.5         30.5         20.25         2.4         23.2           90.5         30.5         30.5         20.25         2.4         23.2           90.5         30.5         30.5         20.25         2.4         114           90.5         30.5         30.25         2.4         114         2.7           90.5         20.5         20.5         2  | 90.5         90.5         26.4         30.5.         26.4         15.6           90.5         90.5         30.5.         26.4         15.6           90.5         80.5         30.5.         4         15.7           90.5         80.5         50.5.         21.4         15.7           90.5         80.5         50.25         4         15.7           90.5         80.25         1         15.6         21.4           90.5         80.25         1         15.2         21.4           90.5         20.25         1         50.25         21.4           90.5         21.4         21.7         20.4         21.4           90.5         21.4         21.7         21.4         21.7           90.5         21.4         21.7         21.4         21.7           90.5         21.5         20.25-2.8         21.4         21.7           90.5         30.5         20.25-2.46         11.7         21.4           216         21.7         20.12         21.4         11.7           216         21.7         20.12         21.4         11.7           216         21.7         21.7  | 90.5         90.5 $20.5$ <td>90.5         <t< td=""><td>90.5         90.5         29.6         30.5         29.6         30.5         20.5         20.5         30.5         <th< td=""><td>90.5         90.5        
90.5         <th< td=""></th<></td></th<></td></t<></td>   | 90.5         90.5 <t< td=""><td>90.5         90.5         29.6         30.5         29.6         30.5         20.5         20.5         30.5         <th< td=""><td>90.5         <th< td=""></th<></td></th<></td></t<>   | 90.5         90.5         29.6         30.5         29.6         30.5         20.5         20.5         30.5 <th< td=""><td>90.5         <th< td=""></th<></td></th<>   | 90.5         90.5 <th< td=""></th<>   |
| s1-864         216         22.69         s1           s05         s05         215         0,00         s0.5           s1-864         216         50,00         s0.5         s0.5           s1-864         216         0,00         s0.25         s0.25         s1.8         s0.26         s1.8         s0.26         s0.21         s0.20         s0.21           s0.265         s1         216         0,00         s0.21         s0.22  
   
   | s1         84         216         22.69         s1           s0.5         s0.5         215         0,00         s0.5         s0.8           s1<-264   
   
  | s1-864         216         22.69         s1           s0.5         s0.5         215         0,00         s0.5           s0.25-s1         216         0,00         s0.2         s0.2           s0.25-s1         216         0,00         s0.2         s0.2           s0.25-s12         216         0,00         s0.2         s0.2           s0.25-s12         216         0,00         s0.2         s0.2           s0.25-s12         216         0,46         s0.2         s0.2           s0.21         s220         220         82.27         z320         s0.2           s0.13         30.3         30.3         80.5         s0.2         s0.2         s0.2           s10-84         n         %R         MIC5         s0.2         s0.3         s0.5         s0.5         s0.5  
   
   
  | s1<-864   | s1:5-s64         216         0.00         s05           s1:5-s05         215         0.00         s00           s1:264         216         5.09         s1           s0:5-s15         216         0.00         s002           s0:25-s16         216         0.00         s002           s0:25-s16         216         0.00         s002           s0:25-s16         210         82.27         s202           s0:25-s16         210         82.27         s202           s0:13         303         93.29         16           s0:55-s16         n         %R         MC5           s0:55-s16         1         %R         MC5           s0:55-s18         305         195/79         16           s0:55-s18         305         195/79         16           s0:55-s18         305         195/79         16           s0:55-s18         305         16/495         305           s0:55-s18         305         16/495         305           s0:5-s16         *         *         80.5           s0:5-s16         *         16/495         305           s0:55-s15         305         305 <td>s1-264         216         22.69         s1           s1-264         216         20.00         s0.5           s1-264         216         50.0         s0.2           s1-264         216         50.0         s0.2           s1-264         216         0.00         s0.2           s0.25-s4         216         0.00         s0.2           s0.25-s46         210         82.27         s20           s0.135         s20         82.27         s20           s0.135         30         22.0         82.27         s20           s0.135         305         307         9         16           s0.25-s46         30         47.95         80.5         80.5           s0.25-s8         305         42.95         80.5         80.5           s0.25-s8         305         42.95         80.5         80.5           s0.5-s8         281         64.93         80.5         20.5     &lt;</td> <td>s1-864         216         20.09         s1           s1-864         216         20.00         s0.5         s1           s1-864         216         50.0         s0.5         s1           s0.25-s16         216         0.00         s0.2         s0.2         s0.2           s0.25-s16         216         0.00         s0.2         s0.5         s0.5</td> <td>s1-864         216         20.00         s05           s1-864         216         20.00         s05           s1-864         216         50.00         s05           s1-864         216         50.00         s02           s0.25-s1         216         0.00         s02           s0.25-s1         216         0.00         s02           s0.25-s1         210         82.27         s20           s0.13         913         %R         MC5           s0.23         220         82.27         s20           s0.13         305        
42.95         s0.5           s0.2-s8         305         42.95         s0.5           s0.5-s8         305         42.95         s0.5           s0.5-s8         305         42.95         s0.5           s0.5-s8         305         42.95         s0.5           s0.5-s8         282         532         20.5           s0.5-s8         282         532         20.5           s0.5-s8         282         29.5         30.5           s0.5-s8         282         20.5         s0.5           s0.5-s86         29.1         4.93</td> <td>s15 - 8d4         216         22.69         s1           s15 - 8d5         215         0.00         s0.2           s12-8d4         216         5.00         s1           s0.25 - s1         216         0.00         s0.2           s0.25 - s1         216         0.00         s0.2           s0.25 - s1         216         0.46         s0.2           s0.25 - s10         32.21         32.2.7         s2.2.7           s0.13         2013         22.2.7         s20.2           s0.25 - s16         219         92.7.7         s202.           s0.13         7.97         s20.2         s2.2.7         s20.2           s0.14         %R         MC5         s20.2         s20.2           s0.15 - s0         52         15.97.9         16         s0.2           s0.5 - s16         29         15.97.9         16         s0.5           s0.5 - s16         29         15.97.9         30.5         30.5           s0.5 - s16         29         16         49.9         864           s0.5 - s16         29         48.3         30.2         30.2           s0.25 - s16         29         48.3         30.2</td> <td>s1- 864         216         22.69         s1           s1- 864         216         20.0         s0         s1           s1- 864         216         50.0         s0         s1           s1- 864         216         50.0         s0         s1           s0.25 - s1         216         0.00         s0         s0         s0           s125 - s1         216         0.46         s0.2         s0         s1           s0.25 - s6         216         0.46         s0.2         s0         s1           s0.25 - s6         201         82.27         s30         s0         s1         s0         s0</td> <td>sf - 864         216         22.69         s1           sf - 864         216         50.00         s0.25           sf - 864         216         50.00         s0.25           sf - 864         216         50.00         s0.25           sf - 265         216         0.00         s0.25           sf - 265         216         0.46         s0.27           sf - 2013         32.27         32.27         32.27           so 13         - 2013         32.27         320           so 14         - 80         29.79         60           so 2013         - 82.27         29.79         60           so 13         - 80         29.79         60           so 2015         30         42.95         30.5           so 14         90         42.95         30.5           so 15-28         30         41.95         30.5           so 15-28         30         41.93         30.2           so 15-28         282         53.2         30.5           so 15-28         282         53.2         30.5           so 105-281         291         4.81         30.2           so 20-55-216         291<td>s1864         216         22.69         s1           s0.5 - s0.5         215         0.00         s0.25           s0.25 - s1         216         0.00         s0.25           s0.25 - s1         216         0.00         s0.25           s0.25 - s1         216         0.00         s0.25           s0.25 - s1         210         92.27         s20.25           s0.25 - s10         32.27         s20.25         s20.25           s0.25 - s0         32.1         s20.27         s20.25           s0.25 - s0         30         4.95         s0.5           s0.25 - s0         30         4.95         s0.5           s0.55 - s16         30         4.95         s0.5           s0.55 - s0         30         4.95         s0.5           s0.55 - s16         30         4.95         s0.5           s0.55 - s16         30         4.95         s0.5           s0.55 - s16         291         4.81         s0.21           s0.55 - s16         291         4.81         s0.21           s0.25 - s06         30.5         7.4.75         s20.2           s0.25 - s16         291         4.81         s0.21</td><td>s18d         216         22.69         s1           s18d         216         20.0         s0.2           s18d         216         50.0         s0.2           s18d         216         50.0         s0.2           s0.25-s16         216         0.00         s0.2           s0.25-s16         216         0.00         s0.2           s0.25-s16         216         0.46         s0.2           s0.21         22.0         82.27         s20           s0.1         2013         307         307         307           s0.5-s16         3         305         49.7         s0.5           s0.5-s16         3         307         49.73         305           s0.5-s16         3         305         49.5         305           s0.5-s16         3         307         44.93         20.5           s0.5-s16         201         4.81         s0.2         30.2           s0.25-s16         201         4.81         s0.2         30.2           s0.25-s16         201         4.81         s0.2         30.2           s0.25-s16         201         4.81         s0.2         s0.2</td><td>s18d         216         20.0         s0.           s18d         216         20.0         s0.           s18d         216         50.0         s0.           s18d         216         50.0         s0.2           s0.25         s16         0.00         s0.2           s0.25         s10         216         0.00         s0.2           s0.25         s10         216         0.00         s0.2           s0.25         s10         220         82.27         s20.2           s0.25         s20         82.27         s20.5         s20.5           s0.55         305         19.79         19.79         16           s0.55         s0.5         s0.5         s0.5         s0.5           s0.55         s0.5         s0.5         s0.5         s0.5           s0.55         s0.5         s0.5         s0.5         s0.5           s0.55         s10         4.81         s0.2         s0.5           s0.55         s10         s0.87         4.81         s0.2           s0.55         s0.6         s0.87         s0.8         s0.5           s0.55         s0.8         s0.8</td><td>s18d         215         20.0         s0.           s18d         216         0.00         s0.2           s18d         216         50.0         s0.2           s18d         216         0.00         s0.2           s0.25 - s16         216         0.00         s0.2           s0.25 - s16         216         0.00         s0.2           s0.25 - s16         216         9.79         s0.2           s0.25 - s16         210         82.27         230           s0.1         82.3         95.79         16           s10-33         305         19.79         16           s0.55-s16         21         30         19.79         16           s0.55-s16         21         4.81         20.2         30.5         30.5           s0.55-s16         21         4.81         20.2         30.5         30.5         30.5           s0.55-s16         21         4.81         20.2         s0.5         s0.5         s0.5           s0.25-s16         21         4.81         20.2         s0.8         30.2         s0.2           s0.05-s16         21         4.81         20.2         s0.6         s0.</td><td>s1-8d         216         20.0         s1           s1-8d         216         20.0         s0           s1-8d         216         0.00         s0           s1-8d         216         0.00         s0           s1-8d         216         0.00         s0           s1-8d         216         0.00         s0           s125-816         216         0.00         s0           s0.25-816         210         82.27         s20           s0-1&lt;2320</td>         220         82.27         s20           s0-1         305         197         19         16           s0-25-816         1         %R         MIC5         s0.5           s0-5-816         1         48         305         40.5         305           s0-5-816         1         4.81         s0.2         30         30         30           s0-5-816         20         4.81         20.3         30         3<td>s18d         216         22.69         s1           s18d         216         20.00         90.2           s18d         216         0.00         90.2           s18d         216         0.00         90.2           s18d         216         0.00         90.2           s18d         216         0.00         90.2           s0.25816         210         82.27         230           s02320         22.01         82.27         230           s02320         230         42.95         80.5           s0.25-86         30.5         42.95         80.5           s0.25-86         30.5         42.95         80.5           s0.25-86         231         64.95         80.5           s0.25-86         231         64.95         80.5           s0.25-86         231         64.95         80.5           s0.55-86         231         64.95         80.5           s0.55-86         231         64.95         80.5           s0.55-86         231         67.3         20.2           s0.55-86         231         67.3         20.2           s0.55-86         231</td><td>s1- 864         216         22.69         51           s1- 864         216         0.00         90.5           s1- 864         216         0.00         90.2           s1- 864         216         0.00         90.2           s1- 864         216         0.00         90.2           s0.25 - s16         216         0.04         90.2           s0.25 - s10         82.27         230        
82.27         230.0           s0.25 - s10         30.5         42.95         80.5         80.5           s0.25 - s10         30.5         42.95         80.5         80.5           s0.5 - s10         30.5         42.95         80.5         80.5           s0.5 - s10         30.5         42.95         80.5         80.5           s0.5 - s10         30.5         41.95         80.2         80.5           s0.55 - s16         201         4.81         50.2         80.2         80.2           s0.55 - s16         201         4.81         50.2         80.2         80.2         80.2           s0.55 - s16         201         4.81         80.2         80.2         80.2         80.2         80.2         80.2         80.2<!--</td--><td>s1- 864         216         22.69         51           s1- 864         216         0.00         90.5           s1-864         216         0.00         90.2           s1-864         216         0.00         90.2           s0.25 - s16         216         0.00         90.2           s0.25 - s16         216         0.46         80.2           s0.25 - s16         210         80.2         80.2           s0.25 - s16         219         9.79         616           s0.25 - s16         291         5.97         90.6           s0.5 - s16         291         64.95         80.5           s0.5 - s16         291         64.95         80.5           s0.5 - s16         291         4.81         50.2           s0.55 - s16         291         4.81         50.2           s0.55 - s16         291         4.81         50.2           s0.55 - s16         291         4.81         50.2           s0.05 - s16         291         5.34         20.2           s0.03         57.44         20.2         50.9         20.2           s0.03         57.44         291         20.2         20.2</td><td>s18d         216         20.0         s1           s18d         216         20.0         s0.2           s18d         216         0.00         s0.2           s18d         216         0.00         s0.2           s18d         216         0.00         s0.2           s18d         216         0.00         s0.2           s18d         21         216         s0.2           s18d         21         32.0         82.27         s20.2           s0.25-s16         21         30         30.5         s0.5           s0.5-s16         21         51         53.7         30.5           s0.5-s16         21         4.81         s0.2         s0.5           s0.5-s16         21         4.81         s0.2         s0.5           s0.5-s16         21         4.81         s0.2         s0.5           s0.55-s16         21         4.81         s0.2         s0.2           s0.55-s16         21         4.81         s0.2         s0.6           s0.55-s16         22         52.4         s0.6         s0.6           s0.55-s16         22         52.4         s0.6         s</td><td>s15 - 8d4         216         22.69         51           s15 - 8d5         215         0.00         90.5           s12-8d4         216         0.00         90.2           s12-8d4         216         0.00         90.2           s12-8d4         216         0.00         90.2           s12-8d4         291         897.9         60.2           s0.25 - 86         291         80.2         80.2           s0.25 - 86         291         4.81         80.6           s0.25 - 86         291         64.95         80.5           s0.5 - 268         291         64.95         80.5           s0.5 - 268         291         4.81         80.2           s0.5 - 268         291         4.81         80.2           s0.5 - 268         291         4.81         80.2           s0.5 - 268         292         53.2         80.2           s0.5 - 268         292         52.4         201           s0.65 - 268         292         52.4         20.2           s0.65 - 268         292         52.4         20.2           s0.65 - 268         292         52.4         20.2           s0.65 - 268</td><td>s1-264         216         22.69         s1           s125-s6,         215         0.00         s0.2           s12-s64,         216         0.00         s0.2           s12-s64,         216         0.00         s0.2           s12-s64,         216         0.00         s0.2           s12-s64,         216         0.00         s0.2           s0.25-s6         216         0.46         s0.2           s0.25-s6         291         9.79         16           s0.25-s6         291         4.81         s0.2           s0.5-s6         293         5.24         s0.2           s0.5-s6         291         4.81         s0.2           s0.13         4.81         s0.2</td><td>s1-8d         216         20.0         s1           s1-8d         216         20.0         s0.2           s1-8d         216         50.0         s0.2           s1-8d         216         50.0         s0.2           s1-8d         216         0.00         s0.2           s0.25 - s16         216         0.00         s0.2           s0.25 - s16         210         82.27         s200           s0-230         220         82.27         s20           s0-25 - s16         21         305         915           s0-25 - s16         21         4.81         s0.5           s0.5 - s16         21         4.81         s0.5           s0.5 - s16         21         4.81         s0.5           s0.5 - s16         21         4.81         s0.2           s0.5 - s16         21         4.81         s0.2           s0.5 - s16         21         4.81         s0.2           s0.5 - s16         22         52.9         52.9         s0.2           s0.5 - s16         22         52.9         52.9         s0.2           s0.5 - s16         22         52.9         52.9         22</td><td>s1-8d         216         22.69         s1           s1-8d         216         20.00         s0.2           s1-8d         216         0.00         s0.2           s1-8d         216         0.00         s0.2           s1-8d         216         0.00         s0.2           s0.25-s16         216         0.00         s0.2           s0.25-s16         216         0.46         s0.2           s0.25-s16         219         30.79         16           s0.25-s16         219         30.5         s0.5           s0.25-s16         219         30.5         s0.5           s0.25-s16         219         41.91         s0.2           s0.25-s16         219         41.91         s0.2           s0.55-s16         219         41.81         s0.2           s0.55-s16         219         41.81         s0.2           s0.55-s16         219         41.81         s0.2           s0.55-s16         219         529         529         s21           s0.55-s16         229         529         529         s21           s0.55-s16         229         529         529         s21      &lt;</td><td>s1-8d         216         22.69         51           s1-8d         216         20.00         90.5           s1-8d         216         50.00         90.2           s1-8d         216         50.00         90.2           s1-8d         216         0.00         90.2           s0.25-s16         216         0.00         90.2           s0.25-s16         216         0.46         90.2           s0.25-s16         219         50.79         50.5           s0.25-s16         219         50.79         50.5           s0.25-s18         30.5         42.95         80.5           s0.5-s18         30.5         41.93         50.2           s0.5-s16         201         4.81         50.2         50.2           s0.5-s16         &lt;</td><td>s1-8d         216         22.69         51           s1-8d         216         20.00         50.5           s1-8d         216         50.0         50.5           s1-8d         216         0.00         50.5           s25-s16         216         0.00         50.5           s0.25-s16         216         0.00         50.2           s0.25-s16         210         30.7         20.2           s0.25-s16         210         30.7         20.9           s0.5-s16         21         30.5         4.9         20.5           s0.5-s16         21         50.7         20.0         50.5           s0.5-s16         21         4.81         20.2         20.3         20.5           s0.5-s16         21         4.81         20.2         20.3         20.2           s0.5-s16         21         4.81         20.2         20.5         20.5           s0.5-s16         22         52.9         52.4         20.5         20.5           s0.5-s16         22         52.9         52.4         20.5         20.5           s0.5-s16         22         52.9         52.4         20.5         20.5</td><td>s1-8d         216         22.69         51           s1-8d         216         20.0         90.2           s1-8d         216         50.0         90.2           s1-8d         216         0.00         90.2           s1-8d         216         0.00         90.2           s0.25 - s16         216         0.00         90.2           s0.25 - s16         210         92.1         230           s0.25 - s16         21         9.1         97.79         16           s0.25 - s16         21         305         915         20.5           s0.5 - s16         21         481         20.7         230.5           s0.5 - s16         21         4.81         20.2         305         41.75         230.5           s0.5 - s16         21         4.81         20.2         30.5         41.75         230.2           s0.5 - s16         21         4.81         20.2         30.6         41.8         30.2           s0.5 - s16         229         52.9         52.9         52.6         50.0         51.6           s0.5 - s16         229         52.9         52.9         52.2         52.2         52.2</td></td></td>   
   | s1-264         216         22.69         s1           s1-264         216         20.00         s0.5           s1-264         216         50.0         s0.2           s1-264         216         50.0         s0.2           s1-264         216         0.00         s0.2           s0.25-s4         216         0.00         s0.2           s0.25-s46         210         82.27         s20           s0.135         s20         82.27         s20           s0.135         30         22.0         82.27         s20           s0.135         305         307         9         16           s0.25-s46         30         47.95         80.5         80.5           s0.25-s8         305         42.95         80.5         80.5           s0.25-s8         305         42.95         80.5         80.5           s0.5-s8         281         64.93         80.5         20.5     <  
   | s1-864         216         20.09         s1           s1-864         216         20.00         s0.5         s1           s1-864         216         50.0         s0.5         s1           s0.25-s16         216         0.00         s0.2         s0.2         s0.2           s0.25-s16         216         0.00         s0.2         s0.5   
   | s1-864         216         20.00         s05           s1-864         216         20.00         s05           s1-864         216         50.00         s05           s1-864         216         50.00         s02           s0.25-s1         216         0.00         s02           s0.25-s1         216         0.00         s02           s0.25-s1         210         82.27         s20           s0.13         913         %R         MC5           s0.23         220         82.27         s20           s0.13         305         42.95         s0.5           s0.2-s8         305         42.95         s0.5           s0.5-s8         305         42.95         s0.5           s0.5-s8         305         42.95         s0.5           s0.5-s8         305         42.95         s0.5           s0.5-s8         282         532         20.5           s0.5-s8         282         532         20.5           s0.5-s8         282         29.5         30.5           s0.5-s8         282         20.5         s0.5           s0.5-s86         29.1         4.93   
   
   | s15 - 8d4         216         22.69         s1           s15 - 8d5         215         0.00         s0.2           s12-8d4         216         5.00         s1           s0.25 - s1         216         0.00         s0.2           s0.25 - s1         216         0.00         s0.2           s0.25 - s1         216         0.46         s0.2           s0.25 - s10         32.21         32.2.7         s2.2.7           s0.13         2013         22.2.7         s20.2           s0.25 - s16         219         92.7.7         s202.           s0.13         7.97         s20.2         s2.2.7         s20.2           s0.14         %R         MC5         s20.2         s20.2           s0.15 - s0         52         15.97.9         16         s0.2           s0.5 - s16         29         15.97.9         16         s0.5           s0.5 - s16         29         15.97.9         30.5         30.5           s0.5 - s16         29         16         49.9         864           s0.5 - s16         29         48.3         30.2         30.2           s0.25 - s16         29         48.3         30.2   
   
   | s1- 864         216         22.69         s1  
        s1- 864         216         20.0         s0         s1           s1- 864         216         50.0         s0         s1           s1- 864         216         50.0         s0         s1           s0.25 - s1         216         0.00         s0         s0         s0           s125 - s1         216         0.46         s0.2         s0         s1           s0.25 - s6         216         0.46         s0.2         s0         s1           s0.25 - s6         201         82.27         s30         s0         s1         s0   
   | sf - 864         216         22.69         s1           sf - 864         216         50.00         s0.25           sf - 864         216         50.00         s0.25           sf - 864         216         50.00         s0.25           sf - 265         216         0.00         s0.25           sf - 265         216         0.46         s0.27           sf - 2013         32.27         32.27         32.27           so 13         - 2013         32.27         320           so 14         - 80         29.79         60           so 2013         - 82.27         29.79         60           so 13         - 80         29.79         60           so 2015         30         42.95         30.5           so 14         90         42.95         30.5           so 15-28         30         41.95         30.5           so 15-28         30         41.93         30.2           so 15-28         282         53.2         30.5           so 15-28         282         53.2         30.5           so 105-281         291         4.81         30.2           so 20-55-216         291 <td>s1864         216         22.69         s1           s0.5 - s0.5         215         0.00         s0.25           s0.25 - s1         216         0.00         s0.25           s0.25 - s1         216         0.00         s0.25           s0.25 - s1         216         0.00         s0.25           s0.25 - s1         210         92.27         s20.25           s0.25 - s10         32.27         s20.25         s20.25           s0.25 - s0         32.1         s20.27         s20.25           s0.25 - s0         30         4.95         s0.5           s0.25 - s0         30         4.95         s0.5           s0.55 - s16         30         4.95         s0.5           s0.55 - s0         30         4.95         s0.5           s0.55 - s16         30         4.95         s0.5           s0.55 - s16         30         4.95         s0.5           s0.55 - s16         291         4.81         s0.21           s0.55 - s16         291         4.81         s0.21           s0.25 - s06         30.5         7.4.75         s20.2           s0.25 - s16         291         4.81         s0.21</td> <td>s18d         216         22.69         s1           s18d         216         20.0         s0.2           s18d         216         50.0         s0.2           s18d         216         50.0         s0.2           s0.25-s16         216         0.00         s0.2           s0.25-s16         216         0.00         s0.2           s0.25-s16         216         0.46         s0.2           s0.21         22.0         82.27         s20           s0.1         2013         307         307         307           s0.5-s16         3         305         49.7         s0.5           s0.5-s16         3         307         49.73         305           s0.5-s16         3         305         49.5         305           s0.5-s16         3         307         44.93         20.5           s0.5-s16         201         4.81         s0.2         30.2           s0.25-s16         201         4.81         s0.2         30.2           s0.25-s16         201         4.81         s0.2         30.2           s0.25-s16         201         4.81         s0.2         s0.2</td> <td>s18d         216         20.0         s0.           s18d         216         20.0         s0.           s18d         216         50.0         s0.           s18d         216         50.0         s0.2           s0.25         s16         0.00         s0.2           s0.25         s10         216         0.00       
 s0.2           s0.25         s10         216         0.00         s0.2           s0.25         s10         220         82.27         s20.2           s0.25         s20         82.27         s20.5         s20.5           s0.55         305         19.79         19.79         16           s0.55         s0.5         s0.5         s0.5         s0.5           s0.55         s0.5         s0.5         s0.5         s0.5           s0.55         s0.5         s0.5         s0.5         s0.5           s0.55         s10         4.81         s0.2         s0.5           s0.55         s10         s0.87         4.81         s0.2           s0.55         s0.6         s0.87         s0.8         s0.5           s0.55         s0.8         s0.8</td> <td>s18d         215         20.0         s0.           s18d         216         0.00         s0.2           s18d         216         50.0         s0.2           s18d         216         0.00         s0.2           s0.25 - s16         216         0.00         s0.2           s0.25 - s16         216         0.00         s0.2           s0.25 - s16         216         9.79         s0.2           s0.25 - s16         210         82.27         230           s0.1         82.3         95.79         16           s10-33         305         19.79         16           s0.55-s16         21         30         19.79         16           s0.55-s16         21         4.81         20.2         30.5         30.5           s0.55-s16         21         4.81         20.2         30.5         30.5         30.5           s0.55-s16         21         4.81         20.2         s0.5         s0.5         s0.5           s0.25-s16         21         4.81         20.2         s0.8         30.2         s0.2           s0.05-s16         21         4.81         20.2         s0.6         s0.</td> <td>s1-8d         216         20.0         s1           s1-8d         216         20.0         s0           s1-8d         216         0.00         s0           s1-8d         216         0.00         s0           s1-8d         216         0.00         s0           s1-8d         216         0.00         s0           s125-816         216         0.00         s0           s0.25-816         210         82.27         s20           s0-1&lt;2320</td> 220         82.27         s20           s0-1         305         197         19         16           s0-25-816         1         %R         MIC5         s0.5           s0-5-816         1         48         305         40.5         305           s0-5-816         1         4.81         s0.2         30         30         30           s0-5-816         20         4.81         20.3         30         3 <td>s18d         216         22.69         s1           s18d         216         20.00         90.2           s18d         216         0.00         90.2           s18d         216         0.00         90.2           s18d         216         0.00         90.2           s18d         216         0.00         90.2           s0.25816         210         82.27         230           s02320         22.01         82.27         230           s02320         230         42.95         80.5           s0.25-86         30.5         42.95         80.5           s0.25-86         30.5         42.95         80.5           s0.25-86         231         64.95         80.5           s0.25-86         231         64.95         80.5           s0.25-86         231         64.95         80.5           s0.55-86         231         64.95         80.5           s0.55-86         231         64.95         80.5           s0.55-86         231         67.3         20.2           s0.55-86         231         67.3         20.2           s0.55-86         231</td> <td>s1- 864         216         22.69         51           s1- 864         216         0.00         90.5           s1- 864         216         0.00         90.2           s1- 864         216         0.00         90.2           s1- 864         216         0.00         90.2           s0.25 - s16         216         0.04         90.2           s0.25 - s10         82.27         230         82.27         230.0           s0.25 - s10         30.5         42.95         80.5         80.5           s0.25 - s10         30.5         42.95         80.5         80.5           s0.5 - s10         30.5         42.95         80.5         80.5           s0.5 - s10         30.5         42.95         80.5         80.5           s0.5 - s10         30.5         41.95         80.2         80.5           s0.55 - s16         201         4.81         50.2         80.2         80.2           s0.55 - s16         201         4.81         50.2         80.2         80.2         80.2           s0.55 - s16         201         4.81         80.2         80.2         80.2         80.2         80.2         80.2         80.2<!--</td--><td>s1- 864         216         22.69         51           s1- 864         216         0.00         90.5           s1-864         216         0.00         90.2           s1-864         216         0.00         90.2           s0.25 - s16         216         0.00         90.2           s0.25 - s16         216         0.46         80.2           s0.25 - s16         210         80.2         80.2           s0.25 - s16         219         9.79         616           s0.25 - s16         291         5.97         90.6           s0.5 - s16         291         64.95         80.5           s0.5 - s16         291         64.95         80.5           s0.5 - s16         291         4.81         50.2           s0.55 - s16         291         4.81         50.2           s0.55 - s16         291         4.81         50.2           s0.55 - s16         291         4.81         50.2           s0.05 - s16         291         5.34         20.2           s0.03         57.44         20.2         50.9         20.2           s0.03         57.44         291         20.2         20.2</td><td>s18d         216         20.0         s1           s18d         216         20.0         s0.2           s18d         216         0.00         s0.2           s18d         216         0.00         s0.2           s18d         216         0.00         s0.2           s18d         216         0.00         s0.2           s18d         21         216         s0.2           s18d         21         32.0         82.27         s20.2           s0.25-s16         21         30         30.5         s0.5           s0.5-s16         21         51         53.7         30.5           s0.5-s16         21         4.81         s0.2         s0.5           s0.5-s16         21         4.81         s0.2         s0.5           s0.5-s16         21         4.81         s0.2         s0.5           s0.55-s16         21         4.81         s0.2         s0.2           s0.55-s16         21         4.81         s0.2         s0.6           s0.55-s16         22         52.4         s0.6         s0.6           s0.55-s16         22         52.4         s0.6         s</td><td>s15 - 8d4         216         22.69         51           s15 - 8d5         215         0.00         90.5           s12-8d4         216         0.00         90.2           s12-8d4         216         0.00         90.2           s12-8d4         216         0.00         90.2           s12-8d4         291         897.9         60.2           s0.25 - 86         291         80.2         80.2           s0.25 - 86         291         4.81         80.6           s0.25 - 86         291         64.95         80.5           s0.5 - 268         291         64.95         80.5           s0.5 - 268         291         4.81         80.2           s0.5 - 268         291         4.81         80.2           s0.5 - 268         291         4.81         80.2           s0.5 - 268         292         53.2         80.2           s0.5 - 268         292         52.4         201           s0.65 - 268         292         52.4         20.2           s0.65 - 268         292         52.4         20.2           s0.65 - 268         292         52.4         20.2           s0.65 - 268</td><td>s1-264         216         22.69         s1           s125-s6,         215         0.00         s0.2           s12-s64,         216         0.00         s0.2           s12-s64,         216         0.00         s0.2           s12-s64,         216         0.00         s0.2           s12-s64,         216         0.00         s0.2           s0.25-s6         216         0.46         s0.2           s0.25-s6         291         9.79         16           s0.25-s6         291         4.81         s0.2           s0.5-s6         293         5.24         s0.2           s0.5-s6         291         4.81         s0.2           s0.13         4.81         s0.2</td><td>s1-8d         216         20.0         s1           s1-8d         216         20.0         s0.2           s1-8d         216         50.0         s0.2           s1-8d         216         50.0         s0.2           s1-8d         216         0.00         s0.2           s0.25 - s16         216         0.00         s0.2           s0.25 - s16         210         82.27         s200           s0-230         220         82.27         s20           s0-25 - s16         21         305         915           s0-25 - s16         21         4.81         s0.5           s0.5 - s16         21         4.81         s0.5           s0.5 - s16         21         4.81         s0.5           s0.5 - s16         21         4.81         s0.2           s0.5 - s16         21         4.81         s0.2           s0.5 - s16         21         4.81         s0.2           s0.5 - s16         22         52.9         52.9         s0.2           s0.5 - s16         22         52.9         52.9         s0.2           s0.5 - s16         22         52.9         52.9         22</td><td>s1-8d         216         22.69         s1           s1-8d        
216         20.00         s0.2           s1-8d         216         0.00         s0.2           s1-8d         216         0.00         s0.2           s1-8d         216         0.00         s0.2           s0.25-s16         216         0.00         s0.2           s0.25-s16         216         0.46         s0.2           s0.25-s16         219         30.79         16           s0.25-s16         219         30.5         s0.5           s0.25-s16         219         30.5         s0.5           s0.25-s16         219         41.91         s0.2           s0.25-s16         219         41.91         s0.2           s0.55-s16         219         41.81         s0.2           s0.55-s16         219         41.81         s0.2           s0.55-s16         219         41.81         s0.2           s0.55-s16         219         529         529         s21           s0.55-s16         229         529         529         s21           s0.55-s16         229         529         529         s21      &lt;</td><td>s1-8d         216         22.69         51           s1-8d         216         20.00         90.5           s1-8d         216         50.00         90.2           s1-8d         216         50.00         90.2           s1-8d         216         0.00         90.2           s0.25-s16         216         0.00         90.2           s0.25-s16         216         0.46         90.2           s0.25-s16         219         50.79         50.5           s0.25-s16         219         50.79         50.5           s0.25-s18         30.5         42.95         80.5           s0.5-s18         30.5         41.93         50.2           s0.5-s16         201         4.81         50.2         50.2           s0.5-s16         &lt;</td><td>s1-8d         216         22.69         51           s1-8d         216         20.00         50.5           s1-8d         216         50.0         50.5           s1-8d         216         0.00         50.5           s25-s16         216         0.00         50.5           s0.25-s16         216         0.00         50.2           s0.25-s16         210         30.7         20.2           s0.25-s16         210         30.7         20.9           s0.5-s16         21         30.5         4.9         20.5           s0.5-s16         21         50.7         20.0         50.5           s0.5-s16         21         4.81         20.2         20.3         20.5           s0.5-s16         21         4.81         20.2         20.3         20.2           s0.5-s16         21         4.81         20.2         20.5         20.5           s0.5-s16         22         52.9         52.4         20.5         20.5           s0.5-s16         22         52.9         52.4         20.5         20.5           s0.5-s16         22         52.9         52.4         20.5         20.5</td><td>s1-8d         216         22.69         51           s1-8d         216         20.0         90.2           s1-8d         216         50.0         90.2           s1-8d         216         0.00         90.2           s1-8d         216         0.00         90.2           s0.25 - s16         216         0.00         90.2           s0.25 - s16         210         92.1         230           s0.25 - s16         21         9.1         97.79         16           s0.25 - s16         21         305         915         20.5           s0.5 - s16         21         481         20.7         230.5           s0.5 - s16         21         4.81         20.2         305         41.75         230.5           s0.5 - s16         21         4.81         20.2         30.5         41.75         230.2           s0.5 - s16         21         4.81         20.2         30.6         41.8         30.2           s0.5 - s16         229         52.9         52.9         52.6         50.0         51.6           s0.5 - s16         229         52.9         52.9         52.2         52.2         52.2</td></td> | s1864         216         22.69         s1           s0.5 - s0.5         215         0.00         s0.25           s0.25 - s1         216         0.00         s0.25           s0.25 - s1         216         0.00         s0.25           s0.25 - s1         216         0.00         s0.25           s0.25 - s1         210         92.27         s20.25           s0.25 - s10         32.27         s20.25         s20.25           s0.25 - s0         32.1         s20.27         s20.25           s0.25 - s0         30         4.95         s0.5           s0.25 - s0         30         4.95         s0.5           s0.55 - s16         30         4.95         s0.5           s0.55 - s0         30         4.95         s0.5           s0.55 - s16         30         4.95         s0.5           s0.55 - s16         30         4.95         s0.5           s0.55 - s16         291         4.81         s0.21           s0.55 - s16         291         4.81         s0.21           s0.25 - s06         30.5         7.4.75         s20.2           s0.25 - s16         291         4.81         s0.21   | s18d         216         22.69         s1           s18d         216         20.0         s0.2           s18d         216         50.0         s0.2           s18d         216         50.0         s0.2           s0.25-s16         216         0.00         s0.2           s0.25-s16         216         0.00         s0.2           s0.25-s16         216         0.46         s0.2           s0.21         22.0         82.27         s20           s0.1         2013         307         307         307           s0.5-s16         3         305         49.7         s0.5           s0.5-s16         3         307         49.73         305           s0.5-s16         3         305         49.5         305           s0.5-s16         3         307         44.93         20.5           s0.5-s16         201         4.81         s0.2         30.2           s0.25-s16         201         4.81         s0.2         30.2           s0.25-s16         201         4.81         s0.2         30.2           s0.25-s16         201         4.81         s0.2         s0.2   
   
  | s18d         216         20.0         s0.           s18d         216         20.0         s0.           s18d         216         50.0         s0.           s18d         216         50.0         s0.2           s0.25         s16         0.00         s0.2           s0.25         s10         216         0.00         s0.2           s0.25         s10         216         0.00         s0.2           s0.25         s10         220         82.27         s20.2           s0.25         s20         82.27         s20.5         s20.5           s0.55         305         19.79         19.79         16           s0.55         s0.5         s0.5         s0.5         s0.5           s0.55         s0.5         s0.5         s0.5         s0.5           s0.55         s0.5         s0.5         s0.5         s0.5           s0.55         s10         4.81         s0.2         s0.5           s0.55         s10         s0.87         4.81         s0.2           s0.55         s0.6         s0.87         s0.8         s0.5           s0.55         s0.8         s0.8  
   
  | s18d         215         20.0         s0.           s18d         216         0.00         s0.2           s18d         216         50.0         s0.2           s18d         216         0.00         s0.2           s0.25 - s16         216         0.00         s0.2           s0.25 - s16         216         0.00         s0.2           s0.25 - s16         216         9.79         s0.2           s0.25 - s16         210         82.27         230           s0.1         82.3         95.79         16           s10-33         305         19.79         16           s0.55-s16         21         30         19.79         16           s0.55-s16         21         4.81         20.2         30.5         30.5           s0.55-s16         21         4.81         20.2         30.5         30.5         30.5           s0.55-s16         21         4.81         20.2         s0.5         s0.5         s0.5           s0.25-s16         21         4.81         20.2         s0.8         30.2         s0.2           s0.05-s16         21         4.81         20.2         s0.6         s0.  
   | s1-8d         216         20.0         s1           s1-8d         216         20.0         s0           s1-8d         216         0.00         s0           s1-8d         216         0.00         s0           s1-8d         216         0.00         s0           s1-8d         216         0.00         s0           s125-816         216         0.00         s0           s0.25-816         210         82.27         s20           s0-1<2320  
   | s18d         216         22.69         s1           s18d         216         20.00         90.2           s18d         216         0.00         90.2           s18d         216         0.00         90.2           s18d         216         0.00         90.2           s18d         216         0.00         90.2           s0.25816         210         82.27         230           s02320         22.01         82.27         230           s02320         230         42.95         80.5           s0.25-86         30.5         42.95         80.5           s0.25-86         30.5         42.95         80.5           s0.25-86         231         64.95         80.5           s0.25-86         231         64.95         80.5           s0.25-86         231         64.95         80.5           s0.55-86         231         64.95         80.5           s0.55-86         231         64.95         80.5           s0.55-86         231         67.3         20.2           s0.55-86         231         67.3         20.2           s0.55-86         231  | s1- 864         216         22.69         51           s1- 864         216         0.00         90.5           s1- 864         216         0.00         90.2           s1- 864         216         0.00         90.2           s1- 864         216         0.00         90.2           s0.25 - s16         216         0.04         90.2           s0.25 - s10         82.27         230         82.27         230.0           s0.25 - s10         30.5         42.95         80.5         80.5           s0.25 - s10         30.5         42.95         80.5         80.5           s0.5 - s10         30.5         42.95         80.5         80.5           s0.5 - s10         30.5         42.95         80.5         80.5           s0.5 - s10         30.5         41.95         80.2         80.5           s0.55 - s16         201         4.81         50.2         80.2         80.2           s0.55 - s16         201         4.81         50.2         80.2         80.2         80.2           s0.55 - s16         201         4.81         80.2         80.2         80.2         80.2         80.2         80.2         80.2 </td <td>s1- 864         216         22.69         51           s1- 864         216         0.00         90.5           s1-864         216         0.00         90.2           s1-864         216         0.00         90.2           s0.25 - s16         216         0.00         90.2           s0.25 - s16         216         0.46         80.2           s0.25 - s16         210         80.2         80.2           s0.25 - s16         219         9.79         616           s0.25 - s16         291         5.97         90.6           s0.5 - s16         291         64.95         80.5           s0.5 - s16         291         64.95         80.5           s0.5 - s16         291         4.81         50.2           s0.55 - s16         291         4.81         50.2           s0.55 - s16         291         4.81         50.2           s0.55 - s16         291         4.81         50.2           s0.05 - s16         291         5.34         20.2           s0.03         57.44         20.2         50.9         20.2           s0.03         57.44         291         20.2         20.2</td> <td>s18d         216         20.0         s1           s18d         216         20.0         s0.2           s18d         216         0.00         s0.2           s18d         216         0.00         s0.2           s18d         216         0.00         s0.2           s18d         216         0.00         s0.2           s18d         21         216         s0.2           s18d         21         32.0         82.27         s20.2           s0.25-s16         21         30         30.5         s0.5           s0.5-s16         21         51         53.7         30.5           s0.5-s16         21         4.81         s0.2         s0.5           s0.5-s16         21         4.81         s0.2         s0.5           s0.5-s16         21         4.81         s0.2         s0.5           s0.55-s16         21         4.81         s0.2         s0.2           s0.55-s16         21         4.81         s0.2         s0.6           s0.55-s16         22         52.4         s0.6         s0.6           s0.55-s16         22         52.4         s0.6         s</td> <td>s15 - 8d4         216         22.69         51           s15 - 8d5         215         0.00         90.5           s12-8d4         216         0.00         90.2           s12-8d4         216         0.00         90.2           s12-8d4         216         0.00         90.2           s12-8d4         291         897.9         60.2           s0.25 - 86         291         80.2         80.2           s0.25 - 86         291         4.81         80.6           s0.25 - 86         291         64.95         80.5           s0.5 - 268         291         64.95         80.5           s0.5 - 268         291         4.81         80.2           s0.5 - 268         291         4.81         80.2           s0.5 - 268         291         4.81         80.2           s0.5 - 268         292         53.2         80.2           s0.5 - 268         292         52.4         201           s0.65 - 268         292         52.4         20.2           s0.65 - 268         292         52.4         20.2           s0.65 - 268         292         52.4         20.2           s0.65 - 268</td> <td>s1-264         216         22.69         s1           s125-s6,         215         0.00         s0.2           s12-s64,         216         0.00         s0.2           s12-s64,         216         0.00         s0.2           s12-s64,         216         0.00         s0.2           s12-s64,         216         0.00         s0.2           s0.25-s6         216         0.46         s0.2
          s0.25-s6         291         9.79         16           s0.25-s6         291         4.81         s0.2           s0.5-s6         293         5.24         s0.2           s0.5-s6         291         4.81         s0.2           s0.13         4.81         s0.2</td> <td>s1-8d         216         20.0         s1           s1-8d         216         20.0         s0.2           s1-8d         216         50.0         s0.2           s1-8d         216         50.0         s0.2           s1-8d         216         0.00         s0.2           s0.25 - s16         216         0.00         s0.2           s0.25 - s16         210         82.27         s200           s0-230         220         82.27         s20           s0-25 - s16         21         305         915           s0-25 - s16         21         4.81         s0.5           s0.5 - s16         21         4.81         s0.5           s0.5 - s16         21         4.81         s0.5           s0.5 - s16         21         4.81         s0.2           s0.5 - s16         21         4.81         s0.2           s0.5 - s16         21         4.81         s0.2           s0.5 - s16         22         52.9         52.9         s0.2           s0.5 - s16         22         52.9         52.9         s0.2           s0.5 - s16         22         52.9         52.9         22</td> <td>s1-8d         216         22.69         s1           s1-8d         216         20.00         s0.2           s1-8d         216         0.00         s0.2           s1-8d         216         0.00         s0.2           s1-8d         216         0.00         s0.2           s0.25-s16         216         0.00         s0.2           s0.25-s16         216         0.46         s0.2           s0.25-s16         219         30.79         16           s0.25-s16         219         30.5         s0.5           s0.25-s16         219         30.5         s0.5           s0.25-s16         219         41.91         s0.2           s0.25-s16         219         41.91         s0.2           s0.55-s16         219         41.81         s0.2           s0.55-s16         219         41.81         s0.2           s0.55-s16         219         41.81         s0.2           s0.55-s16         219         529         529         s21           s0.55-s16         229         529         529         s21           s0.55-s16         229         529         529         s21      &lt;</td> <td>s1-8d         216         22.69         51           s1-8d         216         20.00         90.5           s1-8d         216         50.00         90.2           s1-8d         216         50.00         90.2           s1-8d         216         0.00         90.2           s0.25-s16         216         0.00         90.2           s0.25-s16         216         0.46         90.2           s0.25-s16         219         50.79         50.5           s0.25-s16         219         50.79         50.5           s0.25-s18         30.5         42.95         80.5           s0.5-s18         30.5         41.93         50.2           s0.5-s16         201         4.81         50.2         50.2           s0.5-s16         &lt;</td> <td>s1-8d         216         22.69         51           s1-8d         216         20.00         50.5           s1-8d         216         50.0         50.5           s1-8d         216         0.00         50.5           s25-s16         216         0.00         50.5           s0.25-s16         216         0.00         50.2           s0.25-s16         210         30.7         20.2           s0.25-s16         210         30.7         20.9           s0.5-s16         21         30.5         4.9         20.5           s0.5-s16         21         50.7         20.0         50.5           s0.5-s16         21         4.81         20.2         20.3         20.5           s0.5-s16         21         4.81         20.2         20.3         20.2           s0.5-s16         21         4.81         20.2         20.5         20.5           s0.5-s16         22         52.9         52.4         20.5         20.5           s0.5-s16         22         52.9         52.4         20.5         20.5           s0.5-s16         22         52.9         52.4         20.5         20.5</td> <td>s1-8d         216         22.69         51           s1-8d         216         20.0         90.2           s1-8d         216         50.0         90.2           s1-8d         216         0.00         90.2           s1-8d         216         0.00         90.2           s0.25 - s16         216         0.00         90.2           s0.25 - s16         210         92.1         230           s0.25 - s16         21         9.1         97.79         16           s0.25 - s16         21         305         915         20.5           s0.5 - s16         21         481         20.7         230.5           s0.5 - s16         21         4.81         20.2         305         41.75         230.5           s0.5 - s16         21         4.81         20.2         30.5         41.75         230.2           s0.5 - s16         21         4.81         20.2         30.6         41.8         30.2           s0.5 - s16         229         52.9         52.9         52.6         50.0         51.6           s0.5 - s16         229         52.9         52.9         52.2         52.2         52.2</td>  | s1- 864         216         22.69         51           s1- 864         216         0.00         90.5           s1-864         216         0.00         90.2           s1-864         216         0.00         90.2           s0.25 - s16         216         0.00         90.2           s0.25 - s16         216         0.46         80.2           s0.25 - s16         210         80.2         80.2           s0.25 - s16         219         9.79         616           s0.25 - s16         291         5.97         90.6           s0.5 - s16         291         64.95         80.5           s0.5 - s16         291         64.95         80.5           s0.5 - s16         291         4.81         50.2           s0.55 - s16         291         4.81         50.2           s0.55 - s16         291         4.81         50.2           s0.55 - s16         291         4.81         50.2           s0.05 - s16         291         5.34         20.2           s0.03         57.44         20.2         50.9         20.2           s0.03         57.44         291         20.2         20.2   | s18d         216         20.0         s1           s18d         216         20.0         s0.2           s18d         216         0.00         s0.2           s18d         216         0.00         s0.2           s18d         216         0.00         s0.2           s18d         216         0.00         s0.2           s18d         21         216         s0.2           s18d         21         32.0         82.27         s20.2           s0.25-s16         21         30         30.5         s0.5           s0.5-s16         21         51         53.7         30.5           s0.5-s16         21         4.81         s0.2         s0.5           s0.5-s16         21         4.81         s0.2         s0.5           s0.5-s16         21         4.81         s0.2         s0.5           s0.55-s16         21         4.81         s0.2         s0.2           s0.55-s16         21         4.81         s0.2         s0.6           s0.55-s16         22  
      52.4         s0.6         s0.6           s0.55-s16         22         52.4         s0.6         s  | s15 - 8d4         216         22.69         51           s15 - 8d5         215         0.00         90.5           s12-8d4         216         0.00         90.2           s12-8d4         216         0.00         90.2           s12-8d4         216         0.00         90.2           s12-8d4         291         897.9         60.2           s0.25 - 86         291         80.2         80.2           s0.25 - 86         291         4.81         80.6           s0.25 - 86         291         64.95         80.5           s0.5 - 268         291         64.95         80.5           s0.5 - 268         291         4.81         80.2           s0.5 - 268         291         4.81         80.2           s0.5 - 268         291         4.81         80.2           s0.5 - 268         292         53.2         80.2           s0.5 - 268         292         52.4         201           s0.65 - 268         292         52.4         20.2           s0.65 - 268         292         52.4         20.2           s0.65 - 268         292         52.4         20.2           s0.65 - 268   
   | s1-264         216         22.69         s1           s125-s6,         215         0.00         s0.2           s12-s64,         216         0.00         s0.2           s12-s64,         216         0.00         s0.2           s12-s64,         216         0.00         s0.2           s12-s64,         216         0.00         s0.2           s0.25-s6         216         0.46         s0.2           s0.25-s6         291         9.79         16           s0.25-s6         291         4.81         s0.2           s0.5-s6         293         5.24         s0.2           s0.5-s6         291         4.81         s0.2           s0.13         4.81         s0.2  | s1-8d         216         20.0         s1           s1-8d         216         20.0         s0.2           s1-8d         216         50.0         s0.2           s1-8d         216         50.0         s0.2           s1-8d         216         0.00         s0.2           s0.25 - s16         216         0.00         s0.2           s0.25 - s16         210         82.27         s200           s0-230         220         82.27         s20           s0-25 - s16         21         305         915           s0-25 - s16         21         4.81         s0.5           s0.5 - s16         21         4.81         s0.5           s0.5 - s16         21         4.81         s0.5           s0.5 - s16         21         4.81         s0.2           s0.5 - s16         21         4.81         s0.2           s0.5 - s16         21         4.81         s0.2           s0.5 - s16         22         52.9         52.9         s0.2           s0.5 - s16         22         52.9         52.9         s0.2           s0.5 - s16         22         52.9         52.9         22  | s1-8d         216         22.69         s1           s1-8d         216         20.00         s0.2           s1-8d         216         0.00         s0.2           s1-8d         216         0.00         s0.2           s1-8d         216         0.00         s0.2           s0.25-s16         216         0.00         s0.2           s0.25-s16         216         0.46         s0.2           s0.25-s16         219         30.79         16           s0.25-s16         219         30.5         s0.5           s0.25-s16         219         30.5         s0.5           s0.25-s16         219         41.91         s0.2           s0.25-s16         219         41.91         s0.2           s0.55-s16         219         41.81         s0.2           s0.55-s16         219         41.81         s0.2           s0.55-s16         219         41.81         s0.2           s0.55-s16         219         529         529         s21           s0.55-s16         229         529         529         s21           s0.55-s16         229         529         529         s21      <   
  | s1-8d         216         22.69         51           s1-8d         216         20.00         90.5           s1-8d         216         50.00         90.2           s1-8d         216         50.00         90.2           s1-8d         216         0.00         90.2           s0.25-s16         216         0.00         90.2           s0.25-s16         216         0.46         90.2           s0.25-s16         219         50.79         50.5           s0.25-s16         219         50.79         50.5           s0.25-s18         30.5         42.95         80.5           s0.5-s18         30.5         41.93         50.2           s0.5-s16         201         4.81         50.2         50.2           s0.5-s16         <   | s1-8d         216         22.69         51           s1-8d         216         20.00         50.5           s1-8d         216         50.0         50.5           s1-8d         216         0.00         50.5           s25-s16         216         0.00         50.5           s0.25-s16         216         0.00         50.2           s0.25-s16         210         30.7         20.2           s0.25-s16         210         30.7         20.9           s0.5-s16         21         30.5         4.9         20.5           s0.5-s16         21         50.7         20.0         50.5           s0.5-s16         21         4.81         20.2         20.3         20.5           s0.5-s16         21         4.81         20.2         20.3         20.2           s0.5-s16         21         4.81         20.2         20.5         20.5           s0.5-s16         22         52.9         52.4         20.5         20.5           s0.5-s16         22         52.9         52.4         20.5         20.5           s0.5-s16         22         52.9         52.4         20.5         20.5  | s1-8d         216         22.69         51           s1-8d         216         20.0         90.2           s1-8d         216         50.0         90.2           s1-8d         216         0.00         90.2           s1-8d         216         0.00         90.2           s0.25 - s16         216         0.00         90.2           s0.25 - s16         210         92.1         230           s0.25 - s16         21         9.1         97.79         16           s0.25 - s16         21         305         915         20.5           s0.5 - s16         21         481         20.7         230.5           s0.5 - s16         21         4.81         20.2         305         41.75         230.5           s0.5 - s16         21         4.81         20.2         30.5         41.75         230.2           s0.5 - s16         21         4.81         20.2         30.6         41.8         30.2           s0.5
- s16         229         52.9         52.9         52.6         50.0         51.6           s0.5 - s16         229         52.9         52.9         52.2         52.2         52.2  |
| 7 \$1 \$2 \$1.24<br>2 \$0.25 \$0.25 \$0.25<br>5 \$0.25 \$0.25 \$0.25<br>75 \$320 \$320 \$0.25  
   
   
   | 7 51 2 51-24<br>2 50.25 50.25 50.25<br>5 20.25 50.25 50.25<br>75 2320 2320 50-2<br>2013<br>8 MIC50 MIC90 Ran  
  | 7 51 2 51-24<br>2 50.25 50.25 50.25<br>5 50.25 50.25 50.25<br>75 2320 230 201-20<br>2013<br>80 MIC50 MIC90 Rang<br>88 1 24 51-24<br>2013<br>88 1 24 50.25  
   
   
  | 7         \$1         2         \$1-2           2         \$10         2         \$1-2           5         \$0.25         \$0.25         \$0.25           5         \$0.26         \$0.25         \$0.25           5         \$20.25         \$0.25         \$0.25           5         \$2320         \$202         \$01-2           2013         \$202         \$203         \$203           8         1         \$4         \$0.26           8         \$1         \$4         \$0.26           50.5         \$0.55         \$0.55         \$0.55   | 7         \$1         2         \$1-2           2         \$0.25         \$0.25         \$0.25           5         \$0.25         \$0.25         \$0.25           5         \$0.26         \$0.25         \$0.25           5         \$0.25         \$0.25         \$0.25           7         \$2320         \$2020         \$201-2           8         MIC50         MIC90         Rang           88         1         \$4         \$4           80         \$64         \$1-34           81         \$20.5         \$0.55         \$0.55           80.5         \$0.55         \$0.55         \$0.55           81         \$20.5         \$0.55         \$0.55           81         \$20.5         \$0.55         \$0.55           81         \$20.5         \$0.55         \$0.55           81         \$0.55         \$0.55         \$0.55           80.55         \$0.55         \$0.55         \$0.55  
   
   
   | 7         51         2         51-32           2         50.25         50.25         50.25           5         50.25         50.25         50.25           5         50.25         50.25         50.25           7         201         201         201           7         2012         2023         500-2           8         MIC50         MIC90         Rang           8         MIC50         MIC90         Rang           8         1         24         2013           90         80.5         50.5         50.55           90         864         264         21-34           91         24         50.25         50.55           90         864         264         50.55           905         805         80.55         50.55           90         864         265         50.55           91         264         264         21-34           91         205         50.55         50.55           90         265         265         50.55         50.54           90         264         265         50.55         50.54  
   | 7         51         2         51-32           2         50.25         50.25         50.25           5         50.25         50.25         50.26           7         5         20.25         50.25         20.26           7         201         201         201         201           7         2012         2020         201         201           8         MIC50         MIC90         Rang         2013           8         MIC50         MIC90         Rang         2013           8         1         264         21-24         2025           8         20.5         20.5         20.55         20.55           8         20.5         20.5         20.55         20.55           90         564         264         21-24         20.25           90         565         20.55         20.55         20.55           7         2         264         21-24         21-24           7         2         265         0.55         20.55         20.55           71         2         20.55         20.55         20.55         20.55   
   
   | 7         51         2         51-25         20.25  
   
   | 7         51         2         51-26           2         50.25         50.25         50.25         50.25-           5         80.25         50.25         50.25         201-2           7         8         MIC50         MIC90         Rang           8         1         24         201-2         201-2           9         6         264         51-26         201-2           8         1         24         201-2         201-2           96         264         51-26         50.55         50.55           96         264         51-24         51-24         50.55           91         20.5         50.5         50.5-         50.5-         50.5-           11         20.25         20.25         50.25-         50.25-         50.25-         50.25-           11         20.25         20.25         50.25-         50.25-         50.25-         20.25-         20.25-           11         20.25         20.25         20.25-         20.25-         20.26-         20.26-         20.26-           11         20.25         20.25         20.25-         20.26-         20.26-         20.26-         20.2  
   
   | 7         51         2         51-25         20.25  
   
  | 7         51         2         51-25         20.25   
  | 7         51         2         51-25         20.25     
   20.25         20.25         20.25         20.25         20.25         20.25         20.25         20.25         20.25         20.26         20.25          | 7         51         2         51-32           2         90.25         90.25         90.25         90.25           5         90.25         90.25         90.25         90.25           7         81         2         91.25         90.25           7         80.25         90.25         90.25         90.26           8         MIC50         NIC90         Rang         2013           90         1         84         80.5         2015           91         264         81.4         80.25         90.5           91         264         81.4         80.25         90.5           91         264         81.4         81.4         81.4           91         20.5         90.5         90.5         90.5           91         90.5         90.5         90.5         90.5           91         90.25         90.5         90.5         80.5         80.5           71         2         26.25         90.5         80.5         80.5         80.5         80.5           71         2         2         2         2         2         2         2         2         2  
  | 7         51         2         51-25         52-25         50-25         50-25         50-25         50-25         50-25         50-25         50-25         50-26        
50-26            
   | 7         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         20         25         30         25         30         25         30         20 <th< td=""><td>7         51         2         51         2         51         23         50         25         50         25         50         25         50         25         50         25         50         25         50         25         50         25         50         25         50         25         50         25         50         25         50         25         50         26         20         26         20         26         21</td></th<> <td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td> <td>7         51         2         51         2         51         2         51         23         50         25         50         25         50         25         50         25         50         25         50         25         50      
  25         50         25         50         25         50         25         50         25         50         25         50         20</td> <td>7         51         2         51-25         50-25         50-25         50-25         50-25         50-25         50-25         50-26         50-26         50-26         50-26         50-26         50-26         50-26         50-26         50-26         50-26         50-26         50-26         50-26         50-26         50-26         50-26         50-26         50-26         50-26         20-26</td> <td>7         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         20         25         20         25         20         25         20         25         20         25         20         25         20         25         20         25         20         26         20         26         20         26         20         26         20         25         20         25         20         25         20         25         20         26         20         26         20         26         20         26         20         26         20         26         20         25         20         25         20         25         20         25         20         25         20         25         20         25         20         25         20         25         20         25         20         25         20         25         20         20         20         <th< td=""><td>7         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         21         31         <t< td=""><td>7         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         21         31         <t< td=""><td><math display="block"> \begin{array}{ c c c c c c c c c c c c c c c c c c c</math></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td>7         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         21         31         <t< td=""><td>7         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         21         31         <t< td=""><td>7 <math>51</math> <math>2</math> <math>51-25</math> <math>20.25</math> <math>30.25</math> <math>30.5</math> <math>30.25</math> <math>30.5</math> <math>30.5</math></td></t<></td></t<></td></t<></td></t<></td></th<></td> | 7         51         2         51         2         51         23         50         25         50         25         50         25         50         25         50         25         50         25         50         25         50         25         50         25         50         25         50         25         50         25         50         25         50         26         20         26         20         26         21  
   | $ \begin{array}{c c c c c c c c c c c c c c c c c c c $   | 7         51         2         51         2         51         2         51         23         50         25         50         25         50         25         50         25         50         25         50         25         50         25         50         25         50         25         50         25         50         25         50         25         50         20 
       20     
   | 7         51         2         51-25         50-25         50-25         50-25         50-25         50-25         50-25         50-26         50-26         50-26         50-26         50-26         50-26         50-26         50-26         50-26         50-26         50-26         50-26         50-26         50-26         50-26         50-26         50-26         50-26         50-26         20-26          | 7         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         20         25         20         25         20         25         20         25         20         25         20         25         20         25         20         25         20         26         20         26         20         26         20         26         20         25         20         25         20         25         20         25         20         26         20         26         20         26         20         26         20         26         20         26         20         25         20         25         20         25         20         25         20         25         20         25         20         25         20         25         20         25         20         25         20         25         20         25         20         20         20 <th< td=""><td>7         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         21         31         <t< td=""><td>7         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         21         31         <t< td=""><td><math display="block"> \begin{array}{ c c c c c c c c c c c c c c c c c c c</math></td><td><math display="block"> \begin{array}{c c c c c c c c c c c c c c c c c c c </math></td><td>7         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         21         31         <t< td=""><td>7         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         21         31         <t< td=""><td>7 <math>51</math> <math>2</math> <math>51-25</math> <math>20.25</math> <math>30.25</math> <math>30.5</math> <math>30.25</math> <math>30.5</math> <math>30.5</math></td></t<></td></t<></td></t<></td></t<></td></th<> | 7         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51 
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   | 7         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         21         31 <t< td=""><td>7         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         21         31         <t< td=""><td>7 <math>51</math> <math>2</math> <math>51-25</math> <math>20.25</math> <math>30.25</math> <math>30.5</math> <math>30.25</math> <math>30.5</math> <math>30.5</math></td></t<></td></t<> | 7         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         51         2         21         31 <t< td=""><td>7 <math>51</math> <math>2</math> <math>51-25</math> <math>20.25</math> <math>30.25</math> <math>30.5</math> <math>30.25</math> <math>30.5</math> <math>30.5</math></td></t<> | 7 $51$ $2$ $51-25$ $20.25$ $30.5$ $30.25$ $30.5$  |
| ≤1         ≤0.25 - ≥16         174         1.72           ≤0.25         ≤0.25 - ≥16         174         1.15           ≥320         ≤20 - ≥320         177         84.75   
   
   
   | st s0.25- ≥f6 174 1.72<br>s0.25 s0.25- ≥f6 174 1.15<br>≥320 ≤20- ≥320 177 84.75<br>2012<br>2012<br>2012<br>2012   
  | s1         s0.25- z/6         174         1.72           s0.25         s0.25         z/6         174         1.15           s220         s0.25         z/7         84.75           2012         2012         1.17         84.75           2013         2012         2012         2012           2013         2012         2012         2012           2013         2012         2012         2012           2013         2012         2012         2012           2013         2012         2012         2012  
   
   
  | s1 s0.25- ≥16 174 1.72<br>s0.25 s0.25- ≥16 174 1.15<br>≥320 s20- ≥320 177 84.75<br>2012<br>2012<br>2012<br>2012<br>2012<br>2012<br>2012<br>201  | s1 s0.25- z16 174 1.72<br>s0.25 s0.25- z16 174 1.15<br>z320 s20- z320 177 84.75<br>2012<br>2012<br>2012<br>2012<br>2013<br>2013<br>2015 z16 24<br>205 z16 24<br>205 z16 24<br>205 z16 24 4.13<br>205 z16 26 40<br>205 z16 24 4.13<br>205 z16 26 20<br>205 z16 27 4.13<br>205 z16 26 4.13<br>205 z16 26 20<br>205 z16 27 4.13<br>205 z16 26 26 20<br>205 z16 27 4.13<br>205 z16 26 26 20<br>205 z16 27 4.13<br>205 z16 26 26 20<br>205 z16 27 20 26 26  
   
   
   | st s0.26- zf6 174 1.72<br>s0.25 s0.25- zf6 174 1.15<br>2012 s0.20 177 84.75<br>2012 s012 s017 84.75<br>2012 s012 s17 84.75<br>2013 s012 s120 3130<br>2014 s1-264 227 3130<br>2015 s15-26 21 3130<br>2015 s15-26 21 3138<br>264 s1-264 227 6096<br>265 s15-26 21 4.11<br>264 s1-264 217 207  
   | st s0.26- ≥f6 174 1.72<br>s0.25 s0.25- ≥f6 174 1.15<br>≥320 s20- ≥320 177 84.75<br>2012 s012 s20 s20 s20 s20 s20 s20 s20 s20 s20 s2   
   
   | s1 s0.26- z66 174 1.72<br>s0.25 s0.25- z66 174 1.15<br>2012 s0.25 - z320 177 84.75<br>201 - z01 - z01 - z012<br>2012 s01 - z01 - z013 30<br>201 - z02 - z02 113 84.75<br>201 - z01 - z01 - z01 30<br>201 - z02 - z66 227 31<br>201 - z02 - z66 227 31<br>201 - z02 - z66 227 20<br>21 - z02 - z66 227 20<br>21 - z02 - z66 227 20<br>21 - z02 - z66 227 20<br>22 - z62 20 20 - z61 20<br>22 - z62 20 20 - z61 20<br>22 - z60 22 20 - z01 - z0   
   
  | s1 s0.26- z6 174 1.72<br>s0.25 s0.25- z6 174 1.15<br>2320 s0.25- z6 174 1.15<br>2012 s0.2- z20 177 84.75<br>2012 s0.2 s20 s20 - 320 317<br>2012 s0.2 s0 25- 26 227 53.30<br>24 s1-264 227 53.30<br>25 s0.5-26 227 6.96<br>264 s1-264 227 6.06<br>265 s0.5-26 227 2.07<br>51 s0.25-26 227 7.07<br>51 s0.25 s0.5 s0.5 s0.5 s0.5 s0.5 s0.5 s0.5 s0.   
   
  | si so.25- zi6 iri4 iri5<br>so.25 so.25- zi6 iri4 iri5<br>zor. 2017 84.75<br>zor. 2017 84.75<br>zor. 2017 84.75<br>zor. 2012 rif 84.75<br>zor. 2017 84.75<br>zor. 2012 2015 2017 84.11<br>zor. 2012 2015 2017 75.77<br>zor. 2012 2015 2017 2017 2017 2017 2017 2017 2017 2017   
   | s1 s0.25- z6 174 1.72<br>s0.25 s0.25- z6 174 1.15<br>2320 s0.25- z6 174 1.15<br>2012 s0.2- z20 177 84.75<br>2012 s0.2- z20 177 84.75<br>2015 s0.2- z6 173 81.75<br>2015 s0.2- z6 227 53.30<br>25 s0.5- z6 227 5.29<br>25 s0.5- z6 227 4.11<br>25 s0.5- z6 227 2.07<br>264 s1-264 2.27 6.96<br>25 s0.5- z6 227 2.07<br>21 s1.28<br>20 s10 s20 2.27 7 5.79<br>21 s1.28<br>20 s10 s20 2.27 7 5.79<br>20 s10 s20 2.23 7 5.79<br>20 s10 s20 2.25 s10 s20 2.23 7 5.79<br>20 s10 s20 2.23 7 5.29<br>20 s10 s20 2.20 2.23 7 5.20 2.20 2.23 7 5.   
   
   | s1 s0.25- z6 174 1.72<br>2320 s0.25- z6 174 1.15<br>2012 s0.25 z0 17 84.75<br>2012 s0.25 z0 17 84.75<br>2012 s0.25 z0 17 84.75<br>2012 s0.25 z0 23 21.38<br>24 s0.25 z0 23 21.38<br>26 s1.5 z0 25 z0 4.11<br>26 s1.5 z0 25 z0 4.11<br>21 s0.25 z0 29 21 76.72<br>2012 s0.25 z0 20 76.77<br>2013 s0.25 z0 20 76.77<br>2014 s0 20 20 20 76.77<br>2015 s0.25 z0 4.11<br>2015 s0.25 z0 4.11<br>2016 s0 20 20 20 20 20 20 20 20 20 20 20 20 20   | \$1         \$0.25 - 266         174         1.12           \$225         \$20.5 - 260         177         84.75           \$202         \$202 - 2320         177         84.75           \$201         \$201 - 320         177         84.75           \$202         \$202 - 2320         177         84.75           \$203         \$201 - 320         84.75         84.75           \$204         \$202 - 320         177         84.75           \$203         \$202 - 320         177         84.75           \$204         \$212 - 35.30         35.30         35.30           \$205         \$456         \$27         35.30         37.8           \$204         \$212 - 80.7         \$20.7         35.30         37.7           \$2025         \$402 - 227         \$2.07         30.7         37.7           \$2025         \$202 - 286         \$2.7         4.41         30.7           \$2025         \$202 - 320         23.7         4.41         32.8           \$2025         \$202 - 320         23.7         76.77         30.7           \$2025         \$202 - 320         23.7         76.77         30.8           \$2025         \$202 - 364 <t< td=""><td>\$1         \$0.25- \$16         174         1.72           \$20.25         \$10.25         \$10.25         \$10.25           \$20.25         \$20- \$220         177         \$4,15           \$2012         \$201         77         \$4,15           \$2012         \$201         77         \$4,15           \$2012         \$201         \$201         \$4,15           \$2012         \$201         \$201         \$4,15           \$2012         \$21         \$1,38         \$1,38           \$21         \$21         \$23         \$1,38           \$25         \$205-\$26         \$23         \$1,38           \$25         \$205-\$26         \$27         \$4,11           \$21         \$213         \$1,38           \$25         \$205-\$26         \$27         \$4,11           \$21         \$212         \$217         \$217           \$21         \$205-\$26         \$27         \$4,11           \$21         \$202-\$26         \$27         \$4,11           \$21         \$210-\$22         \$217         \$217           \$21         \$210-\$22         \$217         \$217           \$2105         \$210-\$22         \$217         \$217<!--</td--><td>st s0.25 - zf6 /r14 /r12<br/>2012 201 - z012 - z10 /r17 84./r5<br/>2012 - z01 - z012 - z01 /r13 81./r5<br/>201 - z012 - z01 - z01 /r3 81./r1<br/>201 - z012 - z01 - z01 /r3 81./r1<br/>201 - z012 - z01 - z01 /r3 81./r1<br/>201 - z012 - z01 - z01 /r1 /r1<br/>201 - z01 - z01 /r3 81./r1<br/>201 - z01 - z01 /r1 /r1<br/>201 - z01 /r1 /r1 /r1 /r1 /r1 /r1 /r1 /r1 /r1 /r</td><td>st s0.25 - zf6 /74 1.72<br/>s0.25 s0.25 - zf6 /74 1.15<br/>2012 2017 84.75<br/>2012 2017 84.75<br/>2012 2017 84.75<br/>2012 2017 84.75<br/>2012 2017 84.75<br/>2015 2017 94.11<br/>2012 2016 2017 2017<br/>2012 2016 2017 2017<br/>2012 2016 2017 2017<br/>2012 2016 2016 2017 1011<br/>2012 2016 2016 2017 1011<br/>2012 2012 2017 2017<br/>2012 2017 2017 2017<br/>2012 2017 2017 2017<br/>2013 2017 2017 2017 2017<br/>2013 2017 2017 2017 2017 2017<br/>2013 2017 2017 2017 2017 2017 2017 2017 2017</td><td>si s0.26 - ≥16 /74 /172<br/>s0.25 s0.25 - ≥16 /74 /15<br/>2.00 - ≥320 /77 84.75<br/>2.01 - ≥012 /17 84.75<br/>2.01 - ≥012 /17 84.75<br/>2.01 - ≥02 - ≥320 /17 84.75<br/>2.01 - ≥02 - ≥320 /17 84.75<br/>2.01 - ≥64 2.27 5.33<br/>2.05 - ≥16 2.27 5.29<br/>2.05 - ≥16 2.27 2.07<br/>2.01 - ≥16 2.07 2.08<br/>2.01 - 28 2.26 2.07 2.08 2.07
2.08<br/>2.01 - 28 2.08 2.07 2.08 2.08<br/>2.01 - 28 2.08 2.08 2.08 2.08 2.08<br/>2.01 - 28 2.08 2.08 2.08 2.08 2.08 2.08<br/>2.01 - 28 2.08 2.08 2.08 2.08 2.08 2.08 2.08 2</td><td>\$1         \$0.25- 266         174         1.15           \$2025         \$202- 2320         177         84.75           \$201-2320         177         84.75           \$201-2320         177         84.75           \$201-2320         177         84.75           \$201-2320         177         84.75           \$201-2320         \$202-232         \$1.38           \$201-2320         \$217         \$3.30           \$202-246         \$2.27         \$3.30           \$205-246         \$2.27         \$2.33           \$205-246         \$2.27         \$2.7           \$205-246         \$2.7         \$2.7           \$202-256         \$2.27         \$2.7           \$202-256         \$2.27         \$2.7           \$202-256         \$2.27         \$4.41           \$202-256         \$2.27         \$4.41           \$202-256         \$2.27         \$4.74           \$202-256         \$2.27         \$4.74           \$202-256         \$2.27         \$4.74           \$202-256         \$2.76         \$2.76           \$202-266         \$5.72         \$2.9           \$202-266         \$5.72         \$2.9      <tr< td=""><td>\$1         \$0.25 - \$16         174         1.72           \$20.25         \$1.5         \$2.5         \$1.4         1.15           \$20.25         \$2.0         \$2.0         \$2.0         \$4.75           \$2.01         \$1.71         \$4.75         \$4.75           \$2.01         \$2.01         \$1.71         \$4.75           \$2.01         \$2.01         \$2.01         \$4.15           \$2.01         \$2.01         \$2.01         \$4.15           \$2.01         \$2.01         \$2.01         \$4.11           \$2.01         \$2.02         \$2.01         \$4.11           \$2.01         \$2.01         \$2.01         \$4.11           \$2.05         \$2.05         \$2.01         \$4.11           \$2.01         \$2.02         \$2.01         \$4.11           \$2.01         \$2.01         \$2.01         \$4.11           \$2.01         \$2.01         \$2.01         \$4.11           \$2.01         \$2.02         \$2.01         \$4.11           \$2.01         \$2.02         \$2.01         \$4.11           \$2.01         \$2.01         \$2.01         \$4.11           \$2.01         \$2.01         \$2.01         \$4.11      &lt;</td><td>\$1         \$0.25 - \$6         \$74         \$1.7           \$20.25         \$1.6         \$1.4         \$1.7           \$20.25         \$1.6         \$1.4         \$1.5           \$20.25         \$20 - \$220         \$1.7         \$4.75           \$20.25         \$20 - \$220         \$1.7         \$4.75           \$20.25         \$20 - \$220         \$1.7         \$4.15           \$20.5         \$20 - \$220         \$1.7         \$4.1           \$20.5         \$20 - \$20         \$1.7         \$4.1           \$20.5         \$20 - \$20         \$1.7         \$1.38           \$21         \$1.27         \$2.138         \$2.7           \$21         \$4.138         \$2.25         \$2.7         \$4.1           \$20.5         \$20 -\$264         \$0.1         \$0.6         \$0.6           \$21         \$2.025-\$26         \$2.7         \$4.1         \$2.5         \$2.7           \$21         \$2.025-\$26         \$1.6         \$1.6         \$3.08           \$22.5         \$2.7         \$4.1         \$0.25         \$2.7           \$22.5         \$2.7         \$2.7         \$2.7         \$2.7           \$21.2         \$2.9         \$2.7         \$2.7</td><td>st solution of the second seco</td><td>si s0.25- z66 /74 1.72<br/>2.012 115<br/>2.012 2.017 84.75<br/>2.012 2.012 2.01<br/>2.012 2.012 2.010<br/>2.012 2.012 2.012 2.010<br/>2.012 2.012 2.012 2.010<br/>2.012 2.012 2.012 2.010<br/>2.012 2.012 2.012 2.012 2.010<br/>2.012 2.012 2.012 2.012 2.010<br/>2.012 2.012 2.012 2.012 2.010<br/>2.012 2.012 2.012 2.010 2.010<br/>2.012 2.012 2.012 2.012 2.010 2.010<br/>2.012 2.012 2.012 2.010 2.010 2.010 0.0000 0.0000 0.000 0.0000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0</td><td>≤1         ≤0.26 - ≥16         174         1.12           ≤25         ≤0.25 - ≥16         174         1.15           ≤30         ≥30         177         84.75           ≥64         ≈20 - ≈200         177         84.75           ≥64         ≈12 - ≥64         ≥27         53.30           ≥64         ≈1-≥64         ≥27         53.30           ≥65         ≈1-≥64         ≥27         53.30           ≥65         ≈1-≥64         ≥27         50.7           ≤05         ≈1-≥64         ≥27         50.7           ≤05         ≈1-≥64         ≥27         50.7           ≤05         ≈025-≈16         ≥27         4.41           ≈64         ≈1-≥64         ≥27         50.7           ≤05         ≈025-≈16         ≥27         4.41           ≈22         ≈64         61         9.25           ≥64         ≈22.264         161         9.25           ≥10         ≥302         ≥37         76.72           ≥64         ≈0.25-≈66         57         76.72           ≥7         ≤012         20.7         30.8           ≥64         ≈0.5-≈66         57         76.72</td><td>≤1         \$0.25 - ≥16         174         1.12           \$20.25         \$2.52 - ≥16         174         1.15           ≥30.25         \$2.02 - ≥320         177         84.75           ≥64         \$5.52 - ≥16         774         1.15           ≥64         \$5.52 - ≥16         774         84.75           ≥64         \$5.52 - ≥16         774         84.75           ≥64         \$5.52 - ≥16         74         1.18           ≥64         \$5.52 - ≥16         74         1.18           ≥64         \$5.52 - ≥16         2.71         84.13           ≥64         \$5.56 - ≥16         2.71         4.11           ≥64         \$5.52 - ≥16         2.71         4.11           ≥64         \$5.52 - ≥16         2.77         4.11           ≥64         \$5.52 - ≥16         5.7         4.11           ≥64         \$5.52 - ≥16         5.7         7.6.72           ≥64         \$5.52 - ≥16         5.7         7.6.72           ≥66         \$5.52 - ≥16         5.7         7.6.6           ≥61         \$5.52 - ≥16         5.7         7.6.72           ≥66         \$5.52 - ≥16         5.7         7.6.72      <t< td=""><td>≤1         \$0.25-≥16         174         1.72           \$20.25         ≥12         212         115           ≥20.220         177         84.75           ≥64         \$2.02-220         177         84.75           ≥64         \$1-564         223         \$1-33           ≥64         \$1-564         232         \$1-38           ≥64         \$1-564         232         \$1-38           ≥64         \$1-564         232         \$1-38           ≥64         \$1-564         237         \$0.96           ≥64         \$1-564         237         \$4.11           ≥64         \$1-564         237         \$4.13           ≥64         \$1-564         237         \$4.11           ≥64         \$1-564         237         \$4.11           ≥64         \$1-564         237         \$4.11           ≥64         \$1-564         237         \$4.11           ≥64         \$1-564         237         \$4.11           ≥61         \$1-525         \$27         \$2.9           ≥61         \$1-52         \$2.7         \$2.9           ≥62         \$1-52         \$2.7         \$2.9</td><td>≤1         S0.25- ≥16         174         1.72           50.25         ≤126         74         1.15           2012         2012         77         84.75           2012         2012         77         84.75           2012         2012         77         84.75           2012         2012         2012         53.30           2012         2012         2014         115           2013         2012         201         77         84.75           2015         201         277         60.96         96           2015         201         277         5.27         5.73           2012         515         277         5.73         76.72           2012         516         277         4.41         277           2012         517         527         4.41         277           2012         2012         277         5.73         76.72           2012         211         19.25         276         277         5.73           2012         210.22         210.22         33.33         33.33         33.33           2012         210.12         210.12         30.35</td></t<><td>≤1         \$0.25 - ≥16         174         1.72           \$225         \$20.5 - ≥16         174         1.15           \$202         \$202 - ≥220         177         84.75           \$264         \$275         \$33.30         \$33.30           \$264         \$275         \$33.30         \$41.75           \$264         \$275         \$33.30         \$41.85           \$264         \$275         \$33.30         \$41.85           \$264         \$275         \$33.30         \$41.85           \$264         \$2127         \$33.30         \$21.85           \$265         \$65         \$27         \$41.38           \$21         \$51.20         \$27         \$41.38           \$265         \$61.5         \$21.95         \$21.95           \$2125         \$20.5 = 266         \$16.1         \$9.25           \$2125         \$21.65         \$23.08         \$16.10           \$2125         \$61.56         \$17.61         \$2.26           \$21025         \$61.56         \$17.61         \$2.26           \$2125        
\$20.5 = 205         \$17.61         \$2.26           \$21025         \$20.5 = 205         \$2.26         \$2.26</td></td></tr<></td></td></t<> | \$1         \$0.25- \$16         174         1.72           \$20.25         \$10.25         \$10.25         \$10.25           \$20.25         \$20- \$220         177         \$4,15           \$2012         \$201         77         \$4,15           \$2012         \$201         77         \$4,15           \$2012         \$201         \$201         \$4,15           \$2012         \$201         \$201         \$4,15           \$2012         \$21         \$1,38         \$1,38           \$21         \$21         \$23         \$1,38           \$25         \$205-\$26         \$23         \$1,38           \$25         \$205-\$26         \$27         \$4,11           \$21         \$213         \$1,38           \$25         \$205-\$26         \$27         \$4,11           \$21         \$212         \$217         \$217           \$21         \$205-\$26         \$27         \$4,11           \$21         \$202-\$26         \$27         \$4,11           \$21         \$210-\$22         \$217         \$217           \$21         \$210-\$22         \$217         \$217           \$2105         \$210-\$22         \$217         \$217 </td <td>st s0.25 - zf6 /r14 /r12<br/>2012 201 - z012 - z10 /r17 84./r5<br/>2012 - z01 - z012 - z01 /r13 81./r5<br/>201 - z012 - z01 - z01 /r3 81./r1<br/>201 - z012 - z01 - z01 /r3 81./r1<br/>201 - z012 - z01 - z01 /r3 81./r1<br/>201 - z012 - z01 - z01 /r1 /r1<br/>201 - z01 - z01 /r3 81./r1<br/>201 - z01 - z01 /r1 /r1<br/>201 - z01 /r1 /r1 /r1 /r1 /r1 /r1 /r1 /r1 /r1 /r</td> <td>st s0.25 - zf6 /74 1.72<br/>s0.25 s0.25 - zf6 /74 1.15<br/>2012 2017 84.75<br/>2012 2017 84.75<br/>2012 2017 84.75<br/>2012 2017 84.75<br/>2012 2017 84.75<br/>2015 2017 94.11<br/>2012 2016 2017 2017<br/>2012 2016 2017 2017<br/>2012 2016 2017 2017<br/>2012 2016 2016 2017 1011<br/>2012 2016 2016 2017 1011<br/>2012 2012 2017 2017<br/>2012 2017 2017 2017<br/>2012 2017 2017 2017<br/>2013 2017 2017 2017 2017<br/>2013 2017 2017 2017 2017 2017<br/>2013 2017 2017 2017 2017 2017 2017 2017 2017</td> <td>si s0.26 - ≥16 /74 /172<br/>s0.25 s0.25 - ≥16 /74 /15<br/>2.00 - ≥320 /77 84.75<br/>2.01 - ≥012 /17 84.75<br/>2.01 - ≥012 /17 84.75<br/>2.01 - ≥02 - ≥320 /17 84.75<br/>2.01 - ≥02 - ≥320 /17 84.75<br/>2.01 - ≥64 2.27 5.33<br/>2.05 - ≥16 2.27 5.29<br/>2.05 - ≥16 2.27 2.07<br/>2.01 - ≥16 2.07 2.08<br/>2.01 - 28 2.26 2.07 2.08 2.07 2.08<br/>2.01 - 28 2.08 2.07 2.08 2.08<br/>2.01 - 28 2.08 2.08 2.08 2.08 2.08<br/>2.01 - 28 2.08 2.08 2.08 2.08 2.08 2.08<br/>2.01 - 28 2.08 2.08 2.08 2.08 2.08 2.08 2.08 2</td> <td>\$1         \$0.25- 266         174         1.15           \$2025         \$202- 2320         177         84.75           \$201-2320         177         84.75           \$201-2320         177         84.75           \$201-2320         177         84.75           \$201-2320         177         84.75           \$201-2320         \$202-232         \$1.38           \$201-2320         \$217         \$3.30           \$202-246         \$2.27         \$3.30           \$205-246         \$2.27         \$2.33           \$205-246         \$2.27         \$2.7           \$205-246         \$2.7         \$2.7           \$202-256         \$2.27         \$2.7           \$202-256         \$2.27         \$2.7           \$202-256         \$2.27         \$4.41           \$202-256         \$2.27         \$4.41           \$202-256         \$2.27         \$4.74           \$202-256         \$2.27         \$4.74           \$202-256         \$2.27         \$4.74           \$202-256         \$2.76         \$2.76           \$202-266         \$5.72         \$2.9           \$202-266         \$5.72         \$2.9      <tr< td=""><td>\$1         \$0.25 - \$16         174         1.72           \$20.25         \$1.5         \$2.5         \$1.4         1.15           \$20.25         \$2.0         \$2.0         \$2.0         \$4.75           \$2.01         \$1.71         \$4.75         \$4.75           \$2.01         \$2.01         \$1.71         \$4.75           \$2.01         \$2.01         \$2.01         \$4.15           \$2.01         \$2.01         \$2.01         \$4.15           \$2.01         \$2.01         \$2.01         \$4.11           \$2.01         \$2.02         \$2.01         \$4.11           \$2.01         \$2.01         \$2.01         \$4.11           \$2.05         \$2.05         \$2.01         \$4.11           \$2.01         \$2.02         \$2.01         \$4.11           \$2.01         \$2.01         \$2.01         \$4.11           \$2.01         \$2.01         \$2.01         \$4.11           \$2.01         \$2.02         \$2.01         \$4.11           \$2.01         \$2.02         \$2.01         \$4.11           \$2.01         \$2.01         \$2.01         \$4.11           \$2.01         \$2.01         \$2.01         \$4.11      &lt;</td><td>\$1         \$0.25 - \$6         \$74         \$1.7           \$20.25         \$1.6         \$1.4         \$1.7           \$20.25         \$1.6         \$1.4         \$1.5           \$20.25         \$20 - \$220         \$1.7         \$4.75           \$20.25         \$20 - \$220         \$1.7         \$4.75           \$20.25         \$20 - \$220         \$1.7         \$4.15           \$20.5         \$20 - \$220         \$1.7         \$4.1           \$20.5         \$20 - \$20         \$1.7         \$4.1           \$20.5         \$20 - \$20         \$1.7         \$1.38           \$21         \$1.27         \$2.138         \$2.7           \$21         \$4.138         \$2.25         \$2.7         \$4.1           \$20.5         \$20 -\$264         \$0.1         \$0.6         \$0.6           \$21         \$2.025-\$26         \$2.7         \$4.1         \$2.5         \$2.7           \$21         \$2.025-\$26         \$1.6         \$1.6         \$3.08           \$22.5         \$2.7         \$4.1         \$0.25         \$2.7           \$22.5         \$2.7         \$2.7         \$2.7         \$2.7           \$21.2         \$2.9         \$2.7         \$2.7</td><td>st solution of the second seco</td><td>si s0.25- z66 /74 1.72<br/>2.012 115<br/>2.012 2.017 84.75<br/>2.012 2.012 2.01<br/>2.012 2.012 2.010<br/>2.012 2.012 2.012 2.010<br/>2.012 2.012 2.012 2.010<br/>2.012 2.012 2.012 2.010<br/>2.012 2.012 2.012 2.012 2.010<br/>2.012 2.012 2.012 2.012 2.010<br/>2.012 2.012 2.012 2.012 2.010<br/>2.012 2.012 2.012 2.010 2.010<br/>2.012 2.012 2.012 2.012 2.010 2.010<br/>2.012 2.012 2.012 2.010 2.010 2.010 0.0000 0.0000 0.000 0.0000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0</td><td>≤1         ≤0.26 - ≥16         174         1.12           ≤25         ≤0.25 - ≥16         174         1.15           ≤30         ≥30         177         84.75           ≥64         ≈20 - ≈200         177         84.75           ≥64         ≈12 - ≥64         ≥27         53.30           ≥64         ≈1-≥64         ≥27         53.30           ≥65         ≈1-≥64         ≥27         53.30           ≥65         ≈1-≥64         ≥27         50.7           ≤05         ≈1-≥64         ≥27         50.7           ≤05         ≈1-≥64         ≥27         50.7           ≤05         ≈025-≈16         ≥27         4.41           ≈64         ≈1-≥64         ≥27         50.7           ≤05         ≈025-≈16         ≥27         4.41           ≈22         ≈64         61         9.25           ≥64         ≈22.264         161         9.25           ≥10         ≥302         ≥37         76.72           ≥64         ≈0.25-≈66         57         76.72           ≥7         ≤012         20.7         30.8           ≥64         ≈0.5-≈66         57         76.72</td><td>≤1         \$0.25 - ≥16         174         1.12           \$20.25         \$2.52 - ≥16         174         1.15           ≥30.25         \$2.02 - ≥320         177         84.75           ≥64         \$5.52 - ≥16         774         1.15           ≥64         \$5.52 - ≥16         774         84.75           ≥64         \$5.52 - ≥16         774         84.75           ≥64         \$5.52 - ≥16         74         1.18           ≥64         \$5.52 - ≥16         74         1.18           ≥64         \$5.52 - ≥16         2.71         84.13           ≥64         \$5.56 - ≥16         2.71         4.11           ≥64         \$5.52 - ≥16         2.71         4.11           ≥64         \$5.52 - ≥16         2.77         4.11           ≥64         \$5.52 - ≥16         5.7         4.11           ≥64         \$5.52 - ≥16         5.7         7.6.72           ≥64         \$5.52 - ≥16         5.7         7.6.72           ≥66         \$5.52 - ≥16         5.7         7.6.6           ≥61         \$5.52 - ≥16         5.7         7.6.72           ≥66         \$5.52 - ≥16         5.7         7.6.72      <t< td=""><td>≤1         \$0.25-≥16         174         1.72           \$20.25         ≥12         212         115           ≥20.220         177         84.75           ≥64         \$2.02-220         177         84.75           ≥64         \$1-564         223         \$1-33           ≥64         \$1-564         232         \$1-38           ≥64         \$1-564         232         \$1-38           ≥64         \$1-564         232         \$1-38           ≥64         \$1-564         237         \$0.96           ≥64         \$1-564         237         \$4.11           ≥64         \$1-564         237         \$4.13           ≥64         \$1-564         237        
\$4.11           ≥64         \$1-564         237         \$4.11           ≥64         \$1-564         237         \$4.11           ≥64         \$1-564         237         \$4.11           ≥64         \$1-564         237         \$4.11           ≥61         \$1-525         \$27         \$2.9           ≥61         \$1-52         \$2.7         \$2.9           ≥62         \$1-52         \$2.7         \$2.9</td><td>≤1         S0.25- ≥16         174         1.72           50.25         ≤126         74         1.15           2012         2012         77         84.75           2012         2012         77         84.75           2012         2012         77         84.75           2012         2012         2012         53.30           2012         2012         2014         115           2013         2012         201         77         84.75           2015         201         277         60.96         96           2015         201         277         5.27         5.73           2012         515         277         5.73         76.72           2012         516         277         4.41         277           2012         517         527         4.41         277           2012         2012         277         5.73         76.72           2012         211         19.25         276         277         5.73           2012         210.22         210.22         33.33         33.33         33.33           2012         210.12         210.12         30.35</td></t<><td>≤1         \$0.25 - ≥16         174         1.72           \$225         \$20.5 - ≥16         174         1.15           \$202         \$202 - ≥220         177         84.75           \$264         \$275         \$33.30         \$33.30           \$264         \$275         \$33.30         \$41.75           \$264         \$275         \$33.30         \$41.85           \$264         \$275         \$33.30         \$41.85           \$264         \$275         \$33.30         \$41.85           \$264         \$2127         \$33.30         \$21.85           \$265         \$65         \$27         \$41.38           \$21         \$51.20         \$27         \$41.38           \$265         \$61.5         \$21.95         \$21.95           \$2125         \$20.5 = 266         \$16.1         \$9.25           \$2125         \$21.65         \$23.08         \$16.10           \$2125         \$61.56         \$17.61         \$2.26           \$21025         \$61.56         \$17.61         \$2.26           \$2125         \$20.5 = 205         \$17.61         \$2.26           \$21025         \$20.5 = 205         \$2.26         \$2.26</td></td></tr<></td> | st s0.25 - zf6 /r14 /r12<br>2012 201 - z012 - z10 /r17 84./r5<br>2012 - z01 - z012 - z01 /r13 81./r5<br>201 - z012 - z01 - z01 /r3 81./r1<br>201 - z012 - z01 - z01 /r3 81./r1<br>201 - z012 - z01 - z01 /r3 81./r1<br>201 - z012 - z01 - z01 /r1 /r1<br>201 - z01 - z01 /r3 81./r1<br>201 - z01 - z01 /r1 /r1<br>201 - z01 /r1 /r1 /r1 /r1 /r1 /r1 /r1 /r1 /r1 /r   
   | st s0.25 - zf6 /74 1.72<br>s0.25 s0.25 - zf6 /74 1.15<br>2012 2017 84.75<br>2012 2017 84.75<br>2012 2017 84.75<br>2012 2017 84.75<br>2012 2017 84.75<br>2015 2017 94.11<br>2012 2016 2017 2017<br>2012 2016 2017 2017<br>2012 2016 2017 2017<br>2012 2016 2016 2017 1011<br>2012 2016 2016 2017 1011<br>2012 2012 2017 2017<br>2012 2017 2017 2017<br>2012 2017 2017 2017<br>2013 2017 2017 2017 2017<br>2013 2017 2017 2017 2017 2017<br>2013 2017 2017 2017 2017 2017 2017 2017 2017  
  | si s0.26 - ≥16 /74 /172<br>s0.25 s0.25 - ≥16 /74 /15<br>2.00 - ≥320 /77 84.75<br>2.01 - ≥012 /17 84.75<br>2.01 - ≥012 /17 84.75<br>2.01 - ≥02 - ≥320 /17 84.75<br>2.01 - ≥02 - ≥320 /17 84.75<br>2.01 - ≥64 2.27 5.33<br>2.05 - ≥16 2.27 5.29<br>2.05 - ≥16 2.27 2.07<br>2.01 - ≥16 2.07 2.08<br>2.01 - 28 2.26 2.07 2.08 2.07 2.08<br>2.01 - 28 2.08 2.07 2.08 2.08<br>2.01 - 28 2.08 2.08 2.08 2.08 2.08<br>2.01 - 28 2.08 2.08 2.08 2.08 2.08 2.08<br>2.01 - 28 2.08 2.08 2.08 2.08 2.08 2.08 2.08 2 | \$1         \$0.25- 266         174         1.15           \$2025         \$202- 2320         177         84.75           \$201-2320         177         84.75           \$201-2320         177         84.75           \$201-2320         177         84.75           \$201-2320         177         84.75           \$201-2320         \$202-232         \$1.38           \$201-2320         \$217         \$3.30           \$202-246         \$2.27         \$3.30           \$205-246         \$2.27         \$2.33           \$205-246         \$2.27         \$2.7           \$205-246         \$2.7         \$2.7           \$202-256         \$2.27         \$2.7           \$202-256         \$2.27         \$2.7           \$202-256         \$2.27         \$4.41           \$202-256         \$2.27         \$4.41           \$202-256         \$2.27         \$4.74           \$202-256         \$2.27         \$4.74           \$202-256         \$2.27         \$4.74           \$202-256         \$2.76         \$2.76           \$202-266         \$5.72         \$2.9           \$202-266         \$5.72         \$2.9 <tr< td=""><td>\$1         \$0.25 - \$16         174         1.72           \$20.25         \$1.5         \$2.5         \$1.4         1.15           \$20.25         \$2.0         \$2.0         \$2.0         \$4.75           \$2.01         \$1.71         \$4.75         \$4.75           \$2.01         \$2.01         \$1.71         \$4.75           \$2.01         \$2.01         \$2.01         \$4.15           \$2.01         \$2.01         \$2.01         \$4.15           \$2.01         \$2.01         \$2.01         \$4.11           \$2.01         \$2.02         \$2.01         \$4.11           \$2.01         \$2.01         \$2.01         \$4.11           \$2.05         \$2.05         \$2.01         \$4.11           \$2.01         \$2.02         \$2.01         \$4.11           \$2.01         \$2.01         \$2.01         \$4.11           \$2.01         \$2.01         \$2.01         \$4.11           \$2.01         \$2.02         \$2.01         \$4.11           \$2.01         \$2.02         \$2.01         \$4.11           \$2.01         \$2.01         \$2.01         \$4.11           \$2.01         \$2.01         \$2.01         \$4.11      &lt;</td><td>\$1         \$0.25 - \$6         \$74         \$1.7           \$20.25         \$1.6         \$1.4         \$1.7           \$20.25         \$1.6         \$1.4         \$1.5           \$20.25         \$20 - \$220         \$1.7         \$4.75           \$20.25         \$20 - \$220         \$1.7         \$4.75           \$20.25         \$20 - \$220         \$1.7         \$4.15           \$20.5         \$20 - \$220         \$1.7         \$4.1           \$20.5         \$20 - \$20         \$1.7         \$4.1           \$20.5         \$20 - \$20         \$1.7         \$1.38           \$21         \$1.27         \$2.138         \$2.7           \$21         \$4.138         \$2.25         \$2.7         \$4.1           \$20.5         \$20 -\$264         \$0.1         \$0.6         \$0.6           \$21         \$2.025-\$26         \$2.7         \$4.1         \$2.5         \$2.7           \$21         \$2.025-\$26         \$1.6         \$1.6         \$3.08           \$22.5         \$2.7         \$4.1         \$0.25         \$2.7           \$22.5         \$2.7         \$2.7         \$2.7         \$2.7           \$21.2         \$2.9         \$2.7         \$2.7</td><td>st solution of the second seco</td><td>si s0.25- z66 /74 1.72<br/>2.012 115<br/>2.012 2.017 84.75<br/>2.012 2.012 2.01<br/>2.012 2.012 2.010<br/>2.012 2.012 2.012 2.010<br/>2.012 2.012 2.012 2.010<br/>2.012 2.012 2.012 2.010<br/>2.012 2.012 2.012 2.012 2.010<br/>2.012 2.012 2.012 2.012 2.010<br/>2.012 2.012 2.012 2.012 2.010<br/>2.012 2.012 2.012 2.010 2.010<br/>2.012 2.012 2.012 2.012 2.010 2.010<br/>2.012 2.012 2.012 2.010 2.010 2.010 0.0000 0.0000 0.000 0.0000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0</td><td>≤1         ≤0.26 - ≥16         174         1.12           ≤25         ≤0.25 - ≥16         174         1.15           ≤30         ≥30         177         84.75           ≥64         ≈20 - ≈200         177         84.75           ≥64         ≈12 - ≥64         ≥27         53.30           ≥64         ≈1-≥64         ≥27         53.30           ≥65         ≈1-≥64         ≥27         53.30           ≥65         ≈1-≥64         ≥27         50.7           ≤05         ≈1-≥64         ≥27         50.7           ≤05         ≈1-≥64         ≥27         50.7           ≤05         ≈025-≈16         ≥27         4.41           ≈64         ≈1-≥64         ≥27         50.7           ≤05         ≈025-≈16         ≥27         4.41           ≈22         ≈64         61         9.25           ≥64         ≈22.264         161         9.25           ≥10         ≥302         ≥37         76.72           ≥64         ≈0.25-≈66         57         76.72           ≥7         ≤012         20.7         30.8           ≥64         ≈0.5-≈66         57         76.72</td><td>≤1         \$0.25 - ≥16         174         1.12           \$20.25         \$2.52 - ≥16         174         1.15           ≥30.25         \$2.02 - ≥320         177         84.75           ≥64         \$5.52 - ≥16         774         1.15           ≥64         \$5.52 - ≥16         774         84.75           ≥64         \$5.52 - ≥16         774         84.75           ≥64         \$5.52 - ≥16         74         1.18           ≥64         \$5.52 - ≥16         74         1.18           ≥64         \$5.52 - ≥16         2.71         84.13           ≥64         \$5.56 - ≥16         2.71         4.11           ≥64         \$5.52 - ≥16         2.71        
4.11           ≥64         \$5.52 - ≥16         2.77         4.11           ≥64         \$5.52 - ≥16         5.7         4.11           ≥64         \$5.52 - ≥16         5.7         7.6.72           ≥64         \$5.52 - ≥16         5.7         7.6.72           ≥66         \$5.52 - ≥16         5.7         7.6.6           ≥61         \$5.52 - ≥16         5.7         7.6.72           ≥66         \$5.52 - ≥16         5.7         7.6.72      <t< td=""><td>≤1         \$0.25-≥16         174         1.72           \$20.25         ≥12         212         115           ≥20.220         177         84.75           ≥64         \$2.02-220         177         84.75           ≥64         \$1-564         223         \$1-33           ≥64         \$1-564         232         \$1-38           ≥64         \$1-564         232         \$1-38           ≥64         \$1-564         232         \$1-38           ≥64         \$1-564         237         \$0.96           ≥64         \$1-564         237         \$4.11           ≥64         \$1-564         237         \$4.13           ≥64         \$1-564         237         \$4.11           ≥64         \$1-564         237         \$4.11           ≥64         \$1-564         237         \$4.11           ≥64         \$1-564         237         \$4.11           ≥64         \$1-564         237         \$4.11           ≥61         \$1-525         \$27         \$2.9           ≥61         \$1-52         \$2.7         \$2.9           ≥62         \$1-52         \$2.7         \$2.9</td><td>≤1         S0.25- ≥16         174         1.72           50.25         ≤126         74         1.15           2012         2012         77         84.75           2012         2012         77         84.75           2012         2012         77         84.75           2012         2012         2012         53.30           2012         2012         2014         115           2013         2012         201         77         84.75           2015         201         277         60.96         96           2015         201         277         5.27         5.73           2012         515         277         5.73         76.72           2012         516         277         4.41         277           2012         517         527         4.41         277           2012         2012         277         5.73         76.72           2012         211         19.25         276         277         5.73           2012         210.22         210.22         33.33         33.33         33.33           2012         210.12         210.12         30.35</td></t<><td>≤1         \$0.25 - ≥16         174         1.72           \$225         \$20.5 - ≥16         174         1.15           \$202         \$202 - ≥220         177         84.75           \$264         \$275         \$33.30         \$33.30           \$264         \$275         \$33.30         \$41.75           \$264         \$275         \$33.30         \$41.85           \$264         \$275         \$33.30         \$41.85           \$264         \$275         \$33.30         \$41.85           \$264         \$2127         \$33.30         \$21.85           \$265         \$65         \$27         \$41.38           \$21         \$51.20         \$27         \$41.38           \$265         \$61.5         \$21.95         \$21.95           \$2125         \$20.5 = 266         \$16.1         \$9.25           \$2125         \$21.65         \$23.08         \$16.10           \$2125         \$61.56         \$17.61         \$2.26           \$21025         \$61.56         \$17.61         \$2.26           \$2125         \$20.5 = 205         \$17.61         \$2.26           \$21025         \$20.5 = 205         \$2.26         \$2.26</td></td></tr<> | \$1         \$0.25 - \$16         174         1.72           \$20.25         \$1.5         \$2.5         \$1.4         1.15           \$20.25         \$2.0         \$2.0         \$2.0         \$4.75           \$2.01         \$1.71         \$4.75         \$4.75           \$2.01         \$2.01         \$1.71         \$4.75           \$2.01         \$2.01         \$2.01         \$4.15           \$2.01         \$2.01         \$2.01         \$4.15           \$2.01         \$2.01         \$2.01         \$4.11           \$2.01         \$2.02         \$2.01         \$4.11           \$2.01         \$2.01         \$2.01         \$4.11           \$2.05         \$2.05         \$2.01         \$4.11           \$2.01         \$2.02         \$2.01         \$4.11           \$2.01         \$2.01         \$2.01         \$4.11           \$2.01         \$2.01         \$2.01         \$4.11           \$2.01         \$2.02         \$2.01         \$4.11           \$2.01         \$2.02         \$2.01         \$4.11           \$2.01         \$2.01         \$2.01         \$4.11           \$2.01         \$2.01         \$2.01         \$4.11      <   | \$1         \$0.25 - \$6         \$74         \$1.7           \$20.25         \$1.6         \$1.4         \$1.7           \$20.25         \$1.6         \$1.4         \$1.5           \$20.25         \$20 - \$220         \$1.7         \$4.75           \$20.25         \$20 - \$220         \$1.7         \$4.75           \$20.25         \$20 - \$220         \$1.7         \$4.15           \$20.5         \$20 - \$220         \$1.7         \$4.1           \$20.5         \$20 - \$20         \$1.7         \$4.1           \$20.5         \$20 - \$20         \$1.7         \$1.38           \$21         \$1.27         \$2.138         \$2.7           \$21         \$4.138         \$2.25         \$2.7         \$4.1           \$20.5         \$20 -\$264         \$0.1         \$0.6         \$0.6           \$21         \$2.025-\$26         \$2.7         \$4.1         \$2.5         \$2.7           \$21         \$2.025-\$26         \$1.6         \$1.6         \$3.08           \$22.5         \$2.7         \$4.1         \$0.25         \$2.7           \$22.5         \$2.7         \$2.7         \$2.7         \$2.7           \$21.2         \$2.9         \$2.7         \$2.7   
  | st solution of the second seco  | si s0.25- z66 /74 1.72<br>2.012 115<br>2.012 2.017 84.75<br>2.012 2.012 2.01<br>2.012 2.012 2.010<br>2.012 2.012 2.012 2.010<br>2.012 2.012 2.012 2.010<br>2.012 2.012 2.012 2.010<br>2.012 2.012 2.012 2.012 2.010<br>2.012 2.012 2.012 2.012 2.010<br>2.012 2.012 2.012 2.012 2.010<br>2.012 2.012 2.012 2.010 2.010<br>2.012 2.012 2.012 2.012 2.010 2.010<br>2.012 2.012 2.012 2.010 2.010 2.010 0.0000 0.0000 0.000 0.0000 0.000 0.000 0.000 0.000 0.000 0.000 0.000 0  
   | ≤1         ≤0.26 - ≥16         174         1.12           ≤25         ≤0.25 - ≥16         174         1.15           ≤30         ≥30         177         84.75           ≥64         ≈20 - ≈200         177         84.75           ≥64         ≈12 - ≥64         ≥27         53.30           ≥64         ≈1-≥64         ≥27         53.30           ≥65         ≈1-≥64         ≥27         53.30           ≥65         ≈1-≥64         ≥27         50.7           ≤05         ≈1-≥64         ≥27         50.7           ≤05         ≈1-≥64         ≥27         50.7           ≤05         ≈025-≈16         ≥27         4.41           ≈64         ≈1-≥64         ≥27         50.7           ≤05         ≈025-≈16         ≥27         4.41           ≈22         ≈64         61         9.25           ≥64         ≈22.264         161         9.25           ≥10         ≥302         ≥37         76.72           ≥64         ≈0.25-≈66         57         76.72           ≥7         ≤012         20.7         30.8           ≥64         ≈0.5-≈66         57         76.72  | ≤1         \$0.25 - ≥16         174         1.12           \$20.25         \$2.52 - ≥16         174         1.15           ≥30.25         \$2.02 - ≥320         177         84.75           ≥64         \$5.52 - ≥16         774         1.15           ≥64         \$5.52 - ≥16         774         84.75           ≥64         \$5.52 - ≥16         774         84.75           ≥64         \$5.52 - ≥16         74         1.18           ≥64         \$5.52 - ≥16         74         1.18           ≥64         \$5.52 - ≥16         2.71         84.13           ≥64         \$5.56 - ≥16         2.71         4.11           ≥64         \$5.52 - ≥16         2.71         4.11           ≥64         \$5.52 - ≥16         2.77         4.11           ≥64         \$5.52 - ≥16         5.7         4.11           ≥64         \$5.52 - ≥16         5.7         7.6.72           ≥64         \$5.52 - ≥16         5.7         7.6.72           ≥66         \$5.52 - ≥16         5.7         7.6.6           ≥61         \$5.52 - ≥16         5.7         7.6.72           ≥66         \$5.52 - ≥16         5.7         7.6.72 <t< td=""><td>≤1         \$0.25-≥16         174         1.72           \$20.25         ≥12         212         115           ≥20.220         177         84.75           ≥64         \$2.02-220         177         84.75           ≥64         \$1-564         223         \$1-33           ≥64         \$1-564         232         \$1-38           ≥64         \$1-564         232         \$1-38           ≥64         \$1-564         232         \$1-38           ≥64         \$1-564         237         \$0.96           ≥64         \$1-564         237         \$4.11           ≥64         \$1-564         237         \$4.13           ≥64         \$1-564         237         \$4.11           ≥64         \$1-564         237         \$4.11           ≥64         \$1-564         237         \$4.11           ≥64         \$1-564         237         \$4.11           ≥64         \$1-564         237         \$4.11           ≥61         \$1-525         \$27         \$2.9           ≥61         \$1-52         \$2.7         \$2.9           ≥62         \$1-52         \$2.7         \$2.9</td><td>≤1         S0.25- ≥16         174         1.72           50.25         ≤126         74         1.15           2012         2012         77         84.75           2012         2012         77         84.75           2012         2012         77         84.75           2012         2012         2012         53.30           2012         2012         2014         115           2013         2012         201         77         84.75           2015         201         277         60.96         96           2015         201         277         5.27         5.73           2012         515         277         5.73         76.72           2012         516         277         4.41         277           2012         517         527         4.41         277           2012         2012         277         5.73         76.72           2012         211         19.25         276         277         5.73           2012         210.22         210.22         33.33         33.33         33.33           2012         210.12         210.12         30.35</td></t<> <td>≤1         \$0.25 - ≥16         174         1.72           \$225         \$20.5 - ≥16         174         1.15           \$202         \$202 - ≥220         177         84.75           \$264         \$275         \$33.30         \$33.30           \$264         \$275         \$33.30         \$41.75           \$264         \$275         \$33.30         \$41.85           \$264         \$275         \$33.30         \$41.85           \$264         \$275         \$33.30         \$41.85           \$264         \$2127         \$33.30         \$21.85           \$265         \$65         \$27         \$41.38           \$21         \$51.20         \$27         \$41.38           \$265         \$61.5         \$21.95         \$21.95           \$2125         \$20.5 = 266         \$16.1         \$9.25           \$2125         \$21.65         \$23.08         \$16.10           \$2125         \$61.56         \$17.61         \$2.26           \$21025         \$61.56         \$17.61         \$2.26           \$2125         \$20.5 = 205         \$17.61         \$2.26           \$21025         \$20.5 = 205         \$2.26         \$2.26</td> | ≤1         \$0.25-≥16         174         1.72           \$20.25         ≥12         212         115           ≥20.220         177         84.75           ≥64         \$2.02-220         177         84.75           ≥64         \$1-564         223         \$1-33           ≥64         \$1-564         232         \$1-38           ≥64         \$1-564         232         \$1-38           ≥64         \$1-564         232         \$1-38           ≥64         \$1-564         237         \$0.96           ≥64         \$1-564         237         \$4.11           ≥64         \$1-564         237         \$4.13           ≥64         \$1-564         237         \$4.11           ≥64         \$1-564         237         \$4.11           ≥64         \$1-564         237         \$4.11           ≥64         \$1-564         237         \$4.11           ≥64         \$1-564         237         \$4.11           ≥61         \$1-525         \$27         \$2.9           ≥61         \$1-52         \$2.7         \$2.9           ≥62         \$1-52         \$2.7         \$2.9  | ≤1         S0.25- ≥16         174         1.72           50.25         ≤126         74         1.15           2012         2012         77        
84.75           2012         2012         77         84.75           2012         2012         77         84.75           2012         2012         2012         53.30           2012         2012         2014         115           2013         2012         201         77         84.75           2015         201         277         60.96         96           2015         201         277         5.27         5.73           2012         515         277         5.73         76.72           2012         516         277         4.41         277           2012         517         527         4.41         277           2012         2012         277         5.73         76.72           2012         211         19.25         276         277         5.73           2012         210.22         210.22         33.33         33.33         33.33           2012         210.12         210.12         30.35   | ≤1         \$0.25 - ≥16         174         1.72           \$225         \$20.5 - ≥16         174         1.15           \$202         \$202 - ≥220         177         84.75           \$264         \$275         \$33.30         \$33.30           \$264         \$275         \$33.30         \$41.75           \$264         \$275         \$33.30         \$41.85           \$264         \$275         \$33.30         \$41.85           \$264         \$275         \$33.30         \$41.85           \$264         \$2127         \$33.30         \$21.85           \$265         \$65         \$27         \$41.38           \$21         \$51.20         \$27         \$41.38           \$265         \$61.5         \$21.95         \$21.95           \$2125         \$20.5 = 266         \$16.1         \$9.25           \$2125         \$21.65         \$23.08         \$16.10           \$2125         \$61.56         \$17.61         \$2.26           \$21025         \$61.56         \$17.61         \$2.26           \$2125         \$20.5 = 205         \$17.61         \$2.26           \$21025         \$20.5 = 205         \$2.26         \$2.26   |
| 153         0,00         ≤0.25         ≤0.25           157         81.53         ≥320         ≥320   
   
   
   | 153         0,00         ≤0.25         ≤0.25           157         81.53         ≥320         ≥320           10         %R         MIC50         MIC90  
  | [53         0.00         \$0.25         \$0.25           [57         81.53         \$2320         \$320           1         %R         MIC5         \$40           1         %R         MIC5         \$40           140         \$5.46         1         \$46  
   
   
  | [53         0.00         \$0.25         \$0.25           [57         81.53         \$2320         \$320           n         %R         MIC5         MIC9           [40         \$0.71         16         \$64           [41         \$5.46         1         \$44           1         \$6         \$0.5         \$0.5   | [53         0.00         s0.25         s0.25           [57         81.53         s220         z320           n         %R         MIC5         MIC9           [40         50.71         16         264           [41         35.46         1         24           *         *         s0.5         s0.5           [41         35.46         1         24           *         *         s0.5         20.5           [39         1.44         s0.5         2           [39         1.44         s0.5         2   
   
   
   | IS3         0.00         s0.25         s0.25           IS7         81.53         2320         2320           IS7         81.53         2320         2320           IN         %R         MIC50         MIC90           IN         %S         MIC50         MIC90           IN         %S         A         264           IS9         IS44         264         264           IS9         IS45         265         50.5           IS9         IS45         265         50.5   
   | 153         0.00         50.25         50.25           157         81.53         2320         2320           161         %R         MIC50         MIC90           11         %K         MIC50         MIC90           141         35.46         1         24           4         *         20.5         26.4           139         1.44         26.4         26.5           139         1.44         26.5         50.5           140         10.71         2         26.5           140         1.43         26.5         50.5           140         1.43         26.5         50.5           140         1.43         26.5         50.5  
   
   | [53]         0.00         50.25         50.25           [57]         81.53         220         230           n         %R         MIC50         200           n         %R         MIC50         200           n         %R         MIC50         200           n         %R         MIC50         200           n         %8         MIC50         200           10         50.71         16         264           10         80.71         20.5         20.5           139         14.4         20.5         50.5           140         1.3         20.5         20.5           140         1.3         20.5         20.5           140         1.3         20.5         20.5           141         1.43         20.5         20.5  
   
   | [53]         0,00         50.25         50.25           [57]         81.53         2320         2320 <b>n</b> % <b>R</b> MIC50         MIC90           [40]         50.71         16         264           [41]         55.46         1         24           *         *         20.71         16         264           [40]         53.47         265         2         2           [40]         53.67         30.5         2         2           [40]         53.67         264         264         264           [40]         141         2.05         2         26           [40]         143         2.55         264         264           [40]         143         2.55         26.5         40           [40]         143         2.55         26.5         40           [40]         143         2.55         2.65         40           [40]         143         2.61         21         41           [40]         143         2.62         2.62         41           [40]         143         2.62         2.62         2.62  
   
   | [53]         0,00         50.25         50.25           [57]         81.53         2320         2320           n         %R         MIC50         2320           140         50.71         16         264           141         53.46         1         24           140         53.46         1         24           141         53.46         264         264           140         143         265         2           140         143         265         2           140         143         20.52         20.55           140         143         20.52         20.25           141         71.63         230.25         20.25           141         71.63         2320         2320           141         71.63         2320         2320           141         71.63         2320         2320           141         71.63         2320         2320  
   
  | [53]         0,00         50.25         50.25           [57]         81.53         2320         2320           n         %R         MICS 0         2320           140         50.71         16         264           141         55.46         1         24           141         55.46         1         264           141         55.46         1         24           140         58.57         264         264           140         143         26.5         20.5           140         143         26.5         26.5           140         143         26.5         26.5           140         143         26.5         26.5           140         143         26.5         26.5           140         143         26.5         26.5           140         143         26.25         26.4           141         71.63         2820         2320           141         %R         MIC50         MIC90           161         683         8         264   
  | [53         0.00         s0.25         s0.25           [57         81.53         2320         2320           n         %R         MIC50         MIC90           [40         50.71         16         264           [41         55.46         1         241           [41         55.46         1         24           [43         50.71         16         264           [44         53.57         264         264           [44         53.57         264         264           [44         1.43         20.5         265           [44         1.43         50.5         50.55           [40         1.43         51         264           [40         1.43         51         264           [40         1.43         50.55         50.55           [41         1.163         31         21         264      
    [40         1.63         81         82         20.55           [41         1.63         83         82         20.55           [41         1.63         83         20         20           [42         50.54         50.55   | [53]         0.00         s0.25         s0.25           [57]         81.53         220         220           n         %R         MIC50         MIC90           n         %R         MIC50         MIC90           n         %S.71         16         264           141         35.46         264         264           139         144         264         265           140         10.71         2         265         265           140         1.43         264         264         264           140         1.43         262         20.55         20.55           140         1.43         262         20.55         20.55           141         71.63         262         20.55         20.55           141         1.43         20.25         20.25         20.25           10         68.4         MIC90         20.55         20.25           10         16.33         82         20.25         20.25           10         59.44         20.55         2.5         20.25           101         59.44         2.56         2.5         2.5           101  
  | [53         0.00         s0.25         s0.25           [57]         81.53         s20.25         s20.25 <b>n</b> % <b>R</b> MIC50         MIC90           [40]         50.71         16         264           [41]         55.46         1         241           [41]         55.46         1         24           [41]         55.46         264         264           [42]         53.57         264         264           [40]         58.57         264         264           [40]        
1.43         20.5         20.5           [40]         1.43         56.5         50.55           [40]         1.43         51         54           [40]         1.43         51         54           [40]         1.43         51         54           [40]         1.43         51         54           [40]         1.63         38         564           [61]         16.83         8         56         26           [61]         16.83         8         56         26           [62]         59.4         56.5         27         26  
   | [53         0.00         s0.25         s0.25           [57]         81.53         s20.25         s20.25 <b>n</b> % <b>R</b> MICS 0         MIC9 0           [40]         50.71         16         264           [41]         55.46         1         24           [41]         55.46         1         24           [41]         55.46         264         264           [40]         58.57         264         264           [40]         58.57         264         264           [40]         1.44         20.5         30.5         365           [40]         1.43         20.5         26.5         30.5           [40]         1.43         20.5         30.25         30.25           [40]         1.43         20.55         26.4         41           [40]         1.43         20.55         20.25         20.25           [41]         1.63         8         8         264           [42]         1.63         26.6         26         27           [43]         1.63         8.6         26         27           [44]         1.63         2   
  | IS3         0.00         s0.25         s0.25           IS7         81.53         220         220           II         %R         MIC50         MIC90           II         %R         MIC50         MIC90           II         55.47         16         264           II         51.44         20.5         50.5           II         141         264         264           II         143         20.5         50.5           II         143         26.5         50.5           II         143         26.5         50.5           II     
   143         26.5         50.5           III         143         26.5         50.5           III         143         26.5         50.5           III         143         26.5         50.5           III         520         2320         2320           III         54         26.5         56.5           III         56.6         26.6         26.6           III         53.2         250         2320         2320           III         99.3         26.5         26.5         26.6      1  | [53]         0.00         s0.25         s0.25           [57]         81.53         2320         2320           1         %R         MIC50         MIC90           [40]         50.71         16         264           [41]         58.57         264         264           [40]         1.43         26.5         2           [40]         1.43         26.5         2           [40]         1.43         26.5         2           [40]         1.43         26.5         2           [41]         1.43         26.5         2           [41]         1.43         26.5         2.5           [41]         1.43         26.5         2.5           [42]         1.43         2.5         2.5           [41]         1.43         2.5         2.5           [41]         1.43         2.5         2.5           [42]         2.64         2.6         2.6           [43]         1.43         2.5         2.5           [44]         1.43         2.5         2.5           [44]         1.43         2.6         2.6           [44]        
1.   | $ \begin{array}{ c c c c c c c c c c c c c c c c c c c$   
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   | $ \begin{array}{ c c c c c c c c c c c c c c c c c c c$   | Image: Signed set of the set of   
   | (53)         0.00         50.25         50.25           (57)         81.53         220         220           n         %R         MIC50         MIC90           10         50.71         16         264           141         35.57         2525         252           139         144         264         264           140         141         264         265           139         144         263         265           140         143         264         265           140         143         264         265           141         71.63         262         275           141         143         262         265           141         71.63         2820         2320           1         0.63         286         266           1         16.83         28         265           1         29.61         286         266           1         29.61         276         26           1         20.01         286         266           1         20.01         28.62         27           1         20.02         28.62 </td <td><math display="block"> \begin{array}{ c c c c c c c c c c c c c c c c c c c</math></td> <td><math display="block"> \begin{array}{ c c c c c c c c c c c c c c c c c c c</math></td> <td><math display="block"> \begin{array}{ c c c c c c c c c c c c c c c c c c c</math></td> <td><math display="block"> \begin{array}{ c c c c c c c c c c c c c c c c c c c</math></td> | $ \begin{array}{ c c c c c c c c c c c c c c c c c c c$   | $ \begin{array}{ c c c c c c c c c c c c c c c c c c c$   
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   | 2011<br>2011<br>264 21-264 140<br>264 21-264 141<br>2 2 50.5-266 4<br>141<br>2 2 50.5-268 140<br>2 2 50.5-268 140<br>2 2 51-264 140   
   | 2011<br>2014<br>264 21-264 140<br>264 21-264 140<br>24 50.52-26 141<br>25 50.52-26 140<br>24 51-264 140<br>24 51-264 140<br>24 51-264 140<br>25 50.55 50.25-16 140  
   
   | 2011<br>2014<br>264 21-264 140<br>264 21-264 140<br>24 50.5-26 141<br>23 50.5-26 140<br>24 515-26 140<br>24 515-26 140<br>24 515-26 140<br>24 5125 50.25-66 140<br>2320 510-2320 141  
   
   | 2011           0 MIC90         Range         n           264         \$1-864         40           24         \$0.25-364         41           2         \$0.5-366         4           2         \$0.5-364         40           2         \$0.5-36         4           2         \$0.5-36         4           2         \$0.5-36         4           2         \$0.5-36         4           2         \$0.5-36         4           2         \$0.5-36         4           2         \$0.5-36         40           3         \$1         \$1           5         \$1         \$10           6         \$20.55-36         40           5         \$20.55-36         40           6         \$20.25-36         40           7         \$20-320         41           8         \$10-320         41  
   
   | 2011           2012           264          264          264          264          264          27          265          27          28         30,5-26         41         10           24         20,5-26         41         140         24         140         26         27         26         41         140         26         27         26         41         20         21         20         21         21         20         21         21         20         21         21         21         21         21         21         21         21         21         21         21         21         21         21         21         21         21         21 <th< td=""><td>2011           2012         2011           264         \$1-864         40           264         \$1-864         40           264         \$1-864         40           264         \$5-86         41           27         \$0.5-86         139           286.5         \$0.5-86         41           27         \$0.5-86         140           286.5         \$0.5-86         140           21         \$1-84         140           51         \$1         \$1-9           5         \$0.5-86         140           21         \$1-4         140           22         \$0.5-266         140           320         \$10-320         141           301         \$2025-266         410           310         \$2025-266         410           310         \$2025-266         410           311         \$21-84         101</td><td>2011           0 MIC90         Range         n           ≥64         \$1&gt;60         \$1           ≥64         \$1&gt;60         \$1           ≥64         \$10         \$1           ≥64         \$10         \$1           ≥64         \$0.25-24         \$1           ≥64         \$50.5-26         \$139           ≥65         \$65-26         \$140           20         \$50.5-26         \$140           21         \$51-44         \$140           21         \$51-44         \$140           21         \$51-44         \$140           22         \$60.5-26         \$140           23         \$20.5-26         \$140           20         \$210-220         \$141           21         \$210-220         \$210-220           310         \$22-266         \$10           32         \$20.5-266         \$10           32         \$20.5-266         \$10           32         \$20.5-266         \$10</td><td>2011           0 MIC90         Range         n           264         \$1-864         \$1-864           264         \$1-864         \$1-864           2         \$5.5-246         \$1-91           264         \$5.5-264         \$1-91           264         \$5.5-264         \$1-91           27         \$5.5-264         \$1-91           27         \$5.5-264         \$1-91           21         \$51-864         \$1-90           21         \$51-864         \$1-90           32         \$52-564         \$1-90           31         \$51-864         \$1-90           32         \$50-5-84         \$1-90           31         \$51-864         \$1-90           32         \$20-5-84         \$1-90           31         \$51-864         \$1-90           32         \$210         \$1-90           \$216         \$1-26         \$01           \$216         \$1-26         \$01           \$216         \$1-26         \$01           \$216         \$1-26         \$01           \$217         \$1-26         \$1-26         \$1-26   </td><td>2011           0 MIC90         Range         n           264         \$1:864         410           24         \$1:864         410           2         \$0.25-246         411           2         \$0.5-246         410           264         \$5:864         400           2         \$0.5-246         410           205         \$0.5-266         140           21         \$5:44         410           21         \$5:44         410           21         \$5:44         410           21         \$5:44         410           22         \$6:0.5-266         141           23:0         \$5:25-216         141           20:0         \$5:0.25-216         140           21         \$5:0.25-216         101           23:0         \$2:0.25-216         101           21:0         \$2:0.5-216         101           21:0         \$2:0.5-216         101           21:0         \$2:0.5-216         101           21:0         \$2:0.5-216         101           21:0         \$2:0.5-216         101           21:0         \$2:0.5-216         101</td><td>2011           0 MIC90         Range         n           264         \$1-864         440           23         \$0.25-84         411           24         \$5-864         440           264         \$5-864         440           265         \$65-864         440           264         \$5-864         440           27         \$505-86         140           291         \$51-44         440           21         \$51-44         440           21         \$51-44         440           21         \$51-44         400           22         \$60,25-86         440           20         \$225-866         001           21         \$210         \$200         \$000           21         \$200,5-866         001           32         \$20,5-866         001           216         \$51,26         \$01           216         \$52,266         01           216         \$51,266         01           216         \$51,266         01           216         \$51,266         01           216         \$51,266         01</td><td>2011           2014           2014           2014           2015           21           22           23           24           24           25           265           21          
22           23           24           24           25           205           21           21           21           21           21           21           21           21           21           21           21           21           22           2025           201           21           21           21           21           21           21           21</td><td>2011           2012         2011           mmCy0         Range         n           264         \$1-564         410           21         \$0.5-246         411           22         \$0.5-264         410           24         \$1-564         410           21         \$1-564         410           21         \$1-564         410           21         \$1-564         410           21         \$1-564         410           21         \$1-564         410           21         \$1-564         410           21         \$1-564         410           21         \$1-564         410           21         \$2015         \$210           21         \$2015         \$210           21         \$2011         \$10           21         \$2015         \$21           21         \$1         \$0.25-264         01           21         \$2015         \$21         \$11           21         \$10.25-28         \$11         \$1           210         \$10.25-28         \$10         \$11           210         \$11         \$1</td><td>2011           264         stage         n           264         stage         n           264         stage         141           2         s0.5-264         141           2         s0.5-264         141           2         s0.5-264         140           2         s0.5-264         140           21         s1.26-264         140           21         s1.26-264         140           21         s1.26-264         140           21         s1.26-264         140           21         s2.26-264         101           21         s10-2520         141           21         s10-2520         101           21         s10-26-86         101           21         s10-26         102           21         s10-26         101           21         s10-26         101           21         s10-26         101           216         s12-26         101           216         s12-26         101           216         s12-26         101           216         s10-2-28         11           21         s1-</td><td>2011           264         51-864         410           264         51-864         410           264         51-864         410           23         50.5-246         410           24         51-864         410           23         50.5-286         140           24         51-864         410           21         51-844         410           21         51-44         410           21         51-44         410           21         51-44         410           21         51-44         410           21         51-44         410           21         51-44         410           21         51-44         410           21         51-44         410           21         21         210           21         21         201         201           21         21         21         10           21         21         21         21           21         21         2012-266         011           21         21         2012-361         11           21         21         2012-365&lt;</td><td>2011           2012         2011           264         51-864         410           264         51-864         410           23         50.55-84         411           24         51-864         410           24         51-864         410           23         50.52-86         410           21         51-86         410           21         51-86         410           21         51-86         101           21         51-86         101           32         20.25-266         101           32         20.12-220         41           10         MC90         Range         n           21         51-26         101           21         21-26         101           21         21-26         11           0         MC90         Range         n           21         20.12-28         1         1           21         21-26         1         1           21         21-26         20.12-28         1           21         20.12-28         20.25-216         1           21         20.25-216&lt;</td><td>2011           264         51-864         141           264         51-864         140           264         51-864         140           23         50.55-84         141           24         51-86         140           24         51-86         140           21         51-86         140           21         51-44         140           23         50.52-86         140           21         51-44         140           21         51-44         140           21         51-44         140           21         51-44         140           21         51-44         140           21         51-44         140           21         51-526         101           21         201         201           21         201         201           21         201         201           21         201         201           21         201         201           21         201         201           21         201         201           21         201         201</td><td>2011           264         51-864         410           264         51-864         410           21         50.55-84         411           22         50.55-86         139           24         51-86         140           23         50.5-86         140           24         51-86         141           21         51-44         140           21         51-44         140           21         51-44         140           21         51-44         140           21         51-44         140           21         51-44         140           21         51-44         140           21         51-44         140           21         51-25-266         101           21         2-2         50.25-266         101           216         201         201         1           216         50.25-266         101         1           211         201         4         201         1           25         50.5-265         1         1         1           21         50         50.25-266         1</td><td>2011           2012         2011           264         51-864         410           264         51-864         410           21         20.25-84         411           22         20.52-86         400           24         51-864         410           21         51-86         400           21         51-86         410           21         51-86         101           21         51-86         101           21         51-86         101           22         20.52-86         101           232         20-826         101           21         51-26         101           22         20.52-86         101           232         20-826         101           246         51-26         101           21         20-11         1           0         MIC90         Range         n           51         20-13         2011           21         51-21         21         1           21         320         220-25         2           21         51-31         31         31  </td><td>2011           20125-241         11           2         20,25-241         41           2         30,5-246         4           24         40,5-246         440           24         57-264         440           21         51-5-246         440           21         51-5-246         440           21         51-5-246         440           21         51-5-246         440           21         51-5-246         440           21         51-5-246         440           21         51-5-246         401           21         21-21         2011           21         21-26         201           21         201         201           21         201         201           21         201         201           21         201         201           21         201         201           21         201         201           21         201         201           21         201         201           21         201         201           21         201         201           <td< td=""><td>2011           264         51-864         141           264         51-864         140           264         51-864         140           264         51-864         140           264         51-864         140           264         51-864         140           265         805-86         140           21         51-46         140           23         5025-86         140           21         51-4         140           23         5025-86         101           21         51-26         101           23         205-266         101           266         510         201           21         21         201           266         510         201           261         201         1           27         205-266         101           261         21         201         1           261         21         201         1           261         201         201         1           27         501         201         1           261         21         201         1     &lt;</td><td>2011           264         51-864         61           264         51-864         410           264         51-864         410           264         51-864         410           21         51-864         410           23         50.5-28         139           24         51-86         410           21         51-44         410           21         51-44         410           21         51-44         410           21         51-44         410           21         51-44         410           21         51-44         410           21         51-44         410           21         51-44         410           22         50.25-266         101           21         201         201           21         201         201           21         201         201           21         201         4           21         201         201           21        
201         201           21         201         201           21         201         201</td><td>2011           2000         Range         n           264         5:365-24         41           23         50.55-26         41           24         5:365-28         139           24         5:365-26         410           23         50.55-26         410           24         5:365-26         410           21         5:44         410           23         50.55-26         410           21         5:44         410           23         50.25-26         410           23         20.25-26         011           21         5:44         01           22         50.25-26         01           23         20.25-26         01           21         51-26         01           22         50.5-26         01           23         201         201           21         21         201           21         20.12         1           21         50.5-26         1           23         20.1         3           246         50.5-26         1           25         50.5-26         1</td></td<></td></th<> | 2011           2012         2011           264         \$1-864         40           264         \$1-864         40           264         \$1-864         40           264         \$5-86         41           27         \$0.5-86         139           286.5         \$0.5-86         41           27         \$0.5-86         140           286.5         \$0.5-86         140           21         \$1-84         140           51         \$1         \$1-9           5         \$0.5-86         140           21         \$1-4         140           22         \$0.5-266         140           320         \$10-320         141           301         \$2025-266         410           310         \$2025-266         410           310         \$2025-266         410           311         \$21-84         101   
  | 2011           0 MIC90         Range         n           ≥64         \$1>60         \$1           ≥64         \$1>60         \$1           ≥64         \$10         \$1           ≥64         \$10         \$1           ≥64         \$0.25-24         \$1           ≥64         \$50.5-26         \$139           ≥65         \$65-26         \$140           20         \$50.5-26         \$140           21         \$51-44         \$140           21         \$51-44         \$140           21         \$51-44         \$140           22         \$60.5-26         \$140           23         \$20.5-26         \$140           20         \$210-220         \$141           21         \$210-220         \$210-220           310         \$22-266         \$10           32         \$20.5-266       
 \$10           32         \$20.5-266         \$10           32         \$20.5-266         \$10   | 2011           0 MIC90         Range         n           264         \$1-864         \$1-864           264         \$1-864         \$1-864           2         \$5.5-246         \$1-91           264         \$5.5-264         \$1-91           264         \$5.5-264         \$1-91           27         \$5.5-264         \$1-91           27         \$5.5-264         \$1-91           21         \$51-864         \$1-90           21         \$51-864         \$1-90           32         \$52-564         \$1-90           31         \$51-864         \$1-90           32         \$50-5-84         \$1-90           31         \$51-864         \$1-90           32         \$20-5-84         \$1-90           31         \$51-864         \$1-90           32         \$210         \$1-90           \$216         \$1-26         \$01           \$216         \$1-26         \$01           \$216         \$1-26         \$01           \$216         \$1-26         \$01           \$217         \$1-26         \$1-26         \$1-26   
  | 2011           0 MIC90         Range         n           264         \$1:864         410           24         \$1:864         410           2         \$0.25-246         411           2         \$0.5-246         410           264         \$5:864         400           2         \$0.5-246         410           205         \$0.5-266         140           21         \$5:44         410           21         \$5:44         410           21         \$5:44         410           21    
    \$5:44         410           22         \$6:0.5-266         141           23:0         \$5:25-216         141           20:0         \$5:0.25-216         140           21         \$5:0.25-216         101           23:0         \$2:0.25-216         101           21:0         \$2:0.5-216         101           21:0         \$2:0.5-216         101           21:0         \$2:0.5-216         101           21:0         \$2:0.5-216         101           21:0         \$2:0.5-216         101           21:0         \$2:0.5-216         101  
  | 2011           0 MIC90         Range         n           264         \$1-864         440           23         \$0.25-84         411           24         \$5-864         440           264         \$5-864         440           265         \$65-864         440           264         \$5-864         440           27         \$505-86         140           291         \$51-44         440           21         \$51-44         440           21         \$51-44         440           21         \$51-44         400           22         \$60,25-86         440           20         \$225-866         001           21         \$210         \$200         \$000           21         \$200,5-866         001           32         \$20,5-866         001           216         \$51,26         \$01           216         \$52,266         01           216         \$51,266         01           216         \$51,266         01           216         \$51,266         01           216         \$51,266         01   
   | 2011           2014           2014           2014           2015           21           22           23           24           24           25           265           21           22           23           24           24           25           205           21           21           21           21           21           21           21           21           21           21           21           21           22           2025           201           21           21           21           21           21           21
          21   | 2011           2012         2011           mmCy0         Range         n           264         \$1-564         410           21         \$0.5-246         411           22         \$0.5-264         410           24         \$1-564         410           21         \$1-564         410           21         \$1-564         410           21         \$1-564         410           21         \$1-564         410           21         \$1-564         410           21         \$1-564         410           21         \$1-564         410           21         \$1-564         410           21         \$2015         \$210           21         \$2015         \$210           21         \$2011         \$10           21         \$2015         \$21           21         \$1         \$0.25-264         01           21         \$2015         \$21         \$11           21         \$10.25-28         \$11         \$1           210         \$10.25-28         \$10         \$11           210         \$11         \$1       
   | 2011           264         stage         n           264         stage         n           264         stage         141           2         s0.5-264         141           2         s0.5-264         141           2         s0.5-264         140           2         s0.5-264         140           21         s1.26-264         140           21         s1.26-264         140           21         s1.26-264         140           21         s1.26-264         140           21         s2.26-264         101           21         s10-2520         141           21         s10-2520         101           21         s10-26-86         101           21         s10-26         102           21         s10-26         101           21         s10-26         101           21         s10-26         101           216         s12-26         101           216         s12-26         101           216         s12-26         101           216         s10-2-28         11           21         s1-  
   | 2011           264         51-864         410           264         51-864         410           264         51-864         410           23         50.5-246         410           24         51-864         410           23         50.5-286         140           24         51-864         410           21         51-844         410           21         51-44         410           21         51-44         410           21         51-44         410           21         51-44         410           21         51-44         410           21         51-44         410           21         51-44         410           21         51-44         410           21         21         210           21         21         201         201           21         21         21         10           21         21         21         21           21         21         2012-266         011           21         21         2012-361         11           21         21         2012-365<  | 2011           2012         2011           264         51-864         410           264         51-864         410           23         50.55-84         411           24         51-864         410           24         51-864         410           23         50.52-86         410           21         51-86         410           21         51-86         410           21         51-86         101           21         51-86         101           32         20.25-266         101           32         20.12-220         41           10         MC90         Range         n           21         51-26         101           21         21-26         101           21         21-26         11           0         MC90         Range         n           21         20.12-28         1         1           21         21-26         1         1           21         21-26         20.12-28         1           21         20.12-28         20.25-216         1           21         20.25-216<   
   | 2011           264         51-864         141           264         51-864         140           264         51-864         140           23         50.55-84         141           24         51-86         140           24         51-86         140           21         51-86         140           21         51-44         140           23         50.52-86         140           21         51-44         140           21         51-44         140           21         51-44         140           21         51-44         140           21         51-44         140           21         51-44         140           21         51-526         101           21         201         201           21         201         201           21         201         201           21         201         201           21         201         201           21         201         201           21         201         201           21         201         201   | 2011           264         51-864         410           264         51-864         410           21         50.55-84         411           22         50.55-86         139           24         51-86         140           23         50.5-86         140           24         51-86         141           21         51-44         140           21         51-44         140           21         51-44         140           21         51-44         140           21         51-44         140           21         51-44         140           21         51-44         140           21         51-44         140           21         51-25-266         101           21         2-2         50.25-266         101           216         201         201         1           216         50.25-266         101         1           211         201         4         201         1           25         50.5-265         1         1         1           21         50         50.25-266         1   
  | 2011           2012         2011           264         51-864         410           264         51-864         410           21         20.25-84         411           22         20.52-86         400           24         51-864         410           21         51-86         400           21         51-86         410           21         51-86         101           21         51-86         101           21         51-86         101           22         20.52-86         101           232         20-826         101           21         51-26         101           22         20.52-86         101           232         20-826         101           246         51-26         101           21         20-11         1           0         MIC90         Range         n           51         20-13         2011           21         51-21         21         1           21         320         220-25         2           21         51-31         31         31  | 2011           20125-241         11           2         20,25-241         41           2         30,5-246         4           24         40,5-246         440           24         57-264         440           21         51-5-246         440           21         51-5-246         440           21         51-5-246         440           21         51-5-246         440           21         51-5-246         440           21         51-5-246         440           21         51-5-246         401           21         21-21         2011           21         21-26         201           21         201         201           21         201         201           21         201         201           21         201         201           21         201         201           21         201         201           21         201         201           21         201         201           21         201         201           21         201         201 <td< td=""><td>2011           264         51-864         141           264         51-864         140           264         51-864         140           264         51-864         140           264         51-864         140           264         51-864         140           265         805-86         140           21         51-46         140           23         5025-86         140           21         51-4         140           23         5025-86         101           21         51-26         101           23         205-266         101           266         510         201           21         21         201           266         510         201           261         201         1           27         205-266         101           261         21         201         1           261         21         201         1           261         201         201         1           27         501         201         1           261         21         201         1     &lt;</td><td>2011           264         51-864         61           264         51-864         410           264         51-864         410           264         51-864         410           21         51-864         410           23         50.5-28         139           24         51-86         410           21         51-44         410           21         51-44         410           21         51-44         410           21         51-44         410           21         51-44         410           21         51-44         410           21         51-44         410           21         51-44         410           22         50.25-266         101           21         201         201           21         201         201           21         201         201           21         201         4           21         201         201           21         201         201           21         201         201           21         201         201</td><td>2011           2000         Range         n           264         5:365-24         41           23         50.55-26         41           24         5:365-28         139           24         5:365-26         410           23         50.55-26         410           24         5:365-26         410           21         5:44         410           23         50.55-26         410           21         5:44         410           23         50.25-26         410           23         20.25-26         011           21         5:44         01           22         50.25-26         01           23         20.25-26         01           21         51-26         01           22         50.5-26         01           23         201         201           21         21         201           21         20.12         1           21         50.5-26         1           23         20.1         3           246         50.5-26         1           25         50.5-26         1</td></td<>  | 2011           264         51-864         141           264         51-864         140           264         51-864         140           264         51-864         140           264         51-864         140           264         51-864         140           265         805-86         140           21         51-46         140           23         5025-86         140           21         51-4         140           23         5025-86         101           21         51-26         101
          23         205-266         101           266         510         201           21         21         201           266         510         201           261         201         1           27         205-266         101           261         21         201         1           261         21         201         1           261         201         201         1           27         501         201         1           261         21         201         1     <   | 2011           264         51-864         61           264         51-864         410           264         51-864         410           264         51-864         410           21         51-864         410           23         50.5-28         139           24         51-86         410           21         51-44         410           21         51-44         410           21         51-44         410           21         51-44         410           21         51-44         410           21         51-44         410           21         51-44         410           21         51-44         410           22         50.25-266         101           21         201         201           21         201         201           21         201         201           21         201         4           21         201         201           21         201         201           21         201         201           21         201         201  | 2011           2000         Range         n           264         5:365-24         41           23         50.55-26         41           24         5:365-28         139           24         5:365-26         410           23         50.55-26         410           24         5:365-26         410           21         5:44         410           23         50.55-26         410           21         5:44         410           23         50.25-26         410           23         20.25-26         011           21         5:44         01           22         50.25-26         01           23         20.25-26         01           21         51-26         01           22         50.5-26         01           23         201         201           21         21         201           21         20.12         1           21         50.5-26         1           23         20.1         3           246         50.5-26         1           25         50.5-26         1   |
|  
   
   
   | ood: K. MIC50 A   
  | 0 0 d: K. MIC5 0 MIC5 0 MIC5 0 CIP \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$ \$  
   
   
  | 00d: K. MKS0 MKS0 MKS0 M<br>umoniae CAZ 12<br>CP 20.5   | ood: K.         MICS 0           umoniac         CXZ         12           CIP         ≤0.5         <0.5  
   
   
   | ood: K.         MICS 0           umoniae         CXZ         12           CTP         20.5         20.5           CTX         8         8           CTX         80.5         80.5           FPP         215         20.5  
   | ood: K.         MICS 0  
  | ood: K.         MICS 0   
   
   
   | ood: K.         MIC50         MIC50           umonia         MIC50         MIC50           CA2         12         205           CA2         205         505           CA2         205         505           CA2         205         505           CA2         205         505           CA2         205         515           PM         51         215           MIM<50.25   
   
   | ood: K.         MIC50         <   
  | ood: K.         MIC50         <  
   
  | ood: K.         MIC50         < | ood: K.         MIC50         MIC50           umonia         MIC50         MIC50           CM         12         20.5           CP         20.5         5           PM         20.5         5           PM         20.5         5           V         2320         3320           umania         AN         4           AN         4         4           CS         20.5         5           CN         20.5         5   
   
  | ood: K.         MIC50         <  
  | modif.K.        
MIC50  
  | modi K.         MIC50         <   | ood: K.<br>umoniac         MIC50<br>2.5         MIC50<br>2.5           CAZ         12         12           CAZ         20.5         55           CS         S0.5         55           CTX         8.6         55           CTX         8.5         55           CTX         8.20.5         51           CTX         8.20.5         51           PPM         21         232.6           NMEM         232.5         30.5           SYM         AMCS         232.5           AMM         20.6         M           AMM         232.5         16           AMM         232.5         17           AMM         24.6         M           AMM         24.6         M           AMM         24.6         16           AMM         24.6         1           AMM         24.6         1           AMM         24.7         24.7   
  | ood: K.<br>umoniac         MIC50<br>MIC50         MIC50<br>MIC50         MIC50           umoniac         CAZ         12         20.5           CP         20.5         S0.5         S0.5           CTX         8         S0.5         S0.5           CTX         8         S0.5         S0.5           CTX         8         S0.5         S0.5           CTX         20.5         S0.5         S0.5           PM         20.5         S0.5         S0.5           NME         AN         44         S0.5           MC50         M         Z66         M           MMC6         M         Z66         M           MME         AN         44         S16           PM         Z66         M         Z66           MME         M         Z66         M           MME         M         M         Z66           MME         PM         Z66         M           MeM         M         M         Z66           MME         TGG         1         TGG           MeM         M         Z66         S16           MME         M         Z66   
  | ood: K.         MIC50         < | ood: K.         MIC50         <  
  | ood: K.         MIC50         MIC50           umonia         205         12           CXP         305         305           CSP         305         55           CSP         305         55           CSP         305         51           CSP         305         51           CSP         205         51         22           PM         4         21         22           NMEA         MIC50         N         265           SYT         205         205         265           CS         205         265         265           MIC50         N         216         265           PM         216         21         21           CS         205         265         265           PM         216         21         21           CS         205         265         265           PM         260         37         2320           Unmoniae         25         25         25           SYT         2320         232         232  | ood: K.         MIC50         <  
   | nodi K.         MIC50         <   | ood: K.<br>umoniac         MIC50<br>25         MIC50<br>25           umoniac         CAZ         12           CTX         8         20.5           CTX         8         30.5           CTX         8         31.5           EPP         20.5         31.5           EPP         20.5         31.5           PM         31         22.5           NMC         AN         26.5           SYT         22.5         30.5           SYT         AN         26.5           MMM         AN         26.5           MMM         20.5         26.5           MMM         AN         26.5           MMMO         AN         26.5           AN         AN         26.5           AN         AN         26.5           AN         AN         26.5           AN         AN   | ood: K.<br>umonia.         MIC50<br>12<br>CX         MIC50<br>12<br>S55<br>S55<br>S55<br>S55<br>S55<br>S55<br>S55<br>S55<br>S55<br>S5   | ood: K.         MIC50         <   | ood: K.         MICS 0         MICS 0 |

		value	<b>%R</b>	266.0	0.058		<0.001	0.001**	<0.001	0.622	0.416**	0.267		p- valne	%R	0.021	0.561		0.047	$<0.00^{**}$	⊲0.001	<0.00 l**	<0.001**	0.836		p- value	%В	0.024**	0.001*	<0.00 Pak	- 100.02	,		p- valne	<b>"R</b>	1.000 **	0.617**	0.201**		p- value	% <b>R</b>	1 A D D Hek	TOUUT	
	ä	value	MIC50	-0.00	0.011	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001			p- value	MIC50	<0.001	0.568	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001			p- value	MIC50	0.010	<0.001	40.001	0.001	,		p- value	MIC50	0.067	0.261	0.151		ġ	value	MICSO		,
-		1	% <b>R</b>	13, 13	33.91	*	22.86	11.65	7.67	0.64	0.57	59.53			%R	50.58	40.39	*	56.47	11.37	27.67	9.82	11.53	65.10			<b>%R</b>	2.17	11.69	4.35	00.0	0,00			<b>%R</b>	0.93	1.84	6.48				1 WK	00,00	×
			<b>n</b>	++++	2504	×	: ###	###	2504	###	2297	2501 0			-	866	874 4	*	866	862	947	866	798	874			u	46	77	46	46	46			-	10.8	10.8	10.8				-	-	×
2 0 15		1	Kange	s1-264	≤0.25-≥8	≤0.5-≥16	s1-264	≤0.5-≥8	≤1-≥64	≤0.25-≥16	≤0.25-≥16	≤10-≥320	2 0 15		Rang e	s1-264	≤0.25-≥8	≤0.5-≥16	≤1-≥64	≤0.5-≥8	s1-264	≤0.25-≥16	≤0.25-≥16	≤20-≥320	2 0 15		Range	≤1-16	≤0.25-1	518 <0.5-<0.5	≤0.25-0.5	≤0.25-≤0.25	2 0 15		Rang e	≤1-16	≤0.25-≥4	≤1-≥64	2 0 15		ſ	Kange	0.05-0.05	≤0.5-≤0.5
		MIC 90	m/gu	19	54	≤0.5	≥64	≤0.5	4	≤0.25	≤0.25	≥320	2	M IC 90	na/ml	264	≥4	≤0.5	264	82	≥64	ন	~	<b>z</b> 320	C .	MIC 90	hg/ml	<u>v</u> i	≤0.25	50 F	≤0.25	≤0.25	2	MTC 90	lm/pu	ম	≤0.25	2	4		MIC 90	hg/mi	C.UZ	≤0.5
		MIC 50	lm /gu	52	≤0.25	≤0.5	2	≤0.5	۶	≤0.25	≤0.25	≥320		MICSO	na/m	~	≤0.5	≤0.5	≥64	≤0.5	7	≤0.25	≤0.25	2320		MIC 50	hg/ ml	51	≤0.25	10	≤0.25	≤0.25		MICSO	lm/pu	<del>ا</del>	≤0.25	2			MIC 50	m /gu	C.U≤	≤0.5
	ſ	!	% <b>R</b>	12.54	32.29	*	19.21	0.25	6.59	0.31	0.50	72.39			<b></b>	14.20	36.61	*	50.50	3.21	20,00	2.59	2.79	55.94			ЯК	0,00	17.95	0,00	0.00	0,00			%В	0,00	1.79	7.14			Ę	% <b>K</b>	00,00	×
			<b>n</b>	1001	1601	*	1598	1595	l6 0 9	1591	1590	1597				500	508	*	503	498	535	501	501	508			u	27	39	27	27	25				56	56	56				= -	-	*
2014			Kange	51-264	≤0.25-≥4	≤0.5-≥16	\$1-264	≤0.5-≥8	≤1-≥64	≤0.25-≥16	≤0.25-≥16	≤10-≥320	2014		Rang e	s1-264	≤0.25-≥8	≤0.5-≥16	≤1-≥64	≤0.5-≥8	s1-264	≤0.25-≥16	≤0.25-≥16	≤10-≥320	2014		Range	≤1-≤1	≤0.25-≤0.5	51-51 <0.5-30.5	≤0.25-0.5	≤0.25-≤0.25	2014		Rang e	514	≤0.25-≥4	≤1-≥64	2014			Kange	C7'05-C7'05	51-51
		MIC 90	m/gu	19	≥4	≤0.5	≥64	≤0.5	4	≤0.25	≤0.25	2320		MIC 00	na/ml	264	≥4	-	264	≤0.5	32	0.5	≤0.25	2320		MIC 90	hg/ml	<u>v</u> i	≤0.25	50 E	≤0.25	≤0.25		MIC 90	lm/pu	5	≤0.25	2			MIC 90	Hg/mi	C7: DE	2
		MIC 50	hg/ ml	52	≤0.25	≤0.5	2	≤0.5	۶	≤0.25	≤0.25	≥320		MIC 50	na/m	<u>ک</u>	≤0.25	≤0.5	6	≤0.5	5	≤0.25	≤0.25	2320		MIC 50	hg/ ml	<u>v</u> i	≤0.25	505	≤0.25	≤0.25		MIC50	рд/ т	<del>ا</del>	≤0.25	۶			MIC 50	m /gr	C7:05	۲
	Ī		% <b>R</b>	0070	3 1.58	×	18.77	0.39	6.46	0.66	0.66	70.51			%R	41.28	34.49	*	47.71	2.62	l8.69	0.92	2.45	61.90			%₿	0,00	46.58	0.00	0.00	0,0,0			З.К.	0,00	0.0.0	2.67			Ę	% <b>K</b>	0,00	*
			<b>n</b>	###	2305	*	###	###	###	2287	2285	###			-	654	664	*	654	649	658	654	653	664			u	31	5	31	30	31			-	75	75	75				= <	-	×
2 0 13		1	Kange	s1-264	≤0.25-≥8	≤0.5-≥16	s1-264	≤0.5-≥8	≤1-≥64	≤0.25-≥16	≤0.25-≥16	≤10-≥320	2013		Rang e	s1-264	≤0.25-≥8	≤0.5-≥16	≤1-≥64	≤0.5-≥8	s1-264	≤0.25-≥16	≤0.25-≥16	≤10-≥320	2013		Range	≤1-≤1	≤0.25-1	51-51 en E-en E	≤0.25-0.5	≤0.25-≤0.25	2 0 13		Range	s1-s1	≤0.25-≤0.25	≤1-4	2013		6	Rang e		
		MIC90	lm / Brl	16	≥4	≤0.5	≥64	≤0.5	4	≤0.25	≤0.25	≥320		MIC90	na/ ml	≥64	≥4	≤0.5	≥64	≤0.5	32	≤0.25	≤0.25	≥320		MIC90	hg/ ml	<del>ک</del> ا	≤0.25	105	≤0.25	≤0.25		MIC 9.0	lm/pu	51	≤0.25	2			MIC9.0	im /gu		
		MIC50	m /gr	502	≤0.25	≤0.5	2	≤0.5	v	≤0.25	≤0.25	≥320		MICSO	na/ ml	5	≤0.25	≤0.5	2	≤0.5	2	≤0.25	≤0.25	≥320		MIC50	hg/ ml	51	≤0.25	20 F	≤0.25	≤0.25		MICSO	lm/bri	51	≤0.25	2			MIC50	im /gu		
	ľ	1	% <b>R</b>	11.55	31.13	*	16.10	0.32	5.28	0.63	0.42	75.33			<b>%</b> R	40.80	37.81	*	44.64	2.31	18.13	1.53	1.15	54.58			‰	7.69	28.89	7.69	0.00	0,00			ж.	0.0,0	0.0,0	0.00			Ę	% <b>K</b>	000	×
			= \\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	18.87	1902	*	1888	1879	1893	1892	1887	1897			-	52.2	529	*	52.2	519	557	523	522	528			u	26	45	26	26	26			=	58	58	58				= -	-	*
0 12			Kange	51-264	≤0.25-≥8	≤0.5-≥16	s1-264	≤0.5-≥8	≤1-≥64	≤0.25-≥16	≤0.25-≥16	≤10-≥320	0 12		Rang e	s1-264	≤0.25-≥8	≤0.5-≥16	≤1-≥64	≤0.5-≥8	s1-264	≤0.25-≥16	≤0.25-≥16	≤10-≥320	0 12		Rang e	s1-264	≤0.25-2	<1-264	≤0.25-≤1	≤0.25-≤0.25	0 12		Range	s1-s1	≤0.25-1	≤1-≤1	0 12		ſ	Kange	C7.05-C7.05	51-51
		MIC 90	m/gu	27	2	≤0.5	≥64	≤0.5	2	۲ı	≤0.25	≥320		MIC 9.0	na/ml	264	2	2	≥64	≤0.5	32	۶ı	≤0.25	≥320		MIC 90	hg/ml	۲,	-	50 E	ÇP ₹	≤0.25		MIC 90	lm/pu	2	≤0.25	2			MIC 9.0	m /gr	C7.05	۶
		MIC50	m/gu	2 12	≤0.25	≤0.5	s1	≤0.5	2	2	≤0.25	≥320		MICSO	na/ml	2	≤0.25	≤0.5	2	≤0.5	2	۶	≤0.25	2320		MIC50	hg/ml	۲	≤0.25	51 F	5 1	≤0.25		MICSO	lm/pu	2	≤0.25	2			MICSO	im /gu	C7:0=	ź
	Ī	1	<b>%</b>	8.01	27.10	×	11.92	0.36	3.54	0.71	0.18	76.64			<b>.</b>	35.03	35.22	*	42.54	0.65	10.63	1.27	1.2.7	70.25			‰	20,00	11.36	53.85	00.0	0,00			‰	0,00	0,00	0,00			f	% <b>K</b>	n^*n	×
	_		-	1011	113.3	*	112.4	112.3	112.9	112.8	112.5	113.0			-	3 14	318	*	315	309	320	315	315	316			a	15	44	26	26	15			9	22	22	22				= <	>	*
2011			Range	s1-264	≤0.25-≥4	≤0.5-≥16	51-264	≤0.5-4	≤1-≥64	≤1-≥16	≤0.25-≥16	≤10-≥320	2011		R ang e	s1-264	≤0.25-≥4	≤0.5-8	≤1-≥64	≤0.5-4	51-264	≤1-≥16	≤0.25-≥16	≤10-≥320	2011		Range	51-264	≤0.25-≥16	51-264	≤0.25-≤1	≤0.25-≤0.25	2011		Range	s1s1	≤0.25-≤0.25	51≤1	2011		4	K ang e		
		MIC90	lm /gu	4	*	2	8	≤0.5	٧	2	≤0.25	≥320		M IC 9.0	na/ ml	≥64	\$	2	≥64	≤0.5	32	2	≤0.25	≥320		MIC90	hg/ ml	≥64	≥16	≥64	- VI	≤0.25		M IC 9.0	lm/pu	2	≤0.25	2			MIC90	im /gu		
		MIC50	m/gu	512	≤0.25	≤0.5	۶	≤0.5	۲ı	v	≤0.25	≥320		05.017	ua/ml	5	≤0.25	≤0.5	٧	≤0.5	দ	۶	≤0.25	2320		AIC50	lm/gu	5	≤0.25	4	Ç.D.	≤0.25		05017	lm/pu	<del>ا</del>	≤0.25	۲ı			MIC50	im / Bu		
		*	1.14	CA7.	CIP	CS	CTX	ETP	FEP	Μď	MEM	SXT		-		CAZ	СIР	CS	CTX	ETP	FEP	ΡM	MEM	SXT		A		CAZ	СЪ	CTX	IPM	MEM				CAZ	СIР	CTX			-	e,	5	GM
		Urine: E.	coli											Ilrine · K	pneumoniae											Faeces: Salmo nella	s pp.							Faeces: Shigella	s pp.					U rethral-	N.	go no rrhoea		

AM- Ampicillin, CAZ- Ceftazidime, CIP- Ciprofloxacin, CS- Colistin, CTX- Cefotaxime, ETP- Ertapenem, FEP- Cefepime, IPM-Imipenem, MEM- Meropenem, SXT- Trimethoprim-sulfamethoxazole, AN- Amikacin, GM- Gentamicin, TGC- Tigecycline, FOX-Cefoxitin, OX1- Oxacillin, P- Penicillin (CLSI Breakpoint for non-meningitis S. pneumoniae )

\* CLSI Breakpoint not available

\*\*Pearson chi-square p-values

Note: MIC50 p-values are based on the results of a non-parametric equality-of-medians test.

The following GLASS metrics were generated: proportion of non-susceptible samples out of all samples positive for GLASS pathogens, number of infections caused by GLASS pathogens per specimen type per 100 000 inhabitants, number of infections caused by GLASS pathogens per organism per 100000 inhabitants and number of resistant infections per pathogen and drug per 100 000 inhabitants.

Table 3 illustrates the proportion of non-susceptible samples out of all samples positive for selected GLASS pathogens (See Supplementary Table 3 for all pathogens). While Table 2 reflects the percentage resistance with the total number of positive samples per pathogen-drug combination as a denominator, Table 3 reflects the resistance rates with the total number of samples positive for GLASS pathogens per specimen type as a denominator. Table 3 serves to illustrate the trends in resistance within each specimen type. A statistically significant increase in the proportion of E. coli from blood that were non-susceptible to ceftazidime, cefotaxime, ciprofloxacin and trimethoprim/sulfamethoxazole was evident as was the increase in the proportion of non-susceptible K. pneumoniae against all antibiotics tested. A statistically significant increase in the proportion of Salmonella spp. from faeces that were non-susceptible to ceftazidime, cefotaxime, ciprofloxacin and ertapenem was also observed. Out of 69 pathogen-drug combinations, only 19 had no resistant isolates in at least one year between 2011 and 2015. Most of the pathogens were multi-drug resistant i.e. resistant to three or more classes of antibiotics. E. coli, K. pneumoniae, A. baumannii, Salmonella spp. and S. pneumoniae were multi-drug resistant (S. aureus, Shigella spp. and N. gonorrhoea were tested against less than 3 classes of antibiotics). An escalation of ABR elucidated by GLASS metrics confirmed the general increase in ABR resistance trends described above.

Blood: E. co	oli						Urine: K. pr	ieumon	iae				
	2011	2012	2013	2014	2015	P-value		2011	2012	2013	2014	2015	P-value
AM*	6,98	6,23	6,77	9,83	6,13	0	CAZ	3,92	5,52	6,07	8,86	6,64	< 0.001
CAZ	0,89	1,34	0,99	1,85	1,87	0.007	CIP	3,99	5,18	5,14	7,46	5,35	< 0.001
CIP	1,73	1,97	2,09	3,33	2,68	0.013	CTX	4,77	6,04	7,01	10,18	7,41	< 0.001
CTX	1,23	2,01	1,74	3,33	2,77	< 0.001	ETP	0,07	0,31	0,38	0,64	1,48	<0.001**
ETP	0,00	0,04	0,00	0,15	0,06	0.197**	FEP	1,21	2,62	2,76	4,29	3,97	< 0.001
FEP	0,45	0,71	0,39	0,96	0,74	0.143	IPM	0,14	0,21	0,13	0,52	1,29	<0.001**
IPM	0,00	0,13	0,00	0,00	0,12	0.131**	MEM	0,14	0,16	0,36	0,56	1,39	<0.001**
MEM	0,00	0,08	0,04	0,00	0,06	0.818**	SXT	7,91	8,84	9,23	13,43	8,62	< 0.001
SXT	7,14	6,27	6,41	9,09	4,79	<0.001	Total GLASS pathogens	2808	3859	4451	2494	6600	
Total GLASS pathogens	1792	2391	2823	1353	3363								
Faeces: Sala	nonella	spp.					N. gonorrho	ea					
	2011	2012	2013	2014	2015	P-value		2011	2012	2013	2014	2015	P-value
CAZ	2,94	1,41	0	0	0,37	0.010**	CIP	0	0	0	0	1.85	-
CIP	4,90	9,15	14,35	4,29	3,31	<0.001	Total GLASS pathogens	35	24	34	21	54	
CTX	13,73	1,41	0	0	0,74	< 0.001**							
ETP	10,78	0	0	0	0	< 0.001**							
IPM	0	0	0	0	0	-							
MEM	0	0	0	0	0	-							
Total GLASS pathogens	102	142	237	163	272								

Table 3: Proportion of non-susceptible samples out of all samples positive for GLASS pathogensper specimen type 2011-2015

\* AM- Ampicillin, CIP- Ciprofloxacin, CTX- Cefotaxime, CAZ- Ceftazidime, FEP- Cefepime, IPM- Imipenem, ETP-Ertapenem, MEM- Meropenem, SXT- Trimethoprim-sulfamethoxazole \*\*Fisher's exact p-value, all others are Pearson chi-square p-values

Table 4 illustrates the number of resistant infections for one pathogen per specimen type per 100 000 inhabitants. (See Supplementary Table 4 for all pathogens). The number of resistant infections per 100 000 inhabitants generally increased across all pathogen-drug combinations with the exception of *Salmonella spp.* from faecal samples noting that relatively few faecal samples were included in the

study (n=916) and *Salmonella spp.*/ciprofloxacin was the only pathogen-drug combination for which resistant isolates were identified every year in the study period. Between 2011 and 2015 UTIs and BSIs were the most common infections causing 197 and 119 infections per 100 000 inhabitants (n=10 267 300) respectively while the most common causative pathogen was *E. coli* from urine samples, causing 148 infections per 100 000 inhabitants (n= 10 267 300). In BSIs, *S. aureus* caused the most number of infections (37 per 100 000 inhabitants, n= 10 267 300) while in the most common cause of diarrhoeal infections was *Shigella spp.* (6 per 100 000 inhabitants, n= 10 267 300). *E. coli* isolates from urine samples were responsible for the most number of resistant infections (75 per 100 000 inhabitants resistant to ampicillin, n= 10 267 300) while *K. pneumoniae* infections resistant to trimethoprim-sulfamethoxazole were most common among BSIs (10 per 100 000 inhabitants, n= 10 267 300). Diarrhoeal infections were most commonly caused by *Salmonella spp.* isolates resistant to ciprofloxacin (1 per 100 000 inhabitants, n= 10 267 300).

Blood: E. co	oli						Urine: I	K. pneum	oniae				
	2011	2012	2013	2014	2015	p- value*		2011	2012	2013	2014	2015	p-value*
AM	1,22	1,45	1,86	1,30	2,01	< 0.001							
CAZ	0,16	0,31	0,27	0,24	0,61	0,00	CAZ	1,07	2,07	2,63	2,15	4,27	< 0.001
CIP	0,30	0,46	0,57	0,44	0,88	< 0.001	CIP	1,09	1,95	2,23	1,81	3,44	< 0.001
СТХ	0,21	0,47	0,48	0,44	0,91	< 0.001	СТХ	1,31	2,27	3,04	2,47	4,76	< 0.001
ЕТР	0,00	0,01	0,00	0,02	0,02	0,18	ЕТР	0,02	0,12	0,17	0,16	0,95	< 0.001
FEP	0,08	0,17	0,11	0,13	0,24	0,09	FEP	0,33	0,98	1,20	1,04	2,55	< 0.001
IPM	0,00	0,03	0,00	0,00	0,04	0,16	IPM	0,04	0,08	0,06	0,13	0,83	< 0.001
MEM	0,00	0,02	0,01	0,00	0,02	0,82	MEM	0,04	0,06	0,16	0,14	0,90	< 0.001
SXT	1,25	1,46	1,76	1,20	1,57	< 0.001	SXT	2,16	3,32	4,00	3,26	5,54	< 0.001
Faeces: Sal	monella s <sub>l</sub>	op.					N. gono.	rrhoea					
	2011	2012	2013	2014	2015			2011	2012	2013	2014	2015	
CAZ	0,03	0,02	0,00	0,00	0,01	0,06							
CIP	0,05	0,13	0,33	0,07	0,09	< 0.001	CIP	0,00	0,00	0,00	0,00	0,01	NC
СТХ	0,14	0,02	0,00	0,00	0,02	< 0.001							
ETP	0,11	0,00	0,00	0,00	0,00	< 0.001							
IPM	0,00	0,00	0,00	0,00	0,00	NC							
MEM	0,00	0,00	0,00	0,00	0,00	NC	Total Po	opulation	: 10 267	300			

Table 4: Number of Resistant infections per pathogen and drug per 100 000 inhabitants

\* Pearson chi-square p-value

NC- Not calculated

Resistance data was also compared to the standard treatment guidelines available in South Africa, published by the National Department of Health and the Federation of Infectious Diseases Societies of

Southern Africa (FIDSSA). Table 7 shows the proportion of infections that would be treatable using the antibiotics recommended by these guidelines. The antibiotics in the Table are those used in the Vitek 2 panel of antibiotics. In UTIs, only two thirds of the infections caused by *E. coli* and *K. pneumoniae* could be successfully treated by ciprofloxacin and amoxicillin-clavulanate, which are the first line agents recommended in the treatment guidelines. Nitrofurantoin showed only a 31% susceptibility against UTIs caused by *K. pneumoniae*. Ciprofloxacin, the recommended first line treatment for diarrhoeal infections, would only treat 75% of infections caused by *Salmonella spp.*, however, 99% of diarrhoeal infections caused by *Shigella spp*. were shown to be treatable with ciprofloxacin.

 Table 5: Percentage of Infections Susceptible to Antibiotics Recommended as per Treatment

 Guidelines

Blood Stream Infections*	Cloxacillin	Vancomycin	Ceftriaxone	Gentamicin	Clindamycin
S. aureus	-	96.79% (n=1368)	-	-	96.85% (n= 1367)
E. coli	-	-	-	80.13% (n= 936)	-
K. pneumoniae	-	-	-	40.72% (n= 1196)	-
S. pneumoniae	-	-	-	N/A	-
A. baumannii	-	-	-	37.45% (n= 745)	-
Salmonella spp.	-	-	-	N/A	-
Urinary Tract Infections **	Ciprofloxacin	Amoxicillin- clavulanate	Gentamicin	Fosfomycin	Nitrofurantoin
E. coli	68.31%	67.15%	85.37%	-	87.41%
	(n-953)	(n=9397)	(n=9399)		(n=9383)
K. pneumoniae	62.67%	50.98%	59.01%	-	30.87%
	(n=2893)	(n=2864)	(n=2776)		(n=2860)
Diarrhoeal Infections **	Ciprofloxacin				
Salmonella spp.	75.54%				
	(n=145)				
Shigella spp.	99.06%				
	(n=319)				
Gonorrhoea*	Ceftriaxone	Azithromycin			
N. gonorrhoea	-	-			

\* SAASP Guidelines (Wasserman, et al., 2015)

\*\* Government published Standard Treatment Guidelines (Department of Health Republic of South Africa, 2015)

- Pathogen-drug combination not included in study or no samples found for pathogen-drug combination

### **Discussion:**

Antibiotic resistance trends were investigated in pathogen-drug combinations stipulated in GLASS for the period 2011-2015 in six public hospitals in the province of KwaZulu Natal, South Africa in putative BSIs, UTIs, diarrhoeal infections and gonorrhoeal infections. The antibiotic resistance data was stratified by year and analysed on 3 levels: (1) a trend analysis of resistance including MIC50, MIC90, MIC range and percentage resistance over 5 years was conducted; (2) selected metrics recommended in the GLASS manual were calculated and (3) susceptibility data was compared with existing standard treatment guidelines.

We generated a database of MIC and percentage resistance data including the majority of pathogendrug combinations listed in the GLASS manual. From this data we were able to observe a general increase in percentage resistance during the study period in the majority of pathogen-drug combinations, calculate the proportion of infections caused by each pathogen of interest, calculate the rate of resistance in terms of the population in KwaZulu Natal and correlate the resistance rates with existing treatment guidelines in South Africa.

In South Africa diarrhoeal diseases and sexually transmitted infections (STIs) are major concerns, the former because it is one of the leading causes of infant mortality and the latter because it increases the risk of HIV infection<sup>(6)</sup>. UTIs are amongst the most common infections encountered in both the community and hospital setting and the emergence of resistance in various bacterial species has become a concern worldwide. BSIs are one of the leading nosocomial infections leading to poor treatment outcomes especially in children. In addition to the clinical importance of these infections, blood, urine, faecal and urethral/cervical samples are relatively easy to collect on a routine basis which is why these infections were identified for inclusion in the early implementation of GLASS. Existing ABR surveillance in South Africa has shown a decline in efficacy of older antibiotic drugs such as ampicillin and tetracycline and the emergence of resistance to carbapenems. In BSIs methicillin resistant Staphylococcus aureus (MRSA) as well as extended spectrum β-lactamase (ESBL) producing pathogens are prevalent, while in terms of diarrhoeal infections resistance to fluoroquinolones and third generation cephalosporins is increasing <sup>(3)</sup>. In UTIs there is increasing resistance to third generation cephalosporins and carbapenems and in gonorrhoeal infections first line treatment was changed to oral or intramuscular cephalosporins due to resistance to ciprofloxacin<sup>(4)(7)</sup>. We observed similar resistance trends in our study.

In order to address the problem on AMR, South Africa is amongst the few African countries to have a national AMR strategy framework and the only country with laboratory-based surveillance <sup>(6) (8)</sup> with ABR research on the increase. The Centre for Healthcare Associated Infections, Antimicrobial Resistance and Mycoses, a branch of the NICD, conducts laboratory based antimicrobial resistance surveillance (LARS) and. It was established in 2010 and collects data from sentinel sites. Electronic

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surveillance was implemented in 2013 and collects data from laboratory information systems in order to generate resistance maps. Enhanced surveillance has been implemented for methicillin-resistant *S. aureus* (MRSA) in order to determine the prevalence and extent of nosocomial and community-acquired MRSA infections. Enhanced surveillance is also underway for carbapenem-resistant Enterobacteriaceae (CREs).<sup>(9)</sup>

The results of this study were stratified, as per GLASS requirements, according to specimen type and pathogen-drug combination. These included BSIs, UTIs, diarrhoeal infections and gonorrhoeal infections. The total number of isolates increased more than two-fold from 4737 in 2011 to 10289 in 2015, which could indicate that there is an increase in the use of AST results to guide treatment and rational prescribing. Isolates from blood and urine samples comprised 96.72% (n=33018) of the samples included in the study, suggesting a focus on the treatment of bacteraemia and UTIs guided by AST results. Treatment guidelines published by the South African National Department of Health recommends symptomatic management of acute diarrhoea and only recommends antibiotic therapy in severe cases or where there is a co-morbidity. Gonorrhoeal infections are similarly managed empirically which could explain the limited number of isolates from faecal and urethral or cervical samples. <sup>(10) (11)</sup>

Of the isolates obtained from blood samples, *S. aureus* was the most commonly isolated pathogen followed by *K. pneumoniae* and *E. coli*. While over 3000 *S. aureus* isolates were identified, only 29 were tested against cefoxitin, the antibiotic recommended in the GLASS manual, and the percentage resistance was not calculated as there is no listed CLSI MIC breakpoint for this pathogen-drug combination. As such, resistance in *S. aureus* isolates will be discussed with reference to the MIC data.

As a common cause of nosocomial infections with a known prevalence of multi-drug resistance, existing data has shown that *A. baumannii* is becoming increasingly difficult to treat. A study published in 2012 by Ballot et al. reported that *A. baumannii* was the third most common cause of sepsis-related deaths in neonates in a public hospital in Johannesburg, South Africa. <sup>(12)</sup> Crowther-Gibson et al. reported that only 20 - 40% of *A. baumannii* infections were susceptible to carbapenems in public hospitals in South Africa in 2009 and that in the private sector, the use of carbapenems was becoming necessary due to increasing resistance to fluoroquinolones and third generation cephalosporins. The same paper reported that in the private sector, resistance in *A. baumannii* to imipenem and meropenem was already approximately 33% in 2006. <sup>(7)</sup> It is encouraging to note that resistance to all antibiotics in *A. baumannii* isolates in this study declined between 2011 and 2015 and that colistin and amikacin showed sensitivity of 94% and 89% respectively in 2015. A study conducted in a trauma intensive care unit in Durban, South Africa, in 2009 reported that *A. baumannii* isolates were most susceptible to amikacin, with 43% of isolates being susceptible, suggesting that susceptibility of *A. baumannii* to amikacin has since improved. *A. baumannii* isolates showed an 18 –

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20% decrease in resistance to carbapenems and gentamicin, however, the percentage resistance to these antibiotics in 2015 was still in the region of 50%. These figures are slightly lower than those reported from sentinel public hospitals in South Africa in 2014 carried out by Perovic et al., which reported 66% and 77% resistance to gentamicin and carbapenems respectively and the 2009 study carried out by Ramsamy et al. which reported 87% and 90% resistance in *A. baumannii* isolates to gentamicin and meropenem respectively. <sup>(13) (14)</sup>

S. aureus is a common pathogen isolated in humans and is a leading cause of nosocomial bacteraemia and more recently there have been reports of MRSA isolates from the community which is a cause for increased concern. Fortuin de-Smit et al. reported that MRSA was associated with higher mortality than methicillin sensitive S. aureus and that MRSA isolates were more likely to be resistant to multiple antibiotics from multiple classes. <sup>(15)</sup> In 2006 the incidence of MRSA was reported to be 36% based on data from 5 private hospitals while Ballot et al. reported that 70% of S. aureus isolates were methicillin resistant from blood cultures from neonates at a public hospital South Africa between 2009 and 2010. Perovic et al. also reported methicillin resistance in 46% of S. aureus isolates from blood samples between 2010 and 2012 in 13 public hospitals around South Africa. <sup>(3) (7) (12)</sup> Data from the public sector obtained in 2009 indicated that S. aureus isolates from blood cultures showed a 16 – 76%, 11 – 83% and 28 – 85% susceptibility to cloxacillin, erythromycin and clindamycin respectively. Results from the Ramsamy et al. study in trauma intensive care unit patients reported a relatively high susceptibility of S. aureus isolates to clindamycin, cloxacillin, erythromycin, gentamicin and vancomycin (62 -100%) while only 11% and 16% susceptibility to penicillin and ampicillin was reported.<sup>(7) (14)</sup> The results the Perovic et al. study published in 2015 showed that while 99.8% of methicillin sensitive S. aureus isolates were sensitive to cefoxitin, only 5% of MRSA isolates were susceptible. Cefoxitin was the only antibiotic included in the study for S. aureus isolates as it is a surrogate for testing susceptibility to oxacillin, meaning it is a means of detecting MRSA. Fernandes et al. suggested in a study published in 2005 that cefoxitin resistance could be an easier method of detection methicillin resistance as opposed to the detection of the mecA gene by PCR, which is costly and requires specialised equipment. <sup>(2) (16</sup> The Vitek 2 system provides results of a cefoxitin screen instead of MIC50 and MIC90 readings. A positive cefoxitin screen implies that the isolate is MRSA. Regrettably we were unable to extract and include this data in the results and it is an important limitation that should be addressed in future studies. S. pneumoniae is the leading cause of community-acquired pneumonia but is also the cause of invasive diseases such as bacterial meningitis and sepsis which are associated with high mortality. Resistance to penicillin and other β-lactam antibiotics in S. pneumoniae has been associated with poor clinical outcomes in patients with pneumococcal meningitis, but the implication is less apparent in terms of BSIs. The WHO Antimicrobial Resistance Global Report on Surveillance 2014 report mentions that further resistance data is required in order to establish the effect of reduced susceptibility to penicillins on clinical

outcomes in patients with BSIs. The report noted that in the Africa region, 3% of invasive *S. pneumoniae* (including BSIs and meningitis) isolates showed resistance to penicillin while Ramsamy et al. reported that *S. pneumoniae* isolates from the trauma intensive care unit showed 7% resistance to penicillin, 33% resistance to ampicillin and 100% resistance to cloxacillin. <sup>(14) (17)</sup> In this study AST results were included for *S. pneumoniae* isolates from blood samples against cefotaxime, oxacillin, benzylpenicillin and trimethoprim-sulfamethoxazole. As compared to the other pathogens included in the study, antimicrobial susceptibility data for *S. pneumoniae* was minimal for the GLASS antibiotic panel, with only 11, 5 and 16 isolates tested against cefotaxime, penicillin non-susceptibility in *S. pneumoniae*, thus there is no CLSI breakpoint for this pathogen-drug combination. Between 2011 and 2015, only one isolate each was found to be resistant to cefotaxime and penicillin while 100% resistance was found to trimethoprim-sulfamethoxazole.

K. pneumoniae is a common cause of UTIs and BSIs and is also a major cause of carbapenem resistant infections. K. pneumoniae is also reported to have the highest prevalence of resistance to third and fourth generation cephalosporins out of all of the Enterobacteriaceae. Ballot et al. found that K. pneumoniae was the second most common cause of BSIs in neonates at a public hospital in South Africa with 65% of these isolates being ESBL positive.<sup>(12)</sup> In terms of UTIs, K. pneumoniae isolates showed the most notable increase in resistance to all antibiotics except trimethoprimsulfamethoxazole, with the greatest increase in resistance being a 17% increase in resistance to cefepime. Resistance to carbapenems in isolates from urine samples increased from  $\leq 1\%$  in 2011 to 10% in 2015 and increased by more than 20% in isolates from blood samples. This is more than double the figure of 3-5% resistance to carbapenems reported by Perovic et al. in 2014, while the WHO Antimicrobial Resistance Global Report on Surveillance 2014 reported 0 - 4% resistance to carbapenems in the Africa Region. K. pneumoniae isolates from blood samples showed an increase in resistance of 18% or more to all the antibiotics with the exception of trimethoprim-sulfamethoxazole. These findings are similar to those reported by Perovic et al. in their study of resistance in K. pneumoniae isolates from national sentinel site surveillance in South Africa between 2010 and 2012 which reported that the majority of isolates were ESBL positive and were resistant to third and fourth generation cephalosporins. Resistance to the cephalosporins was found to be in the region of 70% with the exception of cefoxitin, which displayed high sensitivity (>80%) along with the carbapenems, amikacin, colistin, tigecycline and fosfomycin. It is apparent from the results of this study that carbapenem resistance in K. pneumoniae isolates is increasing with an 8 - 11% and a 23 - 25%increase in resistance to carbapenems in isolates from urine and blood samples respectively. (6) (13) (17)

*E. coli* is the most common cause of both community and hospital acquired UTIs and is a common cause of BSIs. In this study *E. coli* isolates accounted for 52% of the isolates, mainly from urine samples. The WHO Antimicrobial Resistance Global Report on Surveillance 2014 showed 2 - 70%

portion of resistance in *E. coli* isolates to third generation cephalosporins and 14 - 71% resistance to fluoroquinolones from national data from the Africa Region. More specifically, the data from AMR surveillance conducted at sentinel public hospitals in South Africa in 2014 reported a 24% resistance to third generation cephalosporins and cefepime, a fourth-generation cephalosporins.<sup>(13)</sup> It was reported by Ballot et al. that all but one of the E. coli isolates from blood cultures from neonates at a public hospital in South Africa were resistant to ampicillin, although all isolates were found to be susceptible to third generation cephalosporins and aminoglycosides. <sup>(12)</sup> The results of this study show that resistance to ampicillin was >80% in isolates from urine and blood samples by 2015 and that there was an increase in resistance in isolates from blood samples from 18% to 27% for ceftazidime and 26% to 40% for ceftriaxone between 2011 and 2015. Resistance to cefepime was found to be lower than the figure reported from 2014 surveillance data with a reported resistance of 11%. <sup>(17)</sup> Resistance in isolates from urine samples was found to be lower than in isolates from blood samples with a 13% resistance to ceftazidime, 23% resistance to ceftriaxone and 8% resistance to cefepime in 2015. Susceptibility to carbapenems was found to be >90% in isolates from blood and urine samples which is consistent with the findings of Ramsamy et al. in 2009. (14) Coetzee et al. reported in 2016 that increasing colistin resistance in E. coli isolates is becoming a serious concern and that the use of colistin as a last resort is becoming more common due to resistance to other antibiotics. Resistance is thought to be spread by the presence of the mcr-1 gene in food animals such as pork and poultry, the presence of which has been confirmed by surveillance of poultry operations in South Africa. The mcr-1 gene has also been detected in colistin-resistant E. coli in hospitalised and outpatient-based patients in South Africa. The percentage resistance data for E. coli and colistin was not calculated as there is currently no CLSI breakpoint for this pathogen-drug combination and the MIC50 and MIC90 results remained stable throughout the study period, however, future studies should monitor resistance in this pathogen-drug combination as resistance to colistin would severely limit treatment options in multidrug resistant E. coli infections. (18)

Salmonella spp. pathogens are a common cause of foodborne illnesses such as gastroenteritis and enteric fever in the case of the Salmonella enterica serotypes Typhi and Paratyphi. Shigella spp. is also major cause of diarrhoeal infections which can be life threatening in children, especially in developing countries. The 2015 GERMS-SA Annual Report identified resistance to ciprofloxacin in Salmonella typhi as well as the emerging resistance to fluoroquinolones in Shigella spp. as a concern.<sup>(8)</sup> This was also highlighted in the WHO Antimicrobial Resistance Global Report on Surveillance 2014 which stated a 0 - 35% and a 0 - 3% proportion of resistance to fluoroquinolones in non-typhoidal Salmonella and Shigella spp. respectively.<sup>(17)</sup> Ciprofloxacin is the antibiotic recommended in the standard treatment guidelines in South Africa for acute diarrhoeal infections caused by Salmonella spp. and Shigella spp. Resistance of Shigella spp. isolates increased from 0%(n=22) in 2011 to 2%(n=108) in 2015, which is comparable to the 1% resistance reported in the GERMS-SA 2015 Annual Report. *Salmonella spp.* isolates from both blood and faecal samples showed either a decrease in resistance or no net change in resistance to all antibiotics and showed a considerable decrease in resistance of 50% to cefotaxime in isolates from faecal samples. In 2015, the resistance of *Salmonella spp.* isolates to ciprofloxacin was 12%, which is less than the figure reported in the GERMS-SA 2015 report of 14% in *S. typhi* isolates and 21% in non-typhoidal *Salmonella* isolates. <sup>(8)</sup>

As an STI, gonorrhoea is a public health concern in South Africa due to the associated increased risk of HIV infection. Resistance to first line therapy for gonorrhoea resulted in the change from ciprofloxacin to cephalosporins in 2008, however, the WHO Antimicrobial Resistance Global Report on Surveillance 2014 reported a decreased in susceptibility to third generation cephalosporins in the Africa Region in 2014.<sup>(17)</sup> In this study only three *N. gonorrhoea* isolates were included over the five years, of which only one showed resistance to ciprofloxacin. Ceftriaxone and cefixime, the third generation cephalosporins recommended in the GLASS antibiotic panel for testing, were not included in this study.

GLASS metrics were consistent with the percentage resistance data and reinforced the existing literature which suggests that there is a decrease in the efficacy of older antibiotics such as ampicillin and trimethoprim-sulfamethoxazole and that emerging resistance to current treatment options is a grave concern as is the case with ciprofloxacin, third generation cephalosporins and carbapenems.

The implication of the increasing resistance shown in the results, especially the prevalence of multidrug resistant infections, is that commonly encountered infections are becoming increasingly difficult to treat. Infections are responsive to a smaller range of broader spectrum antibiotics resulting in their increased use and subsequent selection pressure for resistance. If the current trends continue, untreatable infections will become more common, resulting in poorer clinical outcomes and higher mortality. It is clear that there is an urgent need to implement rational prescribing practices and infection control measures in order to curb the incidence and spread of antibiotic resistance.

The standard treatment guidelines and the essential drugs list are devised and published by the South African National Department of Health for implementation in public health facilities. The aim of these guidelines is to streamline empiric drug therapy and encourage rational prescribing practices. Essack and Connolly carried out a study evaluating the sensitivity of antibiotics listed in the STGs against isolates from a district hospital, regional hospital and tertiary hospital, in Durban, South Africa. Susceptibility was found to be varied across different pathogen-drug combinations as well as between the different facilities. As such institution specific, evidence-based guidelines based on regular surveillance was recommended in order to improve the accuracy and success of empiric therapy.<sup>(19)</sup>The comparison between the trends in resistance and the antibiotics recommended in treatment guidelines showed >65% susceptibility in most pathogens to the recommended agents, with

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the exception of *K. pneumoniae* in UTIs which showed 51 - 63% susceptibility to ciprofloxacin, gentamicin and amoxicillin-clavulanate but only a 31% susceptibility to nitrofurantoin, the drug of choice for the treatment of UTIs in the 2<sup>nd</sup> and 3<sup>rd</sup> trimester of pregnancy and in patients with a severe penicillin allergy. Susceptibility in *A. baumannii* and *K. pneumoniae* from blood samples to gentamicin was between 30% and 40%.

The data obtained during this study has provided a good overview of the trends in ABR in KwaZulu Natal, but the results may not be accurately representative of the true prevalence of resistance. As a retrospective study, the data obtained was limited by what had already been captured in the NHLS database, which only included results positive for microbial growth instead of all samples tested. In addition, due to technical problems data from one of the hospitals was missing for 2014. Many entries were excluded due to insufficient isolate or demographic data, which is an area for improvement in the routine capturing of AST results. Data was not stratified by demographic data such as age and gender; clinical data such as such as diagnosis and number of patient days and facility data such as hospital level and ward type. These parameters would be useful in providing a more detailed analysis of AMR and should be considered for future studies. The data obtained may also be misrepresentative as not all infections necessarily generate a sample for microbiological evaluations because of time and resource constraints and samples sent for AST are likely from patients who are severely ill and have experienced treatment failure. Additionally, not all ill patients seek treatment due to difficulties in accessing healthcare as well as reliance on cultural healing methods. Only 6 public hospitals out of the 71 provincial public hospitals in KwaZulu Natal were included in the study, meaning that community acquired infections and ABR in outlying regions of the province may not have been represented. Future studies should endeavour to include samples from community health settings, as well as try to include more hospitals so as to more accurately represent the status of ABR in KwaZulu Natal.

While some pathogens showed a decline or plateau in resistance to the various antibiotics, the general trend observed is that of an increase in resistance to most of the antibiotics included in this study. This affirms the need for interventions to curb the incidence and spread of resistance such as better prescribing practices, using AST results to guide treatment and antibiotic stewardship. Resources are available to guide rational antibiotic prescribing including standard treatment guidelines published by the South African National Department of Health and other organisations but there is no guarantee that these recommendations are adhered to at ground level.

This study highlights the potential for further research into the trends in resistance and it is apparent that resources are available to obtain the necessary isolates, AST results and demographic data as recommended by the WHO for the monitoring of ABR. This bodes well for the implementation of GLASS in South Africa, as we were able to calculate various metrics based on the GLASS recommendations and the overall analysis gave us a good indication of the general trends in antibiotic resistance in KZN. The ultimate goal of future studies would be to build on the existing knowledge

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base and provide comparable, validated data which can be shared on a global scale in order to guide future interventions against the spread of ABR.

# SUPPLEMENTARY DATA

# Table 1: Antibiotic Panel for AST Analysis per Pathogen

Pathogen	Antibiotic Panel
Acinetobacter baumannii	Amikacin Colistin Ertapenem Gentamicin Imipenem Meropenem Tigecycline
Escherichia coli	Ampicillin Cefepime Cefotaxime Ceftazidime Ciprofloxacin Colistin Cotrimoxazole Ertapenem Imipenem Meropenem
Klebsiella pneumoniae	Cefepime Cefotaxime Ceftazidime Ciprofloxacin Colistin Cotrimoxazole Ertapenem Imipenem Meropenem
Staphylococcus aureus	Cefoxitin
Shigella spp.	Cefotaxime Ceftazidime Ciprofloxacin
Streptococcus pneumoniae	Cefotaxime Trimethoprim/sulfamethoxszole Penicillin G
Salmonella spp.	Cefotaxime Ceftazidime Ciprofloxacin Ertapenem Imipenem Meropenem
Neisseria gonorhhoeae	Ciprofloxacin Gentamicin

# Table 2: Overall AST Results between 2011 and 2015 per specimen type, pathogen and drug

						F	Bloodstream	Infections							
			E. coli				1	K. pneumoniae					A. baumanii		
	MIC50 (mg/l)	MIC90 (mg/l)	Range	n	%R	MIC50 (mg/l)	MIC90 (mg/l)	Range	Ν	%R	MIC50 (mg/l)	MIC90 (mg/l)	Range	n	%R
AM**	≥32	≥32	≤2 - ≥32	946	84.99	-	-	-	-	-	-	-	-	-	-
CIP	$\leq 0.25$	$\geq 4$	≤0.25 - ≥8	953	28.54	1	$\geq 4$	≤0.25 - ≥8	1281	43.56	-	-	-	-	-
CTX	$\leq 1$	≥64	≤1 - ≥64	934	27.52	≥64	≥64	≤1-≥64	1239	70.54	-	-	-	-	-
CAZ	$\leq 1$	16	≤1 - ≥64	934	17.56	16	≥64	≤1 - ≥64	1241	62.29	-	-	-	-	-
FEP	$\leq 1$	8	≤1 - ≥64	935	7.91	2	≥64	≤1 - ≥64	1229	26.53	-	-	-	-	-
IPM	≤0.25	$\leq 1$	≤0.25 - ≥16	933	0.75	≤0.25	≤1	≤0.25 - ≥16	1242	9.98	≥16	$\geq 16$	≤0.25 - ≥16	745	63.33
ETP	≤0.5	≤0.5	≤0.5 - 4	926	0.54	≤0.5	≤0.5	≤0.5 - ≥8	1210	10,00	≤0.5	$\geq 8$	≤0.5 - ≥8	*	*
MEM	≤0.25	≤0.25	≤0.25 - ≥16	914	0.55	≤0.25	≤0.25	≤0.25 - ≥16	1169	8.55	≥16	$\geq 16$	≤0.25 - ≥16	739	64.17
CS	≤0.5	≤0.5	≤0.5 - ≥16	*	*	≤0.25	2	≤0.25 - ≥16	*	*	≤0.5	2	≤0.5-64	720	6.31
SXT	≥320	≥320	≤10 - ≥320	951	78.13	≥320	≥320	≤10 - ≥320	1279	76.54	-	-	-	-	-
TGC	-	-	-	-	-	-	-	-		-	1	2	≤0.12 - ≥8	*	*
GM	-	-	-	-	-	-	-	-		-	≥16	≥16	≤0.5 - ≥16	745	62.55
AN	-	-	-	-	-	-	-	-		-	8	32	≤2 - ≥64	744	14.78
			S. aureus				1	5. pneumoniae				Se	almonella spp.		
	MIC50 (mg/l)	MIC90 (mg/l)	Range	n	%R	MIC50 (mg/l)	MIC90 (mg/l)	Range	Ν	%R	MIC50 (mg/l)	MIC90 (mg/l)	Range	n	%R
CIP	-	-	-	-	-	-	-	-	-	-	≤0.25	≤0.5	≤0.25 - 2	230	25.65
CTX	-	-	-	-	-	≤1	$\leq 1$	≤1 - 2	12	8.33	$\leq 1$	$\leq 1$	≤0.5 - 4	173	2.89
CAZ	-	-	-	-	-	-	-	-	-	-	$\leq 1$	$\leq 1$	≤1 - 4	169	0
FEP	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
IPM	-	-	-	-	-	-	-	-	-	-	≤0.25	$\leq 1$	≤0.25 - 2	172	0.58
ETP	-	-	-	-	-	-	-	-	-	-	≤0.5	≤0.5	≤0.5 - 1	172	2.33
MEM	-	-	-	-	-	-	-	-	-	-	≤0.25	≤0.25	≤0.25 - 1	168	0
CS	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
SXT	-	-	-	-	-	≤20	≥320	≤10 - ≥320	16	100	-	-	-	-	-
FOX	≥64	≥64	≤4 - ≥64	*	*	-	-	-	-	-	-	-	-	-	-
OX1	-	-	-	-	-	≤0.25	0.5	≤0.25 - 0.5	*	*	-	-	-	-	-
Р	-	-	-	-	-	≥0.5	4	≥0.5 - 4	5	20	-	-	-	-	-

						τ	rinary tract	infections		
			E.coli				1	K. pneumoniae		
	MIC50 (mg/l)	MIC90 (mg/l)	Range	n	%R	MIC50 (mg/l)	MIC90 (mg/l)	Range	Ν	%R
SXT**	≥320	≥320	≤10 - ≥320	9431	72.27	≥320	≥320	≤10 - ≥320	2890	64.98
CIP	≤0.25	$\geq 4$	≤0.25 - ≥8	9445	31.69	≤0.25	≤4	≤0.25 - ≥8	2893	37.33
CAZ	$\leq 1$	16	≤1 - ≥64	9384	11.74	$\leq 1$	≥64	≤1 - ≥64	2856	43.84
CTX	$\leq 1$	≥64	≤1 - ≥64	9385	18.57	$\leq 1$	≥64	≤1 - ≥64	2860	49.72
FEP	$\leq 1$	≤4	≤1 - ≥64	9427	6.18	$\leq 1$	32	≤1 - ≥64	3017	20.23
IPM	≤0.25	$\leq 1$	≤0.25 - ≥16	9386	0.6	≤0.25	≤1	≤0.25 - ≥16	2859	4.06
ETP	≤0.5	≤0.5	≤0.5 - ≥8	9370	0.6	≤0.5	≤0.5	≤0.5 - ≥8	2837	5.11
MEM	≤0.25	≤0.25	≤0.25 - ≥16	9184	0.5	≤0.25	≤0.25	≤0.25 - ≥16	2789	4.73
CS	≤0.5	≤0.5	≤0.5 - ≥16	*	*	≤0.5	1	≤0.5 - ≥16	*	*
AM	≥32	≥32	≤2 - ≥32	9433	82.07	-	-	-	-	-

						A	cute Diarrhoe	al Infections		
			Salmonella spp.					Shigella spp.		
	MIC50 (mg/l)	MIC90 (mg/l)	Range	n	%R	MIC50 (mg/l)	MIC90 (mg/l)	Range	Ν	%R
CIP**	≤0.25	≤0.5	≤0.25 - ≥16	145	46.90	≤0.25	≤0.25	≤0.25 - ≥4	319	0.94
CTX	$\leq 1$	4	≤1 - ≥64	156	11.54	≤1	$\leq 1$	≤1 - ≥64	319	4.08
CAZ	$\leq 1$	≤1	≤1 - ≥64	145	4.14	$\leq 1$	≤1	≤1 - 16	319	0.31
IPM	≤0.25	≤1	≤0.25 - ≤1	155	0,00	-	-	-	-	-
ETP	≤0.5	≤0.5	≤0.5 - ≤1	156	7.05	-	-	-	-	-
MEM	≤0.25	≤0.25	≤0.25 - ≤0.25	143	0,00	-	-	-	-	-
							Gonorri	ioea		

			N. gonorrhoea		
	MIC50	MIC90	Range	n	%R
CIP**	≤0.25	≤0.5	≤0.25 - ≤0.5	3	33.33
GM	$\leq 1$	$\leq 1$	≤0.5 - ≤1	*	*

\* CLSI Breakpoint not available

\*\* AM- Ampicillin, CIP- Ciprofloxacin, CTX- Cefotaxime, CAZ- Ceftazidime, FEP- Cefepime, IPM- Imipenem, ETP- Ertapenem, MEM-Meropenem, CS- Colistin, SXT- Trimethoprim-sulfamethoxazole, GM- Gentamicin

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### Proportion of non-susceptible samples out of all Blood samples positive for GLASS pathogens

						· · · · · · · · · · · · · · · · · · ·	P		P	8			
Blood: E. coli	2011		2012		2013		2014		2015			Overall	
	n	%R	n	%R	n	%R	n	%R	n	%R	P- value	n	%R
AM	125	6,98	149	6,23	191	6,77	133	9,83	206	6,13	0.000	804	6,86
CAZ	16	0,89	32	1,34	28	0,99	25	1,85	63	1,87	0.007	164	1,40
CIP	31	1,73	47	1,97	59	2,09	45	3,33	90	2,68	0.013	272	2,32
CTX	22	1,23	48	2,01	49	1,74	45	3,33	93	2,77	0.000	257	2,19
ETP	0	0,00	1	0,04	0	0,00	2	0,15	2	0,06	0.197*	5	0,04
FEP	8	0,45	17	0,71	11	0,39	13	0,96	25	0,74	0.143	74	0,63
IPM MEM	0	0,00	3	0,13	0	0,00	0	0,00	4	0,12	0.131*	1	0,06
SXT	128	7.14	2 150	6.27	181	6.41	123	9,00	 161	1 79	0.010	7/3	6.34
571	120	7,14	150	0,27	101	0,41	125	,0)	101	4,77	0.000	745	0,54
Blood: K pneumoniae	2011	1	2012		2013	1	2014		2015	1		Overall	
	n	%R	n	%R	n	%R	n	%R	n	%R	P- value	n	%R
CAZ	71	3,96	121	5,06	174	6,16	150	11,09	257	7,64	0.000	773	6,59
CIP	50	2,79	96	4,02	131	4,64	89	6,58	192	5,71	0.000	558	4,76
CTX	82	4,58	152	6,36	189	6,70	168	12,42	283	8,42	0.000	874	7,46
ETP	2	0,11	9	0,38	15	0,53	6	0,44	89	2,65	0.000*	121	1,03
FEP	15	0,84	47	1,97	74	2,62	51	3,77	139	4,13	0.000	326	2,78
IPM MEM	2	0,11	12	0,50	14	0,50	5	0,37	91	2,71	0.000	124	1,06
	2	0,11	10	0,42	14	0,50	4	0,50	70	2,08	0.000*	070	0,85
571	101	5,04	170	7,44	220	8,08	165	15,55	209	8,39	0.000	213	6,55
Blood: A. baumanii	2011		2012		2013		2014		2015			Overall	
	n	%R	n	%R	n	%R	n	%R	n	%R	P- value	n	%R
AN	17	0,95	31	1,30	35	1,24	11	0,81	16	0,48	0.007	110	0,94
CS (ab)	6	0,33	11	0,46	12	0,43	10	0,74	8	0,24	0.161	47	0,40
GM	71	3,96	114	4,77	140	4,96	69	5,10	72	2,14	0.000	466	3,98
IPM (ab)	70	3,91	111	4,64	151	5,35	67	4,95	69	2,05	0.000	468	3,99
MEM (ab)	69	3,85	112	4,68	151	5,35	69	5,10	61	1,81	0.000	462	3,94
Dia di Communi	2011	*	2012	*	2013	*	2014	*	2015	*		Overall	
Blood: S. aureus	2011		2012	•	2013		2014	•	2015			Overall	
blood. 5. preumoniue	n 1	%R	n	%R	n n	%R	n	%R	n 1	%R	P-	n	%R
CTY	0	0.00	1	0.04	0	0.00	0	0.00	0	0.00	value	1	0.01
P(sn)	0	0,00	1	0,04	0	0,00	0	0,00	0	0,00	0.472* 0.472*	1	0,01
SXT	2	0,00	4	0,017	3	0,00	1	0,00	6	0,00	0.919*	16	0,01
		- 1		- , -	-	- /		- /		-, -			- 1
Blood: Salmonella spp.	2011		2012		2013		2014		2015			Overall	
	n	%R	n	%R	n	%R	n	%R	n	%R	P- value	n	%R
CAZ	0	0,00	0	0,00	0	0,00	0	0,00	0	0,00	-	0	0,00
CIP	4	0,22	20	0,84	26	0,92	7	0,52	2	0,06	0.000*	59	0,50
CTX	5	0,28	0	0,00	0	0,00	0	0,00	0	0,00	0.000*	5	0,04
ETP	4	0,22	0	0,00	0	0,00	0	0,00	0	0,00	0.001*	4	0,03
IPM MEM	1	0,06	0	0,00	0	0,00	0	0,00	0	0,00	0.268*	1	0,01
MEM Total Blood stream infections caused	1792	0,00	2391	0,00	2823	0,00	1353	0,00	3363	0,00	-	11722	0,00
by GLASS pathogens	1772		2371		2025		1555		3505			11/22	
Propo	tion of n	on-suscer	ntible sar	nples out	of all Ur	ine samn	les positi	ve for GI	ASS pat	thogens	1	I	I
Urine: E. coli	2011		2012		2013	r	2014		2015			Overall	
	n	%R	n	%R	n	%R	n	%R	n	%R	P- value	n	%R
AM	924	32,91	1578	40,89	1879	42,22	1317	52,81	2044	30,97	0.000	7742	38,30
CAZ	90	3,21	218	5,65	267	6,00	200	8,02	327	4,95	0.000	1102	5,45
CIP	307	10,93	592	15,34	728	16,36	517	20,73	849	12,86	0.000	2993	14,81
CTX	134	4,77	304	7,88	429	9,64	307	12,31	569	8,62	0.000	1743	8,62
ETP	4	0,14	6	0,16	9	0,20	4	0,16	29	0,44	0.023*	52	0,26
	40	1,42	100	2,59	148	3,33	106	4,25	192	2,91	0.000	580 56	2,90
MEM	2	0,28	12	0,51	15	0,34	8	0,20	10	0,24	0.010	46	0.28
SXT		30.84	1429	37.03	1626	36.53	1156	46.35	1739	26.35	0.000	6816	33.72
		, -	-	,	-	,		,		,		-	

Urine: K. pneumoniae	2011		2012		2013		2014		2015			Overall	
	n	%R	n	%R	n	%R	n	%R	n	%R	Р-	n	%R
											value		
CAZ	110	3,92	213	5,52	270	6,07	221	8,86	438	6,64	0.000	1252	6,19
CIP	112	3,99	200	5,18	229	5,14	186	7,46	353	5,35	0.000	1080	5,34
CTX	134	4,77	233	6,04	312	7,01	254	10,18	489	7,41	0.000	1422	7,04
ETP	2	0,07	12	0,31	17	0,38	16	0,64	98	1,48	0.000*	145	0,72
FEP	34	1,21	101	2,62	123	2,76	107	4,29	262	3,97	0.000	627	3,10
IPM	4	0,14	8	0,21	6	0,13	13	0,52	85	1,29	0.000*	116	0,57
MEM	4	0,14	6	0,16	16	0,36	14	0,56	92	1,39	0.000*	132	0,65
SXT	222	7,91	341	8,84	411	9,23	335	13,43	569	8,62	0.000	1878	9,29
Total urinary tract infections caused	2808		3859		4451		2494		6600			20212	
by GLASS pathogens													
Propor	tion of n	on-suscep	tible san	nples out	of all Fa	ecal samp	oles posit	ive for G	LASS pa	thogens	1		
Faeces: Salmonella spp.	2011		2012		2013	r	2014	r	2015	r		Overall	1
	n	%R	n	%R	n	%R	n	%R	n	%R	P-	n	%R
	-	2.04			0	0.00	0	0.00		0.05	value		0.55
CAZ	3	2,94	2	1,41	0	0,00	0	0,00	1	0,37	0.010*	6	0,66
CIP	5	4,90	13	9,15	34	14,35	7	4,29	9	3,31	0.000	68	7,42
CIX	14	13,73	2	1,41	0	0,00	0	0,00	2	0,74	0.000*	18	1,97
ETP	11	10,78	0	0,00	0	0,00	0	0,00	0	0,00	0.000*	11	1,20
IPM	0	0,00	0	0,00	0	0,00	0	0,00	0	0,00	-	0	0,00
MEM	0	0,00	0	0,00	0	0,00	0	0,00	0	0,00	-	0	0,00
Faeces: Shigella spp.	2011		2012		2013		2014		2015				
	n	%R	n	%R	n	%R	n	%R	n	%R		0	0,00
CAZ	0	0,00	0	0,00	0	0,00	0	0,00	1	0,37	1.000*	1	0,11
CIP	0	0,00	0	0,00	0	0,00	1	0,61	2	0,74	0.617*	3	0,33
CTX	0	0,00	0	0,00	2	0,84	4	2,45	7	2,57	0.102*	13	1,42
Total Acute Diarrhoeal infections	102		142		237		163		272	2,57		916	
caused by GLASS pathogens													
			L .				<u> </u>						
Proportion (	of non-su	sceptible	samples	out of all	Urethra	l/cervical	samples	positive	for GLAS	SS pathog	gens	0 1	
N. gonorrhoea	2011	0 ( D	2012	0 / D	2013	0 ( D	2014	0 ( D	2015	0 ( D	n	Overall	0 ( <b>D</b>
	n	%К	n	%K	n	%K	n	%K	n	%K	P-	n	%K
	0	0.00	0	0.00	0	0.00	0	0.00	1	1.05	value	1	0.50524
	0	0,00	0	0,00	0	0,00	0	0,00	1	1.85	-	1	0,59524
1 otal Gonorrhoeal infections	35	I	24	I	54		21		54			168	

# Table 4: GLASS Population Measures

nBlood17Urine28Faeces10Urethral/cervical35Population	92 17,45 08 27,35 2 0,99 0,34	n 2931 3859 142 24	28,55 37,59	n 2823	27.50	n						
Blood   17     Urine   28     Faces   10     Urethral/cervical   35     Population	92 17,45 08 27,35 2 0,99 0,34	2931 3859 142 24	28,55 37,59	2823	27.50			Ν		n		
Urine     28       Faeces     10       Urethral/cervical     35       Population	08 27,35 2 0,99 0,34	3859 142 24	37,59	4451	27,50	1353	13,18	3363	32,75	12262,00	119,43	< 0.001
Faeces     10       Urethral/cervical     35       Population	2 0,99 0,34	142 24	1 20	4451	43,35	2494	24,29	6600	64,28	20212,00	196,86	< 0.001
Urethral/cervical 35 Population	0,34	24	1,38	237	2,31	163	1,59	272	2,65	916,00	8,92	< 0.001
Population			0,23	34	0,33	21	0,20	54	0,53	168,00	1,64	0,032
	10267300											+
Blood 20	11	2012	1.00	2013		2014		2015		Overall		p-value
<i>E. coli</i> 39	7 3,87	441	4,30	417	4,06	221	2,15	609	5,93	2085,00	20,31	< 0.001
K. pneumoniae 37	3 3,63	577	5,62	698	6,80	358	3,49	1053	10,26	3059,00	29,79	< 0.001
A. baumanii 24	8 2,42	341	3,32	483	4,70	147	1,43	353	3,44	1572,00	15,31	< 0.001
S. aureus 54	3 5,29	773	7,53	890	8,67	471	4,59	1110	10,81	3787,00	36,88	< 0.001
S. pneumoniae 18	8 1,83	179	1,74	238	2,32	118	1,15	170	1,66	893,00	8,70	< 0.001
Salmonella spp 43	0,42	80	0,78	97	0,94	38	0,37	68	0,66	326,00	3,18	0,001
Urine 20	11	2012	I	2013		2014		2015		Overall		p-value
E. coli 22	02 21,45	2936	28,60	3257	31,72	1907	18,57	4913	47,85	15215,00	148,19	< 0.001
K. pneumoniae 60	6 5,90	923	8,99	1194	11,63	587	5,72	1687	16,43	4997,00	48,67	< 0.001
												1
				2013		2014						4

snigena spp	55	0,54	96	0,94	159	1,55	117	1,14	190	1,85	617,00	6,01	0,001
Urethral/cervical	2011		2012		2013		2014		2015	l	Overall		p-value
N. gonorrhoea	35	0,34	24	0,23	34	0,33	21	0,20	54	0,53	168,00	1,64	0,032
Population		10267300											
	3 CI	ASS Measure	B3· Nu	mber of F	esistant	infection	s ner net	hogen an	d drug n	or 100 00	A inhahitante		
	5.01	2A55 Witasur	<b>D</b> 5. Nu		Constant	meetion	s per pai	nogen an	u ui ug p	1 100 00			
Bloods E soli	2011		2012		2012		2014		2015		Overall		n value
AM	125	1.22	149	1.45	191	1.86	133	1.30	2015	2.01	804.00	7.83	<0.001
CAZ	16	0,16	32	0,31	28	0,27	25	0,24	63	0,61	164,00	1,60	0,001
CIP	31	0,30	47	0,46	59	0,57	45	0,44	90	0,88	272,00	2,65	< 0.001
CTX	22	0,21	48	0,47	49	0,48	45	0,44	93	0,91	257,00	2,50	< 0.001
ETP	0	0,00	1	0,01	0	0,00	2	0,02	2	0,02	5,00	0,05	0,175
IPM	0	0,08	3	0,17	0	0,11	0	0,15	23 4	0,24	74,00	0,72	0,094
MEM	0	0.00	2	0.02	1	0.01	0	0.00	2	0.02	5.00	0.05	0.820
SXT	128	1,25	150	1,46	181	1,76	123	1,20	161	1,57	743,00	7,24	<0.001
Blood: K pneumoniae	2011		2012		2013		2014		2015		Overall		p-value
CAZ	71	0,69	121	1,18	174	1,69	150	1,46	257	2,50	773,00	7,53	<0.001
CIP	50	0,49	96	0,94	131	1,28	89	0,87	192	1,87	558,00	5,43	0,002
ETP	02 2	0.02	9	1,48	169	0.15	6	1,04	203	2,70	874,00 121.00	0,01	<0.001
FEP	15	0,02	47	0,05	74	0,13	51	0,50	139	1,35	326,00	3,18	<0.001
IPM	2	0,02	12	0,12	14	0,14	5	0,05	91	0,89	124,00	1,21	< 0.001
MEM	2	0,02	10	0,10	14	0,14	4	0,04	70	0,68	100,00	0,97	< 0.001
SXT	101	0,98	178	1,73	228	2,22	183	1,78	289	2,81	979,00	9,54	<0.001
Blood: A. baumanii	2011	0.17	2012	0.20	2013	0.24	2014	0.11	2015	0.16	Overall	1.07	p-value
CS (ab)	6	0,17	11	0,30	12	0,34	10	0,11	8	0,10	47.00	0.46	0,225
GM	71	0.69	114	1.11	140	1.36	69	0.67	72	0.70	466.00	4.54	<0.001
IPM (ab)	70	0,68	111	1,08	151	1,47	67	0,65	69	0,67	468,00	4,56	< 0.001
MEM (ab)	69	0,67	112	1,09	151	1,47	69	0,67	61	0,59	462,00	4,50	< 0.001
Blood: S. aureus	*	*	*	*	*	*	*	*	*	*	<u> </u>		
Blood: S. pneumoniae	2011		2012		2013		2014		2015		Overall		p-value
	0	0.00	1	0.01	0	0.00	0	0.00	0	0.00	1.00	0.01	0.523
P (sp)	0	0,00	1	0,01	0	0,00	0	0,00	0	0,00	1,00	0,01	0,523 0,523
P (sp) SXT	0 0 2	0,00 0,00 0,019	1 1 4	0,01 0,01 0,04	0 0 3	0,00 0,00 0,03	0 0 1	0,00 0,00 0,01	0 0 6	0,00 0,00 0,06	1,00 1,00 16,00	0,01 0,01 0,16	0,523 0,523 0,392
P (sp) SXT Blood: Salmonella spp	0 0 2 2011	0,00 0,00 0,019	1 1 4 2012	0,01 0,01 0,04	0 0 3 2013	0,00 0,00 0,03	0 0 1 2014	0,00 0,00 0,01	0 0 6 2015	0,00 0,00 0,06	1,00 1,00 16,00 <b>Overall</b>	0,01 0,01 0,16	0,523 0,523 0,392 <b>p-value</b>
P (sp) SXT Blood: Salmonella spp CAZ	0 0 2 2011 0	0,00 0,00 0,019	1 4 <b>2012</b> 0	0,01 0,01 0,04 0,00	0 0 3 2013 0	0,00 0,00 0,03 0,00	0 0 1 <b>2014</b> 0	0,00 0,00 0,01 0,00	0 0 6 <b>2015</b> 0	0,00 0,00 0,06	1,00 1,00 16,00 <b>Overall</b> 0,00	0,01 0,01 0,16	0,523 0,523 0,392 <b>p-value</b> NC
P (sp) SXT Blood: Salmonella spp CAZ CIP	0 0 2 2011 0 4	0,00 0,00 0,019 0,00 0,04 0,05	1 4 <b>2012</b> 0 20	0,01 0,01 0,04 0,00 0,19	0 0 3 <b>2013</b> 0 26 0	0,00 0,00 0,03 0,00 0,25	0 0 1 <b>2014</b> 0 7	0,00 0,00 0,01 0,00 0,07	0 0 6 <b>2015</b> 0 2	0,00 0,00 0,06 0,00 0,02	1,00 1,00 16,00 <b>Overall</b> 0,00 59,00	0,01 0,01 0,16 0,00 0,57	0,523 0,523 0,392 <b>p-value</b> NC <0.001
P (sp) SXT Blood: Salmonella spp CAZ CIP CTX FTP	0 0 2 2011 0 4 5 4	0,00 0,00 0,019 0,00 0,04 0,05 0,04	1 4 <b>2012</b> 0 20 0	0,01 0,01 0,04 0,00 0,19 0,00	0 0 3 <b>2013</b> 0 26 0	0,00 0,00 0,03 0,00 0,25 0,00	0 0 1 <b>2014</b> 0 7 0	0,00 0,00 0,01 0,00 0,07 0,00 0,00	0 0 6 <b>2015</b> 0 2 0 0	0,00 0,00 0,06 0,00 0,02 0,00 0,00	1,00 1,00 16,00 <b>Overall</b> 0,00 59,00 5,00 4,00	0,01 0,01 0,16 0,00 0,57 0,05 0,04	0,523 0,523 0,392 <b>p-value</b> NC <0.001 <0.001
P (sp) SXT Blood: Salmonella spp CAZ CIP CTX ETP IPM	0 0 2 2011 0 4 5 4 1	0,00 0,00 0,019 0,00 0,04 0,05 0,04 0,01	1 4 <b>2012</b> 0 20 0 0 0 0	0,01 0,01 0,04 0,00 0,19 0,00 0,00 0,00	0 0 3 2013 0 26 0 0 0 0	0,00 0,00 0,03 0,00 0,25 0,00 0,00 0,00	0 0 1 <b>2014</b> 0 7 0 0 0 0	0,00 0,00 0,01 0,00 0,07 0,00 0,00 0,00	0 0 6 2015 0 2 0 0 0 0	0,00 0,00 0,06 0,02 0,00 0,00 0,00	1,00 1,00 16,00 <b>Overall</b> 0,00 59,00 5,00 4,00 1,00	0,01 0,01 0,16 0,00 0,57 0,05 0,04 0,01	0,523 0,523 0,392 <b>p-value</b> NC <0.001 <0.001 <0.001 0.248
P (sp) SXT Blood: Salmonella spp CAZ CIP CTX ETP IPM MEM	0 0 2 2011 0 4 5 4 1 0	0,00 0,00 0,019 0,00 0,04 0,05 0,04 0,01 0,00	1 4 <b>2012</b> 0 20 0 0 0 0 0 0	0,01 0,01 0,04 0,00 0,19 0,00 0,00 0,00 0,00	0 0 3 <b>2013</b> 0 26 0 0 0 0 0	0,00 0,00 0,03 0,00 0,25 0,00 0,00 0,00 0,00	0 0 1 <b>2014</b> 0 7 0 0 0 0 0 0	0,00 0,00 0,01 0,00 0,07 0,00 0,00 0,00	0 0 <b>2015</b> 0 2 0 0 0 0 0 0 0	0,00 0,00 0,06 0,00 0,02 0,00 0,00 0,00	1,00 1,00 16,00 <b>Overall</b> 0,00 59,00 5,00 4,00 1,00 0,00	0,01 0,01 0,16 0,00 0,57 0,05 0,04 0,01 0,00	0,523 0,523 0,392 <b>p-value</b> NC <0.001 <0.001 <0.001 0,248 NC
P (sp) SXT Blood: Salmonella spp CAZ CIP CTX ETP IPM MEM Urine: E. coli	0 0 2 2011 0 4 5 4 1 0 2011	0,00 0,00 0,019 0,00 0,04 0,05 0,04 0,01 0,00	1 4 <b>2012</b> 0 20 0 0 0 0 0 <b>0</b> 2 <b>012</b>	0,01 0,04 0,00 0,19 0,00 0,00 0,00 0,00	0 0 3 <b>2013</b> 0 26 0 0 0 0 0 <b>2013</b>	0,00 0,00 0,03 0,00 0,25 0,00 0,00 0,00 0,00	0 0 1 <b>2014</b> 0 7 0 0 0 0 0 0 2 <b>014</b>	0,00 0,00 0,01 0,00 0,07 0,00 0,00 0,00	0 0 2015 0 2 0 0 0 0 0 2015	0,00 0,00 0,06 0,00 0,02 0,00 0,00 0,00	1,00 1,00 16,00 <b>Overall</b> 0,00 59,00 5,00 4,00 1,00 0,00 <b>Overall</b>	0,01 0,01 0,16 0,00 0,57 0,05 0,04 0,01 0,00	0,523 0,523 0,392 <b>p-value</b> NC <0.001 <0.001 <0.001 0,248 NC <b>p-value</b>
P (sp) SXT Blood: Salmonella spp CAZ CIP CTX ETP IPM MEM Urine: E. coli AM CAZ	0 0 2 2011 0 4 5 4 1 0 2011 924	0,00 0,00 0,019 0,04 0,05 0,04 0,01 0,00 9,00	1 1 4 2012 0 20 0 0 0 0 0 2012 1578	0,01 0,01 0,04 0,00 0,19 0,00 0,00 0,00 0,00 0,00 15,37	0 0 3 2013 0 26 0 0 0 0 0 2013 1879 267	0,00 0,00 0,03 0,00 0,25 0,00 0,00 0,00 0,00 0,00 18,30	0 0 1 2014 0 7 0 0 0 0 0 2014 1317 200	0,00 0,00 0,01 0,00 0,07 0,00 0,00 0,00	0 0 2015 0 2 0 0 0 0 0 2015 2044 227	0,00 0,00 0,06 0,00 0,00 0,00 0,00 0,00	1,00 1,00 16,00 <b>Overall</b> 0,00 59,00 5,00 4,00 1,00 0,00 <b>Overall</b> 7742,00	0,01 0,01 0,16 0,00 0,57 0,05 0,04 0,01 0,00 75,40	p-value           0,523           0,523           0,392           p-value           NC           <0.001
P (sp) SXT Blood: Salmonella spp CAZ CIP CTX ETP IPM MEM Urine: E. coli AM CAZ CIP	0 0 2 2011 0 4 5 4 1 0 2011 924 90 307	0,00 0,00 0,019 0,04 0,05 0,04 0,01 0,00 9,00 0,88 2,99	1 1 4 2012 0 20 0 0 0 0 0 0 0 2012 1578 218 592	$\begin{array}{c} 0,01\\ 0,01\\ 0,04\\ \end{array}$	0 0 2013 0 26 0 0 0 0 0 2013 1879 267 728	0,00 0,00 0,03 0,00 0,25 0,00 0,00 0,00 0,00 18,30 2,60 7,09	0 0 1 2014 0 7 0 0 0 0 0 0 0 2014 1317 200 517	0,00 0,00 0,01 0,00 0,07 0,00 0,00 0,00	0 0 2015 0 2 0 0 0 0 0 0 0 2015 2044 327 849	0,00 0,00 0,06 0,00 0,02 0,00 0,00 0,00	1,00 1,00 16,00 <b>Overall</b> 0,00 59,00 5,00 4,00 1,00 0,00 <b>Overall</b> 7742,00 1102,00 2993,00	0,01 0,01 0,16 0,00 0,57 0,05 0,04 0,01 0,00 75,40 10,73 29,15	p-value           0,523           0,523           0,392           p-value           NC           <0.001
P (sp) SXT Blood: Salmonella spp CAZ CIP CTX ETP IPM MEM Urine: E. coli AM CAZ CIP CTX	0 0 2 2011 0 4 5 4 1 0 2011 924 90 307 134	0,00 0,00 0,019 0,00 0,04 0,05 0,04 0,01 0,00 9,00 0,88 2,99 1,31	1 1 4 2012 0 20 0 0 0 0 0 0 0 2012 1578 218 592 304	$\begin{array}{c} 0.01\\ 0.01\\ 0.04\\ \end{array}$	0 0 3 2013 0 26 0 0 0 0 2013 1879 267 728 429	0,00 0,00 0,03 0,00 0,25 0,00 0,00 0,00 0,00 18,30 2,60 7,09 4,18	0 0 1 2014 0 7 0 0 0 0 0 0 2014 1317 200 517 307	0,00 0,00 0,01 0,00 0,07 0,00 0,00 0,00	0 0 2015 0 2 0 0 0 0 0 0 2015 2015 2015 2015 2015 2015 327 849 569	0,00 0,00 0,06 0,00 0,00 0,00 0,00 0,00	1,00 1,00 16,00 <b>Overall</b> 0,00 59,00 5,00 4,00 1,00 <b>Overall</b> 7742,00 1102,00 2993,00 1743,00	0,01 0,01 0,16 0,00 0,57 0,05 0,04 0,01 0,00 75,40 10,73 29,15 16,98	p-value           0,523           0,523           0,392           p-value           NC           <0.001
P (sp) SXT Blood: Salmonella spp CAZ CIP CTX ETP IPM MEM Urine: E. coli AM CAZ CIP CTX ETP	0 0 2 2011 0 4 5 4 1 0 2011 924 90 307 134 4	0,00 0,00 0,019 0,00 0,04 0,05 0,04 0,01 0,00 9,00 0,88 2,99 1,31 0,04	1 1 4 2012 0 20 0 0 0 0 0 0 0 2012 1578 218 592 304 6	$\begin{array}{c} 0.01\\ 0.01\\ 0.04\\ \end{array}$	0 0 2013 0 26 0 0 0 0 0 2013 1879 267 728 429 9	0,00 0,00 0,03 0,00 0,25 0,00 0,00 0,00 0,00 18,30 2,60 7,09 4,18 0,09	0 0 1 2014 0 7 0 0 0 0 0 0 2014 1317 200 517 307 4	$\begin{array}{c} 0,00\\ 0,00\\ 0,01\\ \hline \\ 0,00\\ 0,07\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ \hline \\ 12,83\\ 1.95\\ 5,04\\ 2.99\\ 0,04\\ \hline \end{array}$	0 0 2015 0 2 0 0 0 0 0 0 0 2015 2044 327 849 569 29	0,00 0,00 0,06 0,00 0,00 0,00 0,00 0,00	1,00 1,00 16,00 <b>Overall</b> 0,00 59,00 5,00 4,00 1,00 0,00 <b>Overall</b> 7742,00 1102,00 2993,00 1743,00 52,00	0,01 0,01 0,16 0,00 0,57 0,05 0,04 0,01 0,00 75,40 10,73 29,15 16,98 0,51	0,523 0,523 0,392 <b>p-value</b> NC <0.001 <0.001 <0.001 0,248 NC <b>p-value</b> <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.0
P (sp) SXT Blood: Salmonella spp CAZ CIP CTX ETP IPM MEM Urine: E. coli AM CAZ CIP CTX ETP FEP	0 0 2 2011 0 4 5 4 1 0 2011 924 90 307 134 4 40	0,00 0,00 0,019 0,04 0,05 0,04 0,01 0,00 9,00 0,88 2,99 1,31 0,04 0,39	1           4           2012           0           20           1578           218           592           304           6           100	$\begin{array}{c} 0.01\\ 0.01\\ 0.04\\ \end{array}$	0 0 3 2013 0 26 0 0 0 0 0 0 0 2013 1879 267 728 429 9 148	$\begin{array}{c} 0,00\\ 0,00\\ 0,03\\ \hline \\ 0,00\\ 0,25\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ \hline \\ 18,30\\ 2,60\\ 7,09\\ 4,18\\ 0,09\\ 1,44\\ \hline \end{array}$	0 0 1 <b>2014</b> 0 7 0 0 0 0 0 0 0 0 <b>2014</b> 1317 200 517 307 4 106	0,00 0,00 0,01 0,00 0,07 0,00 0,00 0,00	0 0 2015 0 2 0 0 0 0 0 0 0 2015 2044 327 849 569 29 192	$\begin{array}{c} 0,00\\ 0,00\\ 0,06\\ \end{array}$ $\begin{array}{c} 0,00\\ 0,02\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ \end{array}$ $\begin{array}{c} 19,91\\ 3,18\\ 8,27\\ 5,54\\ 0,28\\ 1,87\\ \end{array}$	1,00 1,00 16,00 <b>Overall</b> 0,00 59,00 5,00 4,00 1,00 0,00 <b>Overall</b> 7742,00 1102,00 2993,00 1743,00 52,00 586,00	0,01 0,01 0,16 0,00 0,57 0,05 0,04 0,01 0,00 75,40 10,73 29,15 16,98 0,51 5,71	p-value           0,523           0,523           0,392           p-value           NC           <0.001
P (sp) SXT Blood: Salmonella spp CAZ CIP CTX ETP IPM MEM Urine: E. coli AM CAZ CIP CTX ETP FEP IPM	0 0 2 2011 0 4 5 4 1 0 2011 924 90 307 134 4 40 8 2	0,00 0,00 0,019 0,00 0,04 0,05 0,04 0,01 0,00 9,00 0,88 2,99 1,31 0,04 0,39 0,08	1           4           2012           0           20           0           0           0           0           0           0           0           0           0           0           0           2012           1578           218           592           304           6           100           12 $\hat{c}$	0,01 0,01 0,04 0,00 0,19 0,00 0,00 0,00 0,00 0,00 0,00	0 0 3 2013 0 26 0 0 0 0 0 0 0 0 0 0 0 0 0	0,00 0,00 0,03 0,00 0,25 0,00 0,00 0,00 0,00 18,30 2,60 7,09 4,18 0,09 1,44 0,15	0 0 1 2014 0 7 0 0 0 0 0 0 0 0 2014 1317 200 517 307 4 106 5 2	0,00 0,00 0,01 0,07 0,00 0,00 0,00 0,00	0 0 2015 0 2 0 0 0 0 0 0 0 0 0 0 0 0 0	$\begin{array}{c} 0,00\\ 0,00\\ 0,06\\ \end{array}$ $\begin{array}{c} 0,00\\ 0,02\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ \end{array}$ $\begin{array}{c} 19,91\\ 3,18\\ 8,27\\ 5,54\\ 0,28\\ 1,87\\ 0,16\\ 0,16\\ \end{array}$	1,00 1,00 16,00 <b>Overall</b> 0,00 59,00 5,00 4,00 1,00 0,00 <b>Overall</b> 7742,00 1102,00 2993,00 1743,00 52,00 586,00 56,00	0,01 0,01 0,16 0,00 0,57 0,05 0,04 0,01 0,00 75,40 10,73 29,15 16,98 0,51 5,71 0,55 5,71	0,523 0,523 0,523 0,392 <b>p-value</b> NC <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.001 <0.
P (sp) SXT Blood: Salmonella spp CAZ CIP CTX ETP IPM MEM Urine: E. coli AM CAZ CIP CTX ETP FEP IPM MEM SYT	0 0 2 2011 0 4 5 4 1 0 2011 924 90 307 134 4 40 8 2 2 866	0,00 0,00 0,019 0,00 0,04 0,05 0,04 0,01 0,00 9,00 0,88 2,99 1,31 0,04 0,39 0,08 0,02 8,42	1 1 4 2012 0 20 0 0 0 0 0 0 0 0 0 0 0 0 0	0,01 0,01 0,04 0,00 0,19 0,00 0,00 0,00 0,00 0,00 15,37 2,12 5,77 2,96 0,06 0,97 0,12 0,08	0 0 3 2013 0 26 0 0 0 0 0 0 0 2013 1879 267 728 429 9 148 15 15 1626	0,00 0,00 0,03 0,00 0,25 0,00 0,00 0,00 0,00 18,30 2,60 7,09 4,18 0,09 1,44 0,15 0,15	0 0 1 2014 0 7 0 0 0 0 0 0 0 0 2014 1317 200 517 307 4 106 5 8 8 1156	0,00 0,00 0,01 0,07 0,00 0,00 0,00 0,00	0 0 2015 0 2 0 0 0 0 0 0 0 0 0 0 0 0 0	0,00 0,00 0,06 0,02 0,00 0,00 0,00 0,00	1,00 1,00 16,00 <b>Overall</b> 0,00 59,00 5,00 4,00 1,00 0,00 <b>Overall</b> 7742,00 1102,00 2993,00 1743,00 52,00 586,00 56,00 46,00 6816,00	$\begin{array}{c} 0,01\\ 0,01\\ 0,16\\ \hline \\ 0,00\\ 0,57\\ 0,05\\ 0,04\\ 0,01\\ 0,00\\ \hline \\ 75,40\\ 10,73\\ 29,15\\ 16,98\\ 0,51\\ 5,71\\ 0,55\\ 0,45\\ \hline \\ 0,45\\ \hline \\ 66,20\\ \hline \end{array}$	p-value           0,523           0,523           0,392           p-value           NC           <0.001
P (sp) SXT Blood: Salmonella spp CAZ CIP CTX ETP IPM MEM Urine: E. coli AM CAZ CIP CTX ETP FEP IPM MEM MEM SXT Urine: K nneumoniae	0 0 2 2011 0 4 5 4 1 0 2011 924 90 307 134 4 40 8 2 866 2011	0,00 0,00 0,019 0,00 0,04 0,05 0,04 0,01 0,00 9,00 0,88 2,99 1,31 0,04 0,39 0,08 0,02 8,43	1 1 4 2012 0 20 0 0 0 0 0 0 0 0 0 0 0 0 0	0,01 0,01 0,04 0,00 0,19 0,00 0,00 0,00 0,00 0,00 15,37 2,12 5,77 2,96 0,06 0,97 0,12 0,08 13,92	0 0 3 2013 0 26 0 0 0 0 0 0 2013 1879 267 728 429 9 148 15 1626 2013	$\begin{array}{c} 0,00\\ 0,00\\ 0,03\\ \hline \\ 0,00\\ 0,25\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ \hline \\ 0,00\\ 0,00\\ \hline \\ 18,30\\ 2,60\\ 7,09\\ 4,18\\ 0,09\\ 1,44\\ 0,15\\ 0,15\\ 15,84\\ \hline \end{array}$	0 0 1 2014 0 7 0 0 0 0 0 0 0 0 0 0 0 0 0	0,00 0,00 0,01 0,07 0,00 0,00 0,00 0,00	0 0 2015 0 2 0 0 0 0 0 0 0 2015 2044 327 849 569 29 192 16 13 1739 2015	$\begin{array}{c} 0,00\\ 0,00\\ 0,06\\ \hline \\ 0,00\\ 0,02\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ \hline \\ 3,18\\ 8,27\\ 5,54\\ 0,28\\ 1,87\\ 0,16\\ 0,13\\ 16,94\\ \hline \end{array}$	1,00 1,00 16,00 <b>Overall</b> 0,00 59,00 5,00 4,00 1,00 0,00 <b>Overall</b> 7742,00 1102,00 2993,00 1743,00 52,00 586,00 56,00 46,00 6816,00 <b>Overall</b>	$\begin{array}{c} 0,01\\ 0,01\\ 0,16\\ \hline \\ 0,00\\ 0,57\\ 0,05\\ 0,04\\ 0,01\\ 0,00\\ \hline \\ 75,40\\ 10,73\\ 29,15\\ 16,98\\ 0,51\\ 5,71\\ 0,55\\ 0,45\\ 66,39\\ \hline \end{array}$	p-value           0,523           0,523           0,392           p-value           NC           <0.001
P (sp) SXT Blood: Salmonella spp CAZ CIP CTX ETP IPM MEM Urine: E. coli AM CAZ CIP CTX ETP FEP IPM MEM SXT Urine: K. pneumoniae CAZ	0 0 2 2011 0 4 5 4 1 0 2011 924 90 307 134 4 40 8 2 866 2011 110	0,00 0,00 0,019 0,00 0,04 0,05 0,04 0,01 0,00 9,00 0,88 2,99 1,31 0,04 0,39 0,08 0,02 8,43 1,07	1           4           2012           0           20           12           8           1429           2012           213	0,01 0,01 0,04 0,00 0,19 0,00 0,00 0,00 0,00 0,00 15,37 2,12 5,77 2,96 0,06 0,97 0,12 0,08 13,92 2,07	0         0           0         3           2013         0           26         0           0         0           0         0           0         0           0         0           0         0           0         0           0         0           0         0           0         0           0         0           0         0           267         728           429         9           148         15           15         1626           2013         270	0,00 0,00 0,03 0,00 0,25 0,00 0,00 0,00 0,00 0,00 18,30 2,60 7,09 4,18 0,09 1,44 0,15 0,15 15,84 2,63	0 0 1 2014 0 7 0 0 0 0 0 0 0 0 0 0 0 2014 1317 200 517 307 4 106 5 8 1156 2014 221	0,00 0,00 0,01 0,00 0,07 0,00 0,00 0,00	0 0 2015 0 2 0 0 0 0 0 0 0 0 0 0 0 0 0	0,00 0,00 0,06 0,02 0,00 0,00 0,00 0,00	1,00 1,00 16,00 <b>Overall</b> 0,00 59,00 5,00 4,00 1,00 0,00 <b>Overall</b> 7742,00 1102,00 2993,00 1743,00 52,00 586,00 56,00 46,00 <b>Overall</b> 1252,00	$\begin{array}{c} 0,01\\ 0,01\\ 0,16\\ \hline 0,00\\ 0,57\\ 0,05\\ 0,04\\ 0,01\\ 0,00\\ \hline 75,40\\ 10,73\\ 29,15\\ 16,98\\ 0,51\\ 5,71\\ 0,55\\ 0,45\\ 66,39\\ \hline 12,19\\ \end{array}$	p-value           0,523           0,523           0,392           p-value           NC           <0.001
P (sp) SXT Blood: Salmonella spp CAZ CIP CTX ETP IPM MEM Urine: E. coli AM CAZ CIP CTX ETP FEP IPM MEM SXT Urine: K. pneumoniae CAZ CIP	0 0 2 2011 0 4 5 4 1 0 2011 924 90 307 134 4 40 8 2 866 2011 110 112	0,00 0,00 0,019 0,04 0,05 0,04 0,01 0,00 9,00 0,88 2,99 1,31 0,04 0,39 0,08 0,02 8,43 1,07 1,09	1           1           4           2012           0           20           100           12           8           1429           213           200	$\begin{array}{c} 0,01\\ 0,01\\ 0,04\\ \end{array}$	0         0           0         3           2013         0           26         0           0         0           0         0           0         0           0         0           0         0           0         0           0         0           0         0           2013         1879           267         728           429         9           148         15           15         1626           2013         270           229         29	$\begin{array}{c} 0,00\\ 0,00\\ 0,03\\ \hline \\ 0,00\\ 0,25\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ \hline \\ 18,30\\ 2,60\\ 7,09\\ 4,18\\ 0,09\\ 1,44\\ 0,15\\ 0,15\\ 15,84\\ \hline \\ 2,63\\ 2,23\\ \hline \end{array}$	0 0 1 2014 0 7 0 0 0 0 0 0 0 0 0 0 2014 1317 200 517 307 4 1106 5 8 1156 2014 221 186	$\begin{array}{c} 0,00\\ 0,00\\ 0,01\\ \hline \\ 0,00\\ 0,07\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ \hline \\ 12,83\\ 1.95\\ 5.04\\ 2.99\\ 0,04\\ 1.03\\ 0,05\\ 0,08\\ 11,26\\ \hline \\ 2,15\\ 1.81\\ \hline \end{array}$	0 0 2015 0 2 0 0 0 0 0 0 0 0 0 0 0 0 0	$\begin{array}{c} 0,00\\ 0,00\\ 0,06\\ \hline \\ 0,00\\ 0,02\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ \hline \\ 19,91\\ 3,18\\ 8,27\\ 5,54\\ 0,28\\ 1,87\\ 0,16\\ 0,13\\ 16,94\\ \hline \\ 4,27\\ 3,44\\ \end{array}$	1,00 1,00 16,00 <b>Overall</b> 0,00 59,00 5,00 4,00 1,00 <b>Overall</b> 7742,00 1102,00 2993,00 1743,00 52,00 586,00 56,00 46,00 6816,00 <b>Overall</b> 1252,00 1080,00	0,01 0,01 0,16 0,00 0,57 0,05 0,04 0,01 0,00 75,40 10,73 29,15 16,98 0,51 5,71 0,55 0,45 66,39 12,19 10,52	p-value           0,523           0,523           0,392           p-value           NC           <0.001
P (sp) SXT Blood: Salmonella spp CAZ CIP CTX ETP IPM MEM Urine: E. coli AM CAZ CIP CTX ETP FEP IPM MEM SXT Urine: K. pneumoniae CAZ CIP CTX	0 0 2 2011 0 4 5 4 1 0 2011 924 90 307 134 4 40 8 2 866 2011 110 112 134 2 2	0,00 0,00 0,019 0,00 0,04 0,05 0,04 0,01 0,00 9,00 0,88 2,99 1,31 0,04 0,39 0,08 0,02 8,43 1,07 1,09 1,31 0,05	1           1           4           2012           0           20           1578           592           304           6           100           12           8           1429           2012           213           200           23	$\begin{array}{c} 0.01\\ 0.01\\ 0.04\\ \hline \end{array}$	0         0           0         3           2013         0           26         0           0         0           2013         1879           267         728           429         9           148         15           15         1626           2013         270           229         312	$\begin{array}{c} 0,00\\ 0,00\\ 0,03\\ \hline \\ 0,00\\ 0,25\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ \hline \\ 0,00\\ 0,00\\ \hline \\ 18,30\\ 2,60\\ 7,09\\ 4,18\\ 0,09\\ 1,44\\ 0,15\\ 0,15\\ 15,84\\ \hline \\ 2,63\\ 2,23\\ 3,04\\ \hline \\ 3,04\\ \hline \end{array}$	0 0 1 2014 0 7 0 0 0 0 0 0 0 0 0 2014 1317 200 517 307 4 106 5 8 1156 2014 221 186 254 155 165 165 165 165 165 165 165	$\begin{array}{c} 0,00\\ 0,00\\ 0,01\\ \hline \\ 0,00\\ 0,07\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ \hline \\ 12,83\\ 1,95\\ 5,04\\ 2,99\\ 0,04\\ 1,03\\ 0,05\\ 0,08\\ 11,26\\ \hline \\ 2,15\\ 1,81\\ 2,47\\ 1,81\\ 2,45\\ \hline \\ 2,15\\ 1,81\\ 2,45\\ 1,8$	0 0 2015 0 2 0 0 0 0 0 0 0 0 0 0 0 0 0	$\begin{array}{c} 0,00\\ 0,00\\ 0,00\\ 0,06\\ \hline \\ 0,00\\ 0$	1,00 1,00 1,00 16,00 <b>Overall</b> 0,00 59,00 5,00 4,00 1,00 <b>Overall</b> 7742,00 1102,00 2993,00 1743,00 52,00 586,00 56,00 46,00 6816,00 <b>Overall</b> 1252,00 1080,00 1422,00	0,01 0,01 0,16 0,00 0,57 0,05 0,04 0,01 0,00 75,40 10,73 29,15 16,98 0,51 5,71 0,55 0,45 66,39 12,19 10,52 13,85	p-value           0,523           0,523           0,392           p-value           NC           <0.001
P (sp) SXT Blood: Salmonella spp CAZ CIP CTX ETP IPM MEM Urine: E. coli AM CAZ CIP CTX ETP FEP IPM MEM SXT Urine: K. pneumoniae CAZ CIP CTX ETP FEP IPM MEM SXT Urine: E. pneumoniae CAZ CIP	0 0 2 2011 0 4 5 4 1 0 2011 924 90 307 134 4 40 8 2 866 2011 110 112 134 2 34	0,00 0,00 0,019 0,00 0,04 0,05 0,04 0,01 0,00 9,00 0,88 2,99 1,31 0,04 0,39 0,08 0,02 8,43 1,07 1,09 1,31 0,02 0,22	1           1           4           2012           0           20           1578           592           304           6           100           12           8           1429           2012           213           200           233           12	0,01 0,01 0,04 0,00 0,19 0,00 0,00 0,00 0,00 0,00 15,37 2,12 5,77 2,96 0,06 0,97 0,12 0,08 13,92 2,07 1,95 2,27 0,02	0         0           0         3           2013         0           26         0           0         0           26         0           0         0           2013         1879           267         728           429         9           148         15           152         1626           2013         270           229         312           17         122	0,00 0,00 0,03 0,00 0,25 0,00 0,00 0,00 0,00 0,00 18,30 2,60 7,09 4,18 0,09 1,44 0,15 0,15 15,84 2,23 3,04 0,17	0 0 1 2014 0 7 0 0 0 0 0 0 0 2014 1317 200 517 307 4 106 5 8 1156 2014 221 186 254 107	0,00 0,00 0,01 0,00 0,07 0,00 0,00 0,00	0 0 2015 0 2 0 0 0 0 0 0 0 0 0 0 0 0 0	$\begin{array}{c} 0,00\\ 0,00\\ 0,00\\ 0,06\\ \hline \\ 0,00\\ 0$	1,00 1,00 1,00 16,00 <b>Overall</b> 0,00 59,00 5,00 4,00 1,00 <b>Overall</b> 7742,00 1102,00 2993,00 1743,00 52,00 586,00 56,00 46,00 <b>6816,00</b> <b>Overall</b> 1252,00 1080,00 1422,00 1422,00 145,00 627,00	$\begin{array}{c} 0,01\\ 0,01\\ 0,01\\ 0,16\\ \hline \end{array}$	p-value           0,523           0,523           0,392           p-value           NC           <0.001
P (sp) SXT Blood: Salmonella spp CAZ CIP CTX ETP IPM MEM Urine: E. coli AM CAZ CIP CTX ETP FEP IPM MEM SXT Urine: K. pneumoniae CAZ CIP CTX ETP FEP IPM MEM SXT Urine: K. pneumoniae CAZ CIP	0 0 2 2011 0 4 5 4 1 0 2011 924 90 307 134 4 40 8 2 866 2011 110 112 134 2 34 4 4	0,00 0,00 0,019 0,00 0,04 0,05 0,04 0,01 0,00 9,00 0,88 2,99 1,31 0,04 0,39 0,08 0,02 8,43 1,07 1,09 1,31 0,02 0,33 0,04	1           1           4           2012           0           20           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           2012           304           6           100           12           8           1429           2012           213           200           233           12           101           8	0,01 0,01 0,04 0,00 0,19 0,00 0,00 0,00 0,00 0,00 15,37 2,12 5,77 2,96 0,06 0,97 0,12 0,08 13,92 2,27 0,12 0,98 0,08	0         0           0         3           2013         0           26         0           0         0           26         0           0         0           2013         1879           267         728           429         9           148         15           155         1626           2013         270           229         312           17         123           6	$\begin{array}{c} 0,00\\ 0,00\\ 0,03\\ \hline \\ 0,00\\ 0,25\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ \hline \\ 18,30\\ 2,60\\ 7,09\\ 4,18\\ 0,09\\ 1,44\\ 0,15\\ 0,15\\ 15,84\\ \hline \\ 2,23\\ 3,04\\ 0,17\\ 1,20\\ 0,06\\ \hline \end{array}$	0 0 1 2014 0 7 0 0 0 0 0 0 0 2014 1317 200 517 307 4 106 5 8 1156 2014 221 186 254 16 107 13 17 107 13 10 107 13 107 13 107 107 107 107 107 107 107 107	0,00 0,00 0,01 0,00 0,07 0,00 0,00 0,00	0 0 2015 0 2 0 0 0 0 2015 2015 2044 327 849 569 29 192 16 13 1739 2015 438 353 489 98 262 85	$\begin{array}{c} 0,00\\ 0,00\\ 0,00\\ 0,06\\ \hline \\ 0,00\\ 0$	1,00 1,00 1,00 16,00 <b>Overall</b> 0,00 59,00 5,00 4,00 1,00 0,00 <b>Overall</b> 7742,00 1102,00 2993,00 1743,00 52,00 56,00 46,00 6816,00 <b>Overall</b> 1252,00 1080,00 1422,00 1422,00 145,00 627,00 116,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 12,00 <b>Overall</b> 12,00 <b>Overall</b> 12,00 <b>Overall</b> 12,00 <b>Overall</b> 12,00 <b>Overall</b> 12,00 <b>Overall</b> 12,00 <b>Overall</b> 12,00 <b>Overall</b> 12,00 <b>Overall</b> 12,00 <b>Overall</b> 12,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,00 <b>Overall</b> 10,000 <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Overall</b> <b>Ove</b>	0,01 0,01 0,16 0,00 0,57 0,05 0,04 0,01 0,00 75,40 10,73 29,15 16,98 0,51 5,71 0,55 0,45 66,39 12,19 10,52 13,85 1,41 6,11 1,13	p-value           0,523           0,523           0,392           p-value           NC           <0.001
P (sp) SXT Blood: Salmonella spp CAZ CIP CTX ETP IPM MEM Urine: E. coli AM CAZ CIP CTX ETP FEP IPM MEM SXT Urine: K. pneumoniae CAZ CIP CTX ETP FEP IPM MEM SXT Urine: K. pneumoniae	0 0 2 2011 0 4 5 4 1 0 2011 924 90 307 134 4 40 8 2 866 2011 110 112 134 2 34 4 4 4	0,00 0,00 0,019 0,04 0,05 0,04 0,01 0,00 9,00 0,88 2,99 1,31 0,04 0,39 0,08 0,02 8,43 1,07 1,09 1,31 0,02 0,33 0,04 0,04 0,04	1           1           4           2012           0           20           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           1578           218           592           304           6           100           12           8           1429           2012           213           200           233           12           101           8           6	0,01 0,01 0,04 0,00 0,19 0,00 0,00 0,00 0,00 0,00 15,37 2,12 5,77 2,96 0,06 0,97 0,12 0,08 13,92 2,07 1,95 2,27 0,12 0,98 0,08 0,08 0,00 0,00	0         0           0         3           2013         0           26         0           0         26           0         0           26         0           0         0           26         0           0         0           26         0           0         0           2013         1879           267         728           429         9           148         15           15         1626           2013         270           229         312           17         123           6         16	$\begin{array}{c} 0,00\\ 0,00\\ 0,03\\ \hline \\ 0,00\\ 0,25\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ \hline \\ 18,30\\ 2,60\\ 7,09\\ 4,18\\ 0,09\\ 1,44\\ 0,15\\ 0,15\\ 15,84\\ \hline \\ 2,63\\ 2,23\\ 3,04\\ 0,17\\ 1,20\\ 0,06\\ 0,16\\ \hline \end{array}$	0 0 1 2014 0 7 0 0 0 0 0 0 2014 1317 200 517 307 4 106 5 8 1156 2014 221 186 254 16 107 13 14	$\begin{array}{c} 0,00\\ 0,00\\ 0,01\\ \hline \\ 0,00\\ 0,07\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ \hline \\ 12,83\\ 1,95\\ 5,04\\ 2,99\\ 0,04\\ 1,03\\ 0,05\\ 0,08\\ 11,26\\ \hline \\ 2,15\\ 1,81\\ 2,47\\ 0,16\\ 1,04\\ 0,13\\ 0,14\\ \hline \end{array}$	0 0 2015 0 2 0 0 0 0 0 0 0 2015 2044 327 849 569 29 192 16 13 1739 2015 438 353 489 98 262 85 92	$\begin{array}{c} 0,00\\ 0,00\\ 0,00\\ 0,06\\ \hline \\ 0,00\\ 0$	1,00 1,00 1,00 16,00 <b>Overall</b> 0,00 59,00 5,00 4,00 1,00 0,00 <b>Overall</b> 7742,00 1102,00 2993,00 1743,00 52,00 56,00 46,00 6816,00 <b>Overall</b> 1252,00 1422,00 1422,00 1422,00 1422,00 116,00 132,00	$\begin{array}{c} 0,01\\ 0,01\\ 0,16\\ \hline \\ 0,00\\ 0,57\\ 0,05\\ 0,04\\ 0,01\\ 0,00\\ \hline \\ 75,40\\ 10,73\\ 29,15\\ 16,98\\ 0,51\\ 5,71\\ 0,55\\ 0,45\\ 66,39\\ \hline \\ 12,19\\ 10,52\\ 13,85\\ 1,41\\ 6,11\\ 1,13\\ 1,29\\ \hline \end{array}$	p-value           0,523           0,392           p-value           NC           <0.001
P (sp) SXT Blood: Salmonella spp CAZ CIP CTX ETP IPM MEM Urine: E. coli AM CAZ CIP CTX ETP FEP IPM MEM SXT Urine: K. pneumoniae CAZ CIP CTX ETP FEP IPM MEM SXT CIP CTX ETP FEP IPM MEM SXT	0 0 2 2011 0 4 5 4 1 0 2011 924 90 307 134 4 40 8 2 866 2011 110 112 134 2 34 4 4 222	0,00 0,00 0,019 0,00 0,04 0,05 0,04 0,01 0,00 9,00 0,88 2,99 1,31 0,04 0,39 0,08 0,02 8,43 1,07 1,09 1,31 0,02 0,33 0,04 0,04 0,04 2,16	1           1           4           2012           0           20           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           0           1578           218           592           304           6           100           12           8           1429           2012           213           2000           233           12           101           8           6           341	$\begin{array}{c} 0.01\\ 0.01\\ 0.04\\ \hline \\ 0.00\\ 0.19\\ 0.00\\ 0.00\\ 0.00\\ \hline \\ 0.00\\ 0.00\\ \hline \\ 15,37\\ 2.12\\ 5,77\\ 2.96\\ 0.06\\ 0.97\\ 0.12\\ 0.08\\ 13,92\\ \hline \\ 2.07\\ 1.95\\ 2.27\\ 0.12\\ 0.98\\ 0.06\\ \hline \\ 0.98\\ 0.06\\ \hline \\ 3.32\\ \hline \end{array}$	0         0           0         3           2013         0           26         0           0         0           267         728           429         9           148         15           1626         2013           270         229           312         17           123         6           16         411	$\begin{array}{c} 0,00\\ 0,00\\ 0,03\\ \hline \\ 0,00\\ 0,25\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ \hline \\ 18,30\\ 2,60\\ 7,09\\ 4,18\\ 0,09\\ 1,44\\ 0,15\\ 0,15\\ 15,84\\ \hline \\ 2,c3\\ 3,04\\ 0,17\\ 1,20\\ 0,06\\ 0,16\\ 4,00\\ \hline \end{array}$	0 0 1 2014 0 7 0 0 0 0 0 0 0 2014 1317 200 517 307 4 106 5 8 1156 2014 221 186 254 16 107 13 14 335	$\begin{array}{c} 0,00\\ 0,00\\ 0,01\\ \hline \\ 0,00\\ 0,07\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ \hline \\ 12,83\\ 1,95\\ 5,04\\ 2,99\\ 0,04\\ 1,03\\ 0,05\\ 0,08\\ 11,26\\ \hline \\ 2,15\\ 1,81\\ 2,47\\ 0,16\\ 1,04\\ 0,13\\ 0,14\\ 3,26\\ \hline \end{array}$	0           0           6           2015           0           2           0           2015           438           353           489           98           262           85           92           569	$\begin{array}{c} 0.00\\ 0.00\\ 0.00\\ 0.06\\ \hline \\ 0.00\\ 0$	1,00 1,00 1,00 16,00 <b>Overall</b> 0,00 59,00 5,00 4,00 1,00 0,00 <b>Overall</b> 7742,00 1742,00 1742,00 1743,00 52,00 56,00 46,00 6816,00 <b>Overall</b> 1252,00 1452	$\begin{array}{c} 0,01\\ 0,01\\ 0,01\\ 0,16\\ \hline \end{array}$	p-value           0,523           0,523           0,392           p-value           NC           <0.001
P (sp) SXT Blood: Salmonella spp CAZ CIP CTX ETP IPM MEM Urine: E. coli AM CAZ CIP CTX ETP FEP IPM MEM SXT Urine: K. pneumoniae CAZ CIP CTX ETP FEP IPM MEM SXT Urine: Salmonella	0 0 2 2011 0 4 5 4 1 0 2011 924 90 307 134 4 40 8 2 2011 112 134 2 34 4 4 222 2011	0,00         0,00         0,019         0,04         0,05         0,04         0,00         9,00         0,88         2,99         1,31         0,04         0,02         8,43         1,07         1,31         0,02         0,33         0,04         0,02         1,31         0,02         0,33         0,04         0,04	1           1           4           2012           0           20           0           0           0           0           0           0           0           0           0           0           0           0           2012           1578           218           592           304           6           100           12           8           1429           2012           213           2000           233           12           101           8           6           341           2012	$\begin{array}{c} 0,01\\ 0,01\\ 0,04\\ \hline \\ 0,00\\ 0,19\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ \hline \\ 0,97\\ 0,12\\ 0,08\\ 13,92\\ \hline \\ 2,27\\ 0,12\\ 0,98\\ 0,06\\ \hline \\ 3,32\\ \hline \end{array}$	0         0           0         3           2013         0           26         0           0         0           267         728           429         9           148         15           155         1626           2013         270           229         312           17         123           6         16           411         2013	$\begin{array}{c} 0,00\\ 0,00\\ 0,03\\ \hline \\ 0,00\\ 0,25\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ \hline \\ 18,30\\ 2,60\\ 7,09\\ 4,18\\ 0,09\\ 1,44\\ 0,15\\ 0,15\\ 15,84\\ \hline \\ 2,63\\ 2,23\\ 3,04\\ 0,17\\ 1,20\\ 0,06\\ 0,16\\ 4,00\\ \hline \end{array}$	0 0 1 2014 0 7 0 0 0 0 0 0 0 2014 1317 200 517 307 4 106 5 8 1156 2014 221 186 254 16 107 13 14 335 2014	$\begin{array}{c} 0,00\\ 0,00\\ 0,01\\ \hline \\ 0,00\\ 0,07\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ \hline \\ 12,83\\ 1,95\\ 5,04\\ 2,99\\ 0,04\\ 1,03\\ 0,05\\ 0,08\\ 11,26\\ \hline \\ 2,15\\ 1,81\\ 2,47\\ 0,16\\ 1,04\\ 0,13\\ 0,14\\ 3,26\\ \hline \end{array}$	0 0 2015 0 2 0 0 0 0 2 0 0 0 0 2 0 0 0 0 2 0 0 0 0 2 0 0 0 0 2 0 0 0 0 0 0 2 0 0 0 0 0 0 0 0 0 0 0 0 0	$\begin{array}{c} 0.00\\ 0.00\\ 0.00\\ 0.06\\ \hline \\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ \hline \\ 0.00\\ 0.00\\ \hline \\ 0.00\\ 0.00\\ \hline \\ 0.00\\ \hline 0.00\\ \hline \\ 0.00\\ \hline 0.00\\ \hline$	1,00 1,00 1,00 16,00 <b>Overall</b> 0,00 59,00 5,00 4,00 1,00 0,00 <b>Overall</b> 7742,00 1102,00 2993,00 1743,00 52,00 586,00 56,00 46,00 6816,00 <b>Overall</b> 1252,00 1080,00 1422,00 145,00 627,00 116,00 132,00 1878,00 <b>Overall</b>	$\begin{array}{c} 0,01\\ 0,01\\ 0,01\\ 0,16\\ \hline \end{array}$	p-value           0,523           0,523           0,392           p-value           NC           <0.001
P (sp) SXT Blood: Salmonella spp CAZ CIP CTX ETP IPM MEM Urine: E. coli AM CAZ CIP CTX ETP FEP IPM MEM SXT Urine: K. pneumoniae CAZ CIP CTX ETP FEP IPM MEM SXT FEP IPM MEM SXT Faeces: Salmonella spp. CAZ	0 0 2 2011 0 4 5 4 1 0 2011 924 90 307 134 4 40 8 2 2011 110 112 134 2 34 4 4 2 2011 2 2 2 2 2 2 2 2 2 2 2 2 2	0,00 0,00 0,019 0,00 0,04 0,05 0,04 0,00 0,00 9,00 0,88 2,99 1,31 0,04 0,39 0,08 0,02 8,43 1,07 1,09 1,31 0,02 0,33 0,04 0,04 2,16	1         4         2012         0         20         2012         12         8         1429         2012         213         2000         233         12         101         8         6         341         2012         2	0,01 0,01 0,04 0,00 0,19 0,00 0,00 0,00 0,00 0,00 0,00	0         0           0         3           2013         0           26         0           0         0           267         728           429         9           148         15           15         1626           2013         270           229         312           17         123           6         16           411         2013           0         0	0,00 0,00 0,03 0,00 0,25 0,00 0,00 0,00 0,00 0,00 0,00	0 0 1 2014 0 7 0 0 0 0 0 0 2014 1317 200 517 307 4 106 5 8 1156 2014 221 186 254 16 107 13 14 335 2014 0 0 0 0 0 0 0 0 0 0 0 0 0	0,00 0,00 0,01 0,00 0,07 0,00 0,00 0,00	0 0 2015 0 2 0 0 0 0 0 2 0 0 0 0 0 2 0 0 0 0 0 2 0 0 0 0 2 0 0 0 0 0 0 0 2 0 0 0 0 0 0 0 0 0 0 0 0 0	$\begin{array}{c} 0,00\\ 0,00\\ 0,00\\ 0,06\\ \end{array}$ $\begin{array}{c} 0,00\\ 0,02\\ 0,00\\ 0,$	1,00 1,00 1,00 16,00 <b>Overall</b> 0,00 59,00 5,00 4,00 1,00 0,00 <b>Overall</b> 7742,00 1742,00 1743,00 52,00 586,00 56,00 46,00 6816,00 <b>Overall</b> 1252,00 1080,00 1422,00 145,00 627,00 116,00 132,00 1878,00 <b>Overall</b> 6,00 <b>Overall</b> 1252,00 16,00 16,00 16,00 1252,00 116,00 16,00 1252,00 16,00 16,00 1252,00 10,00 110,00 1252,00 10,00 1252,00 10,000 145,00 16,00 17,00 17,00 16,00 17,00 16,	$\begin{array}{c} 0,01\\ 0,01\\ 0,01\\ 0,16\\ \hline \end{array}$	p-value           0,523           0,523           0,392           p-value           NC           <0.001
P (sp) SXT Blood: Salmonella spp CAZ CIP CTX ETP IPM MEM Urine: E. coli AM CAZ CIP CTX ETP FEP IPM MEM SXT Urine: K. pneumoniae CAZ CIP CTX ETP FEP IPM MEM SXT Urine: S. almonella spp. CAZ CIP	0 0 2 2011 0 4 5 4 1 0 2011 924 90 307 134 4 40 8 8 8 6 2011 112 134 2 34 4 4 222 2011 3 5	0,00 0,00 0,019 0,00 0,04 0,05 0,04 0,01 0,00 9,00 0,88 2,99 1,31 0,04 0,39 0,08 0,02 8,43 1,07 1,09 1,31 0,02 0,33 0,04 0,04 2,16 0,03 0,05	1           1           4           2012           0           20           0           0           0           0           0           0           0           0           0           0           0           0           2012           1578           592           304           6           100           12           8           1429           2012           213           2000           233           12           101           8           6           341           2012           2           13	0,01 0,01 0,04 0,00 0,19 0,00 0,00 0,00 0,00 0,00 0,00	0         0           0         3           2013         0           26         0           0         0           267         728           429         9           148         15           155         1626           2013         270           229         312           17         123           6         16           411         2013           0         34	$\begin{array}{c} 0,00\\ 0,00\\ 0,03\\ \hline \\ 0,00\\ 0,25\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ \hline \\ 18,30\\ 2,60\\ 7,09\\ 4,18\\ 0,00\\ 1,44\\ 0,15\\ 15,84\\ \hline \\ 2,63\\ 2,23\\ 3,04\\ 0,17\\ 1,20\\ 0,06\\ 0,16\\ 4,00\\ \hline \\ 0,00\\ 0,33\\ \hline \end{array}$	0 0 1 2014 0 7 0 0 0 0 0 2014 1317 200 517 307 4 106 5 8 1156 2014 221 186 254 16 107 13 14 335 2014 0 7 0 7 0 0 0 0 0 0 0 0 0 0 0 0 0	$\begin{array}{c} 0,00\\ 0,00\\ 0,01\\ \hline \\ 0,00\\ 0,07\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ \hline \\ 12,83\\ 1.95\\ 5.04\\ 2.99\\ 0.04\\ 1.03\\ 0.05\\ 0.08\\ 11,26\\ \hline \\ 2,15\\ 1.81\\ 2.47\\ 0.16\\ 1.04\\ 0.13\\ 0.14\\ 3.26\\ \hline \\ 0,00\\ 0.07\\ \hline \end{array}$	0 0 2015 0 2 0 0 0 0 2 0 0 0 0 0 2 0 0 0 2 0 0 0 0 2 0 0 0 0 0 0 2 0 0 0 0 2 0 0 0 0 0 0 0 0 0 0 0 0 0	$\begin{array}{c} 0,00\\ 0,00\\ 0,00\\ 0,06\\ \hline \end{array}$	1,00 1,00 1,00 16,00 <b>Overall</b> 0,00 59,00 5,00 4,00 1,00 <b>Overall</b> 7742,00 1742,00 1742,00 1743,00 52,00 586,00 56,00 46,00 6816,00 <b>Overall</b> 1252,00 1080,00 1422,00 145,00 627,00 116,00 132,00 1878,00 <b>Overall</b> 6,00 68,00	0,01           0,01           0,16           0,00           0,57           0,05           0,04           0,01           0,00           75,40           10,73           29,15           16,98           0,51           5,71           0,55           0,45           66,39           12,19           10,52           13,85           1,41           6,11           1,13           1,29           18,29           0,06           0,66	p-value           0,523           0,523           0,392           p-value           NC           <0.001
P (sp) SXT Blood: Salmonella spp CAZ CIP CTX ETP IPM MEM Urine: E. coli AM CAZ CIP CTX ETP FEP IPM MEM SXT Urine: K. pneumoniae CAZ CIP CTX ETP FEP IPM MEM SXT Urine: K. pneumoniae CAZ CIP CTX ETP FEP IPM MEM SXT Faeces: Salmonella spp. CAZ CIP CTX	0 0 2 2011 0 4 5 4 1 0 2011 924 90 307 134 4 4 4 4 2 2011 110 112 134 2 34 4 4 222 2011 3 5 14	0,00 0,00 0,019 0,00 0,04 0,05 0,04 0,01 0,00 9,00 0,88 2,99 1,31 0,04 0,39 0,08 0,02 8,43 1,07 1,09 1,31 0,02 0,33 0,04 0,04 0,02 0,33 0,04 0,04 0,05 0,04 0,00 0,00 0,00 0,00 0,04 0,00 0,00 0,04 0,00 0,00 0,04 0,00 0,04 0,00 0,04 0,00 0,04 0,00 0,04 0,00 0,04 0,00 0,04 0,02 0,04 0,02 0,03 0,04 0,02 0,33 0,04 0,05 0,04 0,05 0,04 0,05 0,04 0,02 0,33 0,04 0,05 0,04 0,05 0,05 0,04 0,05 0,04 0,05 0,02 0,33 0,04 0,05 0,04 0,05 0,04 0,05 0,04 0,05 0,04 0,05 0,04 0,05 0,04 0,05 0,04 0,05 0,04 0,05 0,04 0,05 0,04 0,05 0,04 0,05 0,04 0,05 0,04 0,05 0,04 0,05 0,04 0,05 0,04 0,05 0,04 0,05 0,014	1           1           4           2012           0           20           0           0           0           0           0           0           0           0           0           0           0           0           2012           1578           592           304           6           100           12           8           1429           2012           213           2000           233           12           101           8           6           341           2           13           2	0,01 0,01 0,04 0,00 0,19 0,00 0,00 0,00 0,00 0,00 0,00	0         0           0         3           2013         0           26         0           0         0           267         728           429         9           148         15           155         1626           2013         270           229         312           17         123           6         16           411         2013           0         34           0         34	$\begin{array}{c} 0,00\\ 0,00\\ 0,03\\ \hline \\ 0,00\\ 0,25\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ \hline \\ 18,30\\ 2,60\\ 7,09\\ 4,18\\ 0,00\\ 1,44\\ 0,15\\ 0,15\\ 15,84\\ \hline \\ 2,63\\ 2,23\\ 3,04\\ 0,17\\ 1,20\\ 0,06\\ 0,16\\ 4,00\\ \hline \\ 0,00\\ 0,33\\ 0,00\\ \hline \end{array}$	0 0 1 2014 0 7 0 0 0 0 2014 1317 200 517 307 4 106 5 8 1156 2014 221 186 254 16 107 13 14 335 2014 0 7 0 0 0 0 0 0 0 0 0 0 0 0 0	$\begin{array}{c} 0,00\\ 0,00\\ 0,01\\ \hline \\ 0,00\\ 0,07\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ 0,00\\ \hline \\ 12,83\\ 1.95\\ 5,04\\ 2.99\\ 0,04\\ 1,03\\ 0,05\\ 0,08\\ 11,26\\ \hline \\ 2,15\\ 1.81\\ 2.47\\ 0,16\\ 1.04\\ 0,13\\ 0,14\\ 3,26\\ \hline \\ 0,00\\ 0,07\\ 0,00\\ \hline \end{array}$	0 0 2015 0 2 0 0 0 0 2 0 0 0 0 2 0 0 0 0 2 0 0 0 0 2 0 0 0 0 0 0 2 0 0 0 0 0 0 0 0 0 0 0 0 0	$\begin{array}{c} 0,00\\ 0,00\\ 0,00\\ 0,06\\ \hline \end{array}$	1,00 1,00 1,00 16,00 <b>Overall</b> 0,00 59,00 5,00 4,00 1,00 <b>Overall</b> 7742,00 1102,00 2993,00 1743,00 52,00 586,00 56,00 46,00 6816,00 <b>Overall</b> 1252,00 1422,00 145,00 627,00 116,00 132,00 1878,00 <b>Overall</b> 6,00 68,00 18,00	0,01           0,01           0,01           0,16           0,00           0,57           0,05           0,04           0,01           0,00           75,40           10,73           29,15           16,98           0,51           5,71           0,55           0,45           66,39           12,19           10,52           13,85           1,41           6,11           1,13           1,29           18,29           0,06           0,66           0,18	p-value           0,523           0,523           0,392           p-value           NC           <0.001

ETP	11	0,11	0	0,00	0	0,00	0	0,00	0	0,00	11,00	0,11	< 0.001
IPM	0	0,00	0	0,00	0	0,00	0	0,00	0	0,00	0,00	0,00	NC
MEM	0	0,00	0	0,00	0	0,00	0	0,00	0	0,00	0,00	0,00	NC
Faeces: Shigella spp.	2011		2012		2013		2014		2015		Overall		p-value
CAZ	0	0,00	0	0,00	0	0,00	0	0,00	1	0,01	1,00	0,01	1,000
CIP	0	0,00	0	0,00	0	0,00	1	0,01	2	0,02	3,00	0,03	0,646
CTX	0	0,00	0	0,00	2	0,02	4	0,04	7	0,07	13,00	0,13	0,152
N. gonorrhoea	2011		2012		2013		2014		2015		Overall		p-value
CIP (ng)	0	0,00	0	0,00	0	0,00	0	0,00	1	0,01	1,00	0,01	NC
Population		10267300											

# **References:**

- Global Action Plan on Antimicrobial Resistance [Internet]. Geneva: World Health Organisation; 2015[cited 2016 Jun 12]. 19 p. Available from: http://www.who.int/drugresistance/global\_action\_plan/en/
- Global Antimicrobial Surveillance System: Manual for Early Implementation [Internet]. Geneva: World Health Organisation; 2015 [cited 2016 Feb 26]. 36 p. Available from: <u>http://www.who.int/drugresistance/surveillance/en/</u>
- Perovic O, Iyaloo S, Kularatne R, Lowman W, Bosman N, Wadula J, Seetharam S, Duse A, Mbelle N, Bamford C, Dawood H, Mahaber Y, Bhola P, Abrahams S, Singh-Moodley A. Prevalence and Trends of Staphylococcus aureus Bacteraemia in Hospitalized Patients in South Africa, 2010 to 2012: Laboratory-Based Surveillance Mapping of Antimicrobial Resistance and Molecular Epidemiology. PLoS ONE [Internet]. 2015 Dec [cited 2017 Nov 20] 10(12): 1-14. Available from: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0145429.

doi:10.1371/journal.pone.0145429

- Perovic O, Duse A, Elliott G, Swe Swe-Han K, Kularatne R, Lowman W, Nana T, Lekalakala R, Fortuin de-Smidt M, Marais E. National sentinel site surveillance for antimicrobial resistance in Klebsiella pneumoniae isolates in South Africa, 2010 2012. S Afr Med J [Internet]. 2014 Aug [cited 2017 Dec 2] 104(8): 563-568. Available from: http://www.samj.org.za/index.php/samj/article/view/7617. doi:10.7196/SAMJ.7617
- 5. Census 2011 South Africa [Internet]. (place unknown): Adrian Frith. 2011. Place 5, KwaZulu Natal; [cited 2017 Dec 2]. Available from: https://census2011.adrianfrith.com/place/5
- Gelband H, Duse, A. The Global Antibiotic Resistance Partnership (GARP): Executive Summary. S Afr Med J [Internet]. 2011 Aug [cited 2017 Jul 16] 101(8): 552-555. Available from: http://www.samj.org.za/index.php/samj/article/view/5091
- Crowther-Gibson P, Govender N, Lewis DA, Bamford C, Brink A. Part IV. GARP: Human Infections and Antibiotic Resistance. S Afr Med J [Internet]. 2011 Aug [cited 2017 Jul 16] 101(8): 567-578. Available from: http://www.samj.org.za/index.php/samj/article/view/5102. doi:10.7196/SAMJ.5102.
- Crowther-Gibson P, Erasmus L, Govender N, Keddy K, Perovic O, Quan V, von Gottberg A, von Mollendorf C. GERMS South Africa Anual Report 2015. Johannesburg: National Institute for Communicable Diseases [Internet] 2015 [cited 2017 Dec 5] 36p. Available from: http://www.nicd.ac.za/index.php/publications/germs-annual-reports/
- National Institute for Communicable Diseases: Centre for Healthcare-Associated Infections, Antimicrobial Resistance and Mycoses [Internet]. (place unknown): National Institute for Communicable Diseases; c2017.: Research and Surveillance. 2017 [cited 2017 Dec 3].
Available from: http://www.nicd.ac.za/index.php/centres/centre-for-healthcare-associated-infections-antimicrobial-resistance-and-mycoses/

- 10. Standard Treatment Guidelines and Essential Medicines List for South Africa: Hospital Level (Adults) 4<sup>th</sup> ed [internet]. Republic of South Africa: National Department of Health; 2015 [cited 2017 Oct 28]. p 1.16; 7.15 7.16. Available from: http://www.health.gov.za/index.php/component/phocadownload/category/286-hospital-level-adults
- 11. Wasserman S, Boyles T, Mendelson M. A Pocket Guide to Antibiotic Prescribing for Adults in South Africa, 2015 [Internet]. [place unkown] Federation of Infectious Diseases Societies of Southern Africa; 2015 [ cited 2017 Nov 1]. p40 – 44, 49 – 50. Available from: http://www.fidssa.co.za/Content/Documents/SAASP\_Antibiotic\_Guidelines\_2015.pdf
- Ballot DE, Nana T, Sriruttan C, Cooper PA. Bacterial Bloodstream Infections in Neonates in a Developing Country. ISRN Paediatrics [Internet]. 2012 [cited 2017 Dec 4] 2012: 6p. Available from: https://www.hindawi.com/archive/2012/508512/. http://dx.doi.org/10.5402/2012/508512
- 13. Perovic O, Chetty V, Iyaloo S. Antimicrobial Resistance Surveillance from Sentinel Public Hospitals, South Africa, 2014. Communicable Diseases Surveillance Bulletin [Internet]. 2014: 13(1): 12p. Available from: http://www.nicd.ac.za/assets/files/Antimicrobial%20resistance%20surveillance.pdf
- 14. Ramsamy Y, Muckart DJJ, Han KSS. Microbiological surveillance and antimicrobial stewardship minimise the need for ultrabroad-spectrum combination therapy for treatment of nosocomial infections in a trauma intensive care unit: An audit of an evidence-based empiric antimicrobial policy. S Afr Med J[Internet]. 2013 Mar [cited 2017 Dec 4] 103 (6): 371 -376. Available from: http://www.samj.org.za/index.php/samj/article/view/6459/5121. DOI:10.7196/SAMJ.6459
- 15. Fortuin de-Smidt MC, Singh-Moodley A, Badat R, Quan V, Kularatne R, Nana T, Lekalala R, Govender NP, Perovic O. Staphylococcus aureus bacteraemia in Gauteng academic hospitals, South Africa. Int J Infect Dis [Internet]. 2015 Jan [cited 2017 Dec 4] 30: 41 48. Available from: http://www.ijidonline.com/article/S1201-9712(14)01658-0/fulltext. DOI: http://dx.doi.org/10.1016/j.ijid.2014.10.011
- CJ, Fernandes LA, Collignon P. Cefoxitin resistance as a surrogate marker for the detection of methicillin-resistant Staphylococcus aureus. J Antimicrob Chemother [Internet]. 2005 Apr [cited 2017 Dec 4] 55(4): 506 – 510. Available from: https://academic.oup.com/jac/article/55/4/506/801206 . https://doi.org/10.1093/jac/dki052

- 17. Antimicrobial resistance: global report on surveillance [Internet]. Geneva: World Health Organisation; 2014 [cited 2017 Nov 10]. 232 p. Available from: http://www.who.int/drugresistance/documents/surveillancereport/en/
- Coetzee J, Corcoran C, Prentice E, Moodley M, Mendelson M, Poirel L, Nordmann P, Brink AJ. Emergence of plasmid-mediated colistin resistance (MCR-1) among Escherichia coli isolated from South African patients. S Afr Med J [Internet]. 2016 May [cited 2017 Dec 4] 106(5): 449 – 450. Available from: http://www.samj.org.za/index.php/samj/article/view/10710/7298. DOI:10.7196/SAMJ.2016.v106i5.10710
- Essack SY, Connolly C. Treatment guidelines and nosocomial infections: The South African experience. Afr J Microbiol Res [Internet]. 2011 Sep [cited 2017 Dec 4] 5(2): 3122 – 3125. Available from: http://www.academicjournals.org/journal/AJMR/articleabstract/6A4230113436. DOI: 10.5897/AJMR10.346

### **CHAPTER 3: CONCLUSION, LIMITATIONS AND RECOMMENDATIONS**

### **3.1** Conclusion

A retrospective analysis of trends in antibiotic resistance (ABR) was conducted on data obtained from six public hospitals in KwaZulu Natal. The specimen types, pathogens and antibiotics included in the study were based on the guidelines published in the GLASS manual for early implementation. MIC and percentage resistance data was compiled for priority pathogens from blood, urine, faecal and urethral/ cervical samples representing blood stream infections (BSIs), urinary tract infections (UTIs), acute diarrhoeal infections and gonorrhoeal infections. The antibiotic resistance data was stratified by year and analysed on 3 levels: (1) a trend analysis of resistance including MIC50, MIC90, MIC ranges and percentage resistance over 5 years was conducted; (2) selected metrics recommended in the GLASS manual were calculated and (3) susceptibility data was compared with existing standard treatment guidelines.

The following were the main conclusions in relation to the aim and objectives:

- 1. A database of BSIs, UTIs, diarrhoeal infections and gonorrhoeal infections was generated including specimen type, isolate identification and AST data.
- 2. The proportion of BSIs, UTIs and diarrhoeal infections caused by the respective pathogens of interest were summarised as follows:
  - Urine samples accounted for 61% (n= 33 018) of all isolates included in the study
  - *E. coli* from blood and urine samples was the most commonly isolated pathogen (52%, n= 33 018)
  - Of the 11 722 positive blood samples, the most common causative pathogens were *S. aureus* (32%), *K. pneumoniae* (26%) *and E. coli* (18%).
  - Of the 20 212 positive urine samples, the most common causative pathogens were *E. coli* (75%) followed by *K. pneumoniae* (25%).
  - Of the 916 stool samples, the most common causative pathogens were *Shigella spp*. (67%) *and Salmonella spp*. (33%)
  - Only 168 gonorrhoeal infections were explored over the 5year period.
- 3. The trends in resistance between 2011 and 2015 were as follows:
  - The majority of isolates were multi-drug resistant
  - Resistance to third and fourth generation cephalosporins and fluoroquinolones increased in *K. pneumoniae*, *E. coli* and *Shigella spp.* isolates as did carbapenem resistance in *K. pneumoniae* and *E. coli*.
  - Resistance in *A. baumannii* and *Salmonella spp.* isolates decreased or plateaued against all antibiotics.
- 4. In terms of standard treatment guidelines:

- BSIs: Treatment guidelines were only available for *S. aureus*. Susceptibility to vancomycin was 97% (n= 1368)
- Only 50 68%% of UTIs were treatable with the first line agents ciprofloxacin and amoxicillin-clavulanate.
- Seventy-five percent and 99% of the 145 and 319 diarrhoeal infections caused by Salmonella spp. and Shigella spp. could be have been successfully treated with ciprofloxacin

# 3.2. Limitations:

- 5. Antibiotic susceptibility data was only available for samples positive for bacterial growth.
- 6. Only 6 out of 71 public hospitals in KwaZulu Natal were included in the study.
- 7. Available data did not allow stratification into community and hospital acquired infections.
- 8. As a retrospective study, the data was limited to what was already captured in the National Health Laboratory Services (NHLS) database
- 9. The results may not be representative of the true extent of ABR in KwaZulu Natal as not all infections necessarily generate a sample for microbiological evaluations because of time and resource constraints. Additionally, not all ill patients seek treatment due to difficulties in accessing healthcare as well as reliance on cultural healing methods.
- 10. The data was collected before the release of the GLASS manual by the WHO and therefore does not meet all the requirements stipulated therein.

# 3.3. Recommendations:

- Robust, representative surveillance is necessary to establish a baseline of ABR in KwaZulu Natal and South Africa.
- More facilities should be included in future studies including community health centres and private facilities in order for data to be accurately representative of the true extent of ABR in community and hospital settings.
- Data capturing standards should be improved to minimise the number of entries that had to be excluded and to allow better correlation of demographic and clinical data with resistance trends.
- Standard treatment guidelines should be informed by surveillance data to ensure the efficacy of empiric treatment.
- Increasing resistance to cephalosporins and fluoroquinolones, which are commonly used in the treatment of infections caused by *E. coli, K. pneumoniae, Salmonella spp. and Shigella spp.*, should be monitored and the treatment guidelines modified according to latest surveillance data.

• The increasing incidence of carbapenem resistance, especially in *K. pneumoniae*, should be monitored.

# 3.4. Significance:

- To our knowledge, this is the first South African report on ABR using GLASS metrics.
- This study implemented the GLASS methodology and is therefore an indication of the capacity to implement surveillance according to these standards in South Africa. Shortcomings of this study can be used to improve the design of future studies so that better quality and representative data can be obtained.
- According to the 2014 WHO report on surveillance, data on ABR in the Africa region is scarce and there is limited evidence available on the true extent of ABR in the region (World Health Organisation, 2014). This study somewhat addresses this surveillance gap in a single province of KwaZulu-Natal in South Africa.

# **References:**

World Health Organisation, 2014. *Antimicrobial Resistance Global Report on Surveillance. [Online]* Available at: http://www.who.int/drugresistance/documents/surveillancereport/en/ [Accessed 10 December 2017]