ADC 2016 Report
on Bacterial Resistance in Cultures
from SEHOS and General Practitioners
in Curaçao

Willemstad, November 2017

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1. Executive Summary

The department of Microbiology at ADC periodically reports on antibiotic resistance in the bacteria that are isolated from cultures received from the Sint Elisabeth Hospital (SEHOS) and from general practitioners.
Analyzed and reported in a format that is similar to formats like WHONET, EARSS and NethMap, these data provide insight in the current state of antibiotic resistance in Curaçao.
The data is primarily geared towards decision-making in the medical field: professionals who need to choose optimal *empirical* antibiotics for patients with life-threatening infections in the hospital as well as the general practitioner needing to know how effective empirical antibiotics for urinary tract infections are going to be. For policymakers at various levels, the data can be used to assess the efficacy of interventions in antimicrobial stewardship activities, assess the need for new antibiotics and compare the situation of Curaçao to other countries.

Looking at the data in the 2016 report, gram-positive bacteria, most notably MRSA, and gram-negative resistance are a reason for concern. The presence of MRSA in bloodcultures is indicative of a far larger reservoir of MRSA in patients. The prevalence of MRSA in patients has to be high in order to result in actual cases of MRSA sepsis. The data in this report suggest that efforts to counter MRSA in SEHOS indeed reduce the numbers of sepsis caused by MRSA.
Gram-negative bacteria can become resistant to all antibiotics in the medical arsenal. The gram-negatives reported here indeed illustrate that ability. Carbapenems represent a last-resort antibiotic and resistance to carbapenem antibiotics should be a priority in any effort to counter antibiotic resistance.

Clindamycin and ciprofloxacin data as well as 3rd generation cephalosporins are all represented in this report. All have their own resistance rates and dynamics in time, when looking at the years under observation. It is currently not possible to expect efficacy from these antibiotics when, used empirically, due to the rates of resistance present. If resistance can be reduced effectively, these antibiotics may become a reliable empirical choice once again.

It must be encouraging to all participants in the field of medicine that many trends indeed show improvement over the years reported here. It is a compliment to all who take care when prescribing antibiotics by doing this with caution and by adhering to guidance. It shows that all the effort to monitor and counter the spread of resistant bacteria is effective and indeed can reverse the trend of ever increasing resistance to antibiotics. If Curaçao keeps up its efforts to counter the threats of antibiotic resistance, physicians can keep on prescribing cheap and trusted antibiotics with good effects and avoid the dreadful ‘post-antibiotic era’ where healthcare outcomes are severely impacted negatively by the evolving antibiotic resistance in our bacteria.

2. Introduction

This is ADC's 2016 annual report on bacterial resistance in Curaçao. It shows the presence of resistance to the most common antibiotics used in the local medical field. The report is meant to serve clinicians and policy-makers with periodical reports on bacterial resistance.

Just like in the previous analysis, results from repeated testing were filtered out to avoid bias. Filtering for repeated cultures was done equal to WHONET or NethMap methods. Only the first species per material per person per year is included. This method delivers figures that are very suitable to base empirical therapies upon, in and outside the hospital. It does however underestimate the total burden of antibiotic resistance encountered in the clinic. Patients with infections that are more difficult to treat, are likely to visit their doctor more often and get cultured more frequently. Bacteria can acquire more resistance over the course of time, yet any isolates that were cultured later in time, are excluded from the analysis.

The data reported here provides a basic understanding of antibacterial resistance rates that allows clinicians to choose the empirical therapies that they need to treat their patients safely. Also, with this data, local guidelines for antibiotic therapies can be optimized periodically. The year-to-year changes are visualized and can provide feedback for antimicrobial stewardship activities.

3. Methods

Cultures with a positive result from January 1st, 2010 up to December 31st, 2015 were extracted from the laboratory information system at ADC. The cultures were categorized based on the requesting entity (either SEHOS or general practice), using the *Instelling*-field in the database, selecting 'HA' or 'KLIN'. This approach does omit cultures from sources like specialist outpatients or long stay facilities which could be relevant populations.

Bias from repeated testing was avoided by applying filtering according to the NethMap methodology. This means that only the first bacterial species per material, per patient, per year is entered. Repeatedly cultured organisms from persistent or recurrent infections in the same year are thus effectively filtered to show only the first *E. coli K. pneumoniae,* etc. of the year in a single patient.

Susceptibility was tested on the automated VITEK II system with S/I/R interpretations based on yearly updated Clinical and Laboratory Standards Institute (CLSI) criteria. Most amoxicillin susceptibility tests are based on ampicillin as an indicator antibiotic according to CLSI guidelines. Flucloxacillin susceptibility in staphylococci is determined by cefoxitin testing, the most sensitive marker for the detection of PBP2a phenotypes like methicillin-resistant *Staphylococcus aureus* (MRSA).
Piperacillin has shown erratic patterns of susceptibility in *Pseudomonas aeruginosa* for which no explanation was found after an investigation that was done together with the manufacturer.
It was decided not to report any piperacillin results in the analysis. Previous experience indicated a clinically relevant role for the AmpC-positive *Enterobacteriaceae* (type-II *Enterobacteriaceae*). These bacteria carry a chromosomal resistance gene that makes them resistant to penicillins and 2nd and 3rd generation cephalosporins. The inducible nature of this chromosome makes susceptibility testing unreliable for these betalactam antibiotics. The most important representative species of this class of bacteria appears to be *Enterobacter cloacae*. Apart from its AmpC-related resistance, it can carry all the genes for resistance to other classes of antibiotics too. It is associated with carbapenem resistance in part due to carbapenemases other than the typical KPC or NDM-1 carbapenemases. In the 2015 analysis, *E. cloacae* isolates from blood cultures were added to the graphical reports because of these concerns.

4. Results

4.1. Isolates from blood cultures

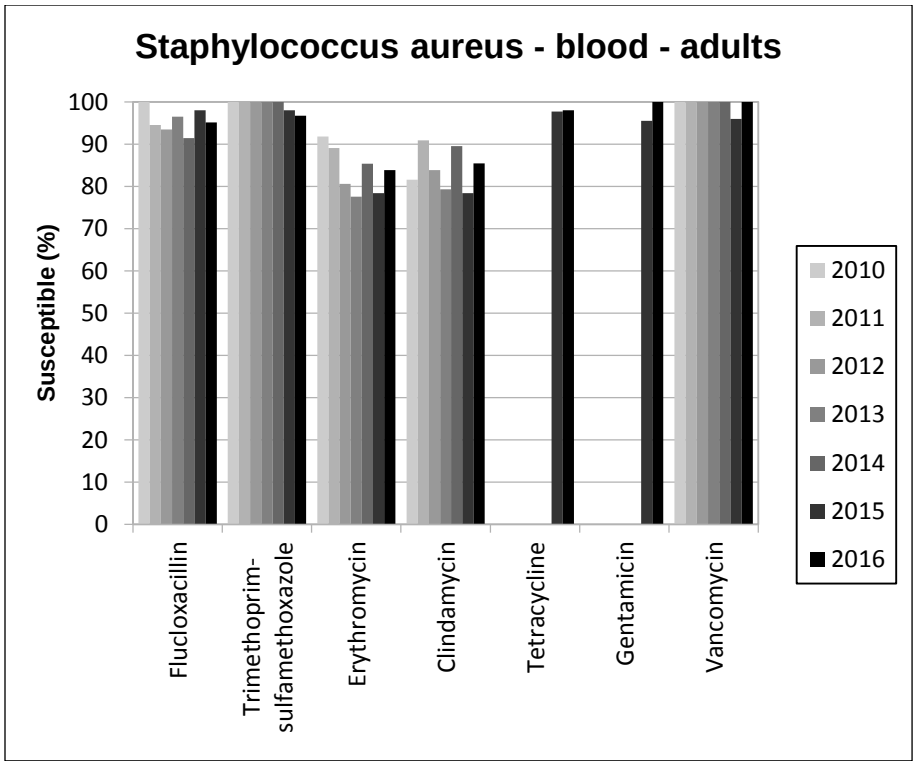
Blood cultures are an important marker for severe infection since they are the consequence of infections that cause a large enough bacteremia to be detected by the blood culture system. Usually these infections are sepsis and septic shock or endovascular infections like endocarditis. Over one third of blood cultures showed skin flora like coagulase-negative staphylococci (CNS) or diphtheroid rods, making the CNS the numerically largest group of bacteria in blood cultures (data not shown). These non-pathogens are only relevant in specific clinical entities like central venous catheter-related blood stream infections and are not part of this report. The most relevant gram-positive pathogens in clinical and numerical ways, that are included in this analysis, are *Staphylococcus aureus and Enterococcus faecalis*. For the gram-negatives, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis* and *Pseudomonas aeruginosa* are included.

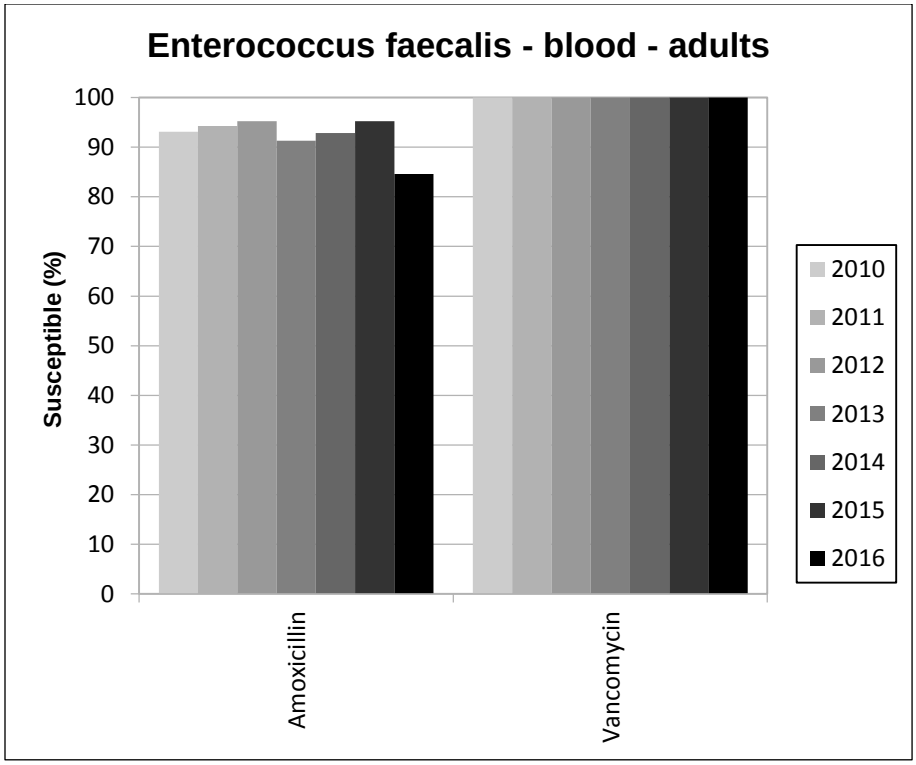
	2012	2013	2014	2015	2016
S. aureus	62	58	48	52	63
E. faecalis	21	23	28	21	14
E. coli	81	97	75	93	108
K. pneumoniae	52	65	61	64	62
E. cloacae	20	22	21	21	29
P. mirabilis	17	17	19	17	13
P. aeruginosa	23	14	20	34	32

4.1.1. Results from blood cultures, gram-positives

Representative gram-positive bacteria from bloodcultures are *Staphylococcus aureus* and *Enterococcus faecalis*. All *E. faecalis* are vancomycin susceptible and over 90% is susceptible to amoxicillin, a pattern that was stable over the observed timeframe. *S. aureus* showed resistance to some degree to all antibiotics reported. Before 2015 no data was available for gentamicin, nor for tetracycline, the marker antibiotic for doxycycline. The 2015 and 2016 data show a small percentage resistant to cotrimoxazole (trimethoprim-sulfamethoxazole). Vancomycin resistance in 2015 was due to VISA/GISA-like isolates and not due to VRSA. Vancomycin resistance disappeared again in 2016.

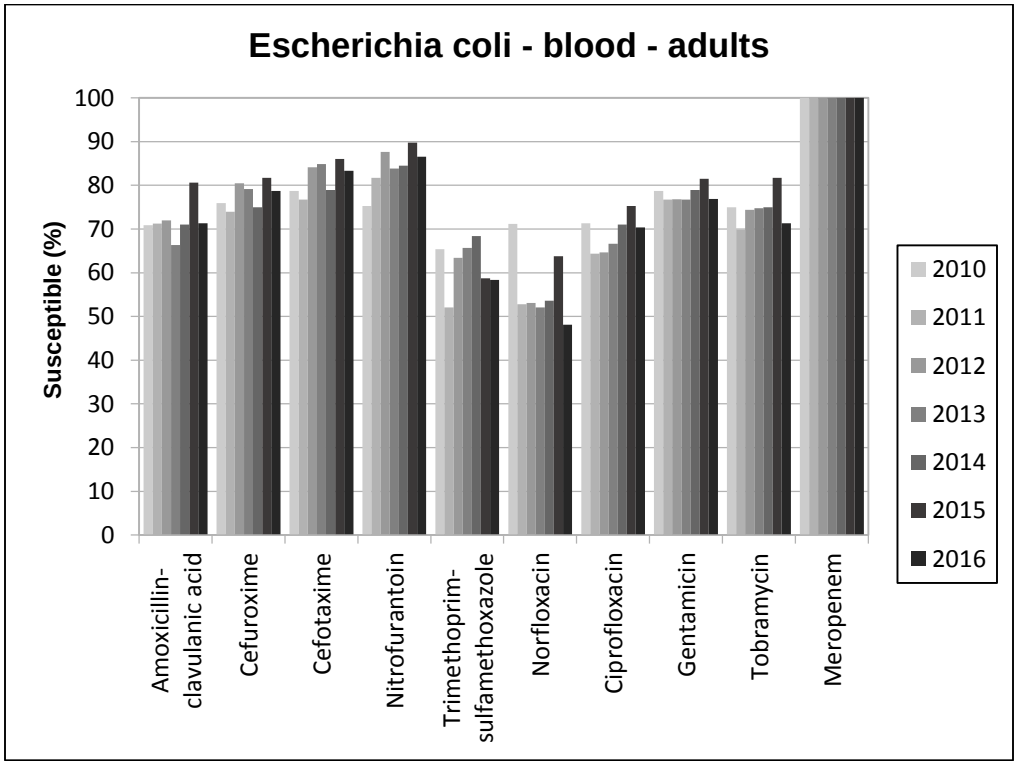
The most important trend up to 2015 was the increasing presence of MRSA, indicated by the percentage of flucloxacillin resistant isolates. In blood cultures, the percentage rose during the previous five years from 0 to 9% in 2014. This very alarming trend appeared to regress in 2015 and is still improving in 2016 compared to 2014. Efforts to counter MRSA in SEHOS were actively continued in 2015 and 2016. For macrolides and lincosamides like erythromycin and clindamycin, there is substantial resistance in 2016 around 15%. For empirical coverage of *S. aureus*, resistance to clindamycin should be taken into consideration. Severe infections which require empirical S. aureus coverage should be commenced with intravenous flucloxacillin and vancomycin, optionally combined with gentamicin. Empirical therapy for milder *S. aureus* infections should preferably include agents like cotrimoxazole and doxycycline. Empirical coverage of *Enterococcus faecalis* species is effectively achieved in most cases with amoxicillin and ultimately with vancomycin.


Staphylococcus aureus - blood - adults
Susceptible (%)
100
90
80
70
60
50
40
30
20
10
0
Flucloxacillin
Trimethoprim-sulfamethoxazole
Erythromycin
Clindamycin
Tetracycline
Gentamicin
Vancomycin
2010
2011
2012
2013
2014
2015
2016


Enterococcus faecalis - blood - adults
Susceptible (%)
100
90
80
70
60
50
40
30
20
10
0
Amoxicillin
Vancomycin
2010
2011
2012
2013
2014
2015
2016

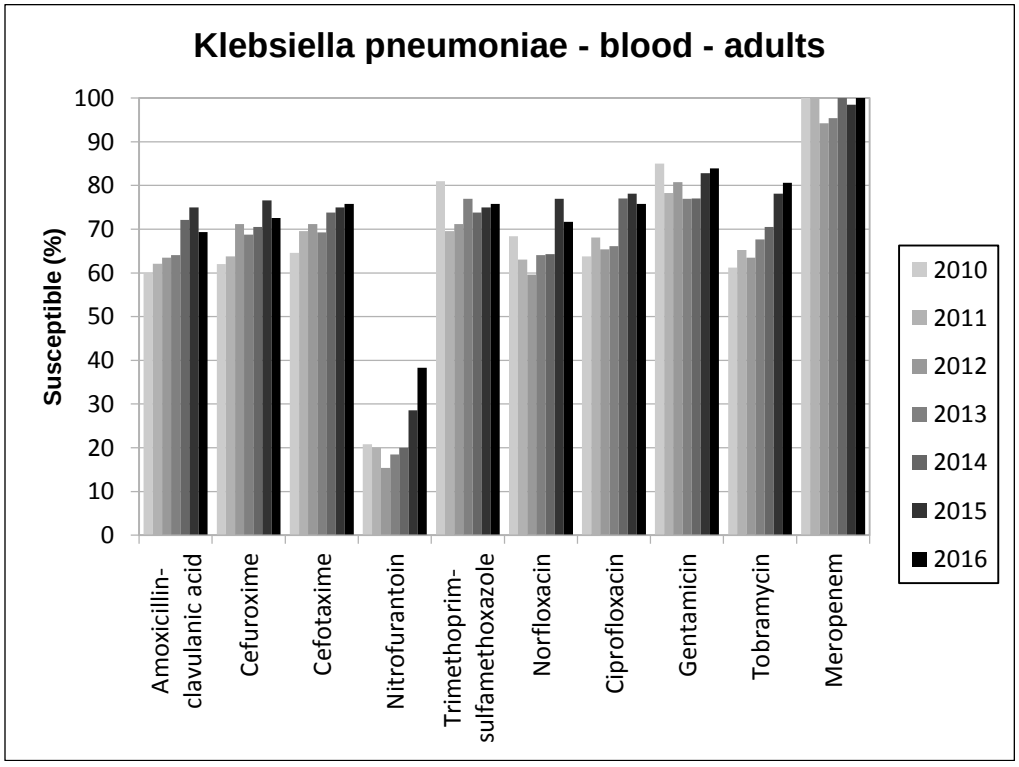
4.1.2. Results from blood cultures, *E. coli*

Gram-negative bacteria from blood cultures are represented in this report by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis* and *Pseudomonas aeruginosa*. Overall, 2016 showed more resistance than 2015 in *E. coli* isolates. Resistance to 3rd generation cephalosporins like cefotaxime, indicative of the presence of ESBL enzymes, was over 15% and resistance to fluoroquinolones like ciprofloxacin was highly prevalent with 30% being resistant to ciprofloxacin. No carbapenem resistance was detected in 2016.



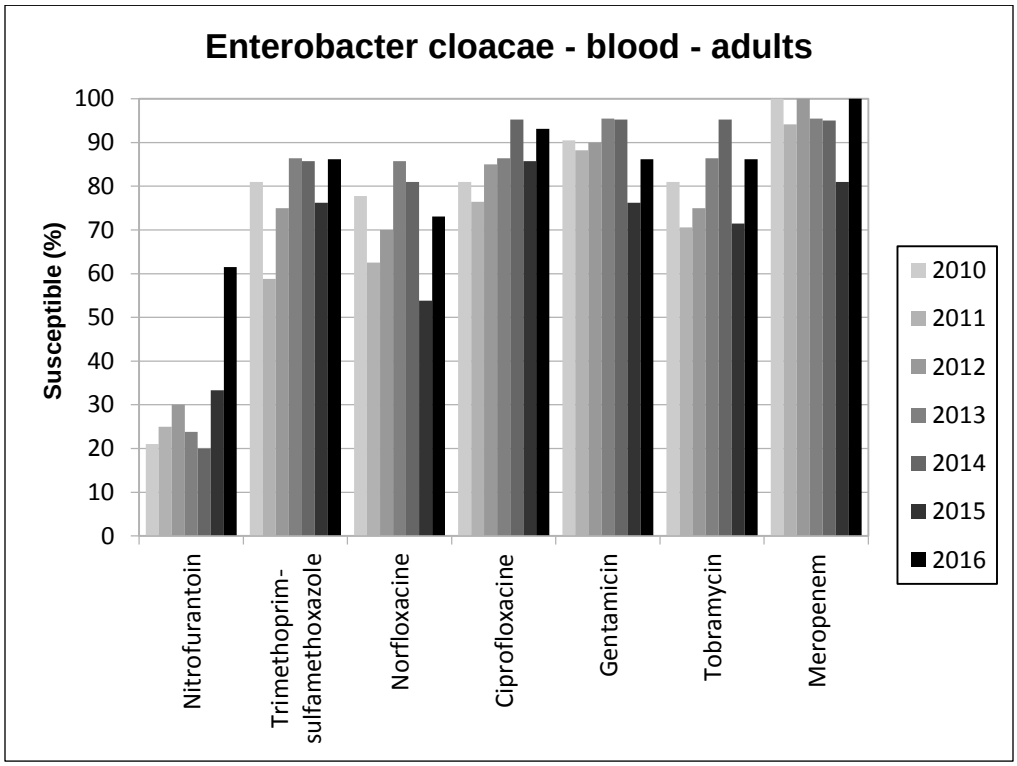
4.1.3. Results from blood cultures, *K. pneumoniae*

Overall, *K. pneumoniae* is more resistant than *E. coli*. Up to 25% is resistant to 3rd generation cephalosporins, indicative of ESBL. Susceptibility to fluoroquinolones was between 70% and 80% for norfloxacin and ciprofloxacin. Meropenem susceptibility was reduced in the years of the KPC carbapenemase outbreak, 2012 and 2013. 2016 shows a 100% susceptibility to meropenem indicating a reduction of carbapenemases present in sepsis patients. The continued efforts to reduce meropenem use and isolate patients with carbapenem-resistant bacteria, are likely to contribute to the observed reduction of carbapenem resistant isolates in blood cultures. *K. pneumoniae* is intrinsically resistant to amoxicillin which is not included in this report.



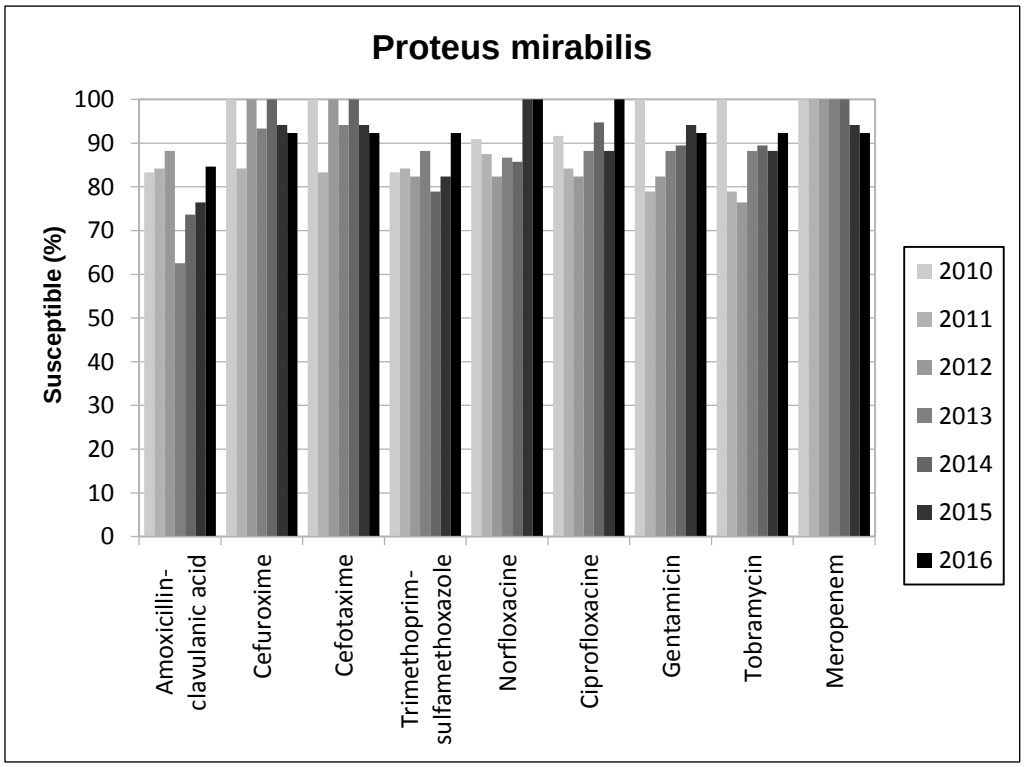
4.1.4. Results from blood cultures, *E. cloacae*

Enterobacter species are intrinsically resistant to penicillins and cephalosporins due to the presence of a chromosomal betalactamase, called AmpC. *Enterobacteriaceae* species with chromosomal AmpC grouped together are referred to as 'type II *Enterobacteriaceae'*. This group of bacteria shares the inducible AmpC phenotype susceptibility pattern, leaving fewer options for antibiotic therapy. High-risk wards like ICU and NICU commonly experience a high colonization pressure from type II *Enterobacteriaceae* due to the frequent use of penicillin-inhibitor combinations (like amoxicillin-clavulanic acid) and cephalosporins. The presence of AmpC or ESBL readily warrants the use of carbapenems for antibiotic therapy. Susceptibility of *E. cloacae* to meropenem was notably reduced in 2015 but not in 2016.



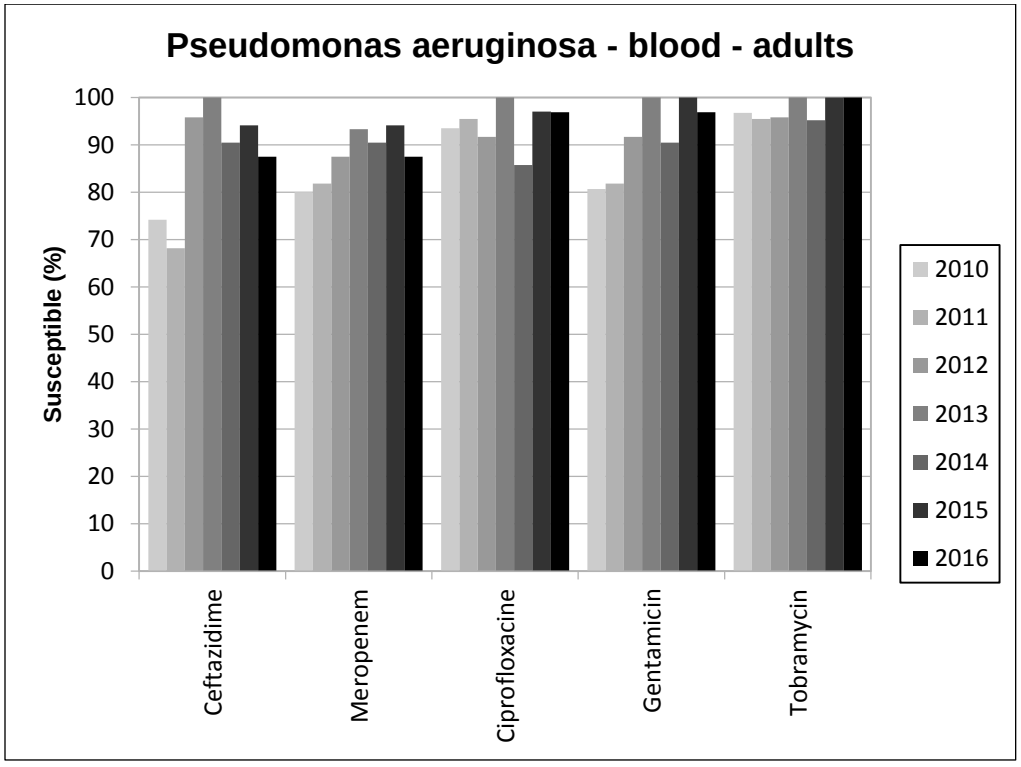
4.1.5. Results from blood cultures, *P. mirabilis*

Clinical isolates of *P. mirabilis*, showed less overall resistance than any of the other enterobacteriaceae. Quinolone resistance was absent in 2016 isolates. Meropenem resistance was detected and confirmed in some isolates (but not all) in 2015 and 2016. The application of additional meropenem MIC testing is of additional value to distinguish with certainty between true carbapenemase producers and false high meropenem MIC's reported by the VITEK II expert system. *Proteus* are intrinsically resistant to nitrofurantoin, which is not included in the graph.



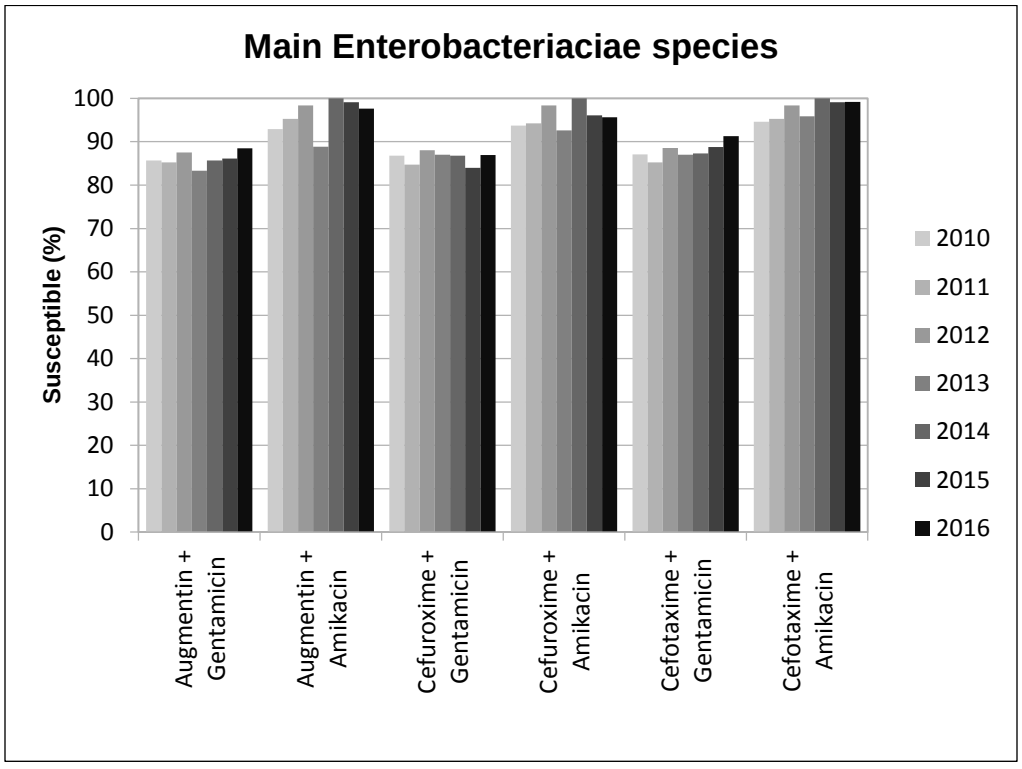
4.1.6. Results from blood cultures, *P. aeruginosa*

Isolates of *P. aeruginosa* showed high rates of susceptibility to all antibiotics with anti-pseudomonal activity in 2015 and 2016. For ceftazidime and gentamicin, susceptibility clearly improved when compared to the years 2010 and 2011. For both ceftazidime and meropenem, less than 90% of isolates were susceptible. The aminoglycosides showed over 95% susceptibility, as did the only oral agent for pseudomonas: ciprofloxacin. Piperacillin susceptibility was omitted from the report due to irrational results. Piperacillin is easily replaced by ceftazidime for pseudomonal coverage in clinical practice.



4.1.7. Combined Efficacy of Betalactam plus Aminoglycoside Antibiotics for *Enterobacteriaceae* Species

Sepsis treatment is nearly always started empirically without having culture results to guide therapy. Gram-negative sepsis may require the combined use of a betalactam antibiotic with an aminoglycoside. For the combined susceptibility, the *Enterobacteriaceae* species were selected from the dataset using the same filtering for repeated cultures as previously described. Genera included are *Escherichia*, *Klebsiella*, *Citrobacter*, *Salmonella*, *Raoultella*, *Proteus*, *Serratia*, *Morganella*, and *Providencia*. Isolates were regarded susceptible when either one drug in the combinations was tested as susceptible. If both drugs resulted in resistant or partial resistant, the combined result was regarded as resistant. As can be seen, the combinations yielded high percentages of susceptibility. Combinations with amikacin resulted in over 95% susceptibility, combinations with gentamicin resulted in lower percentages.



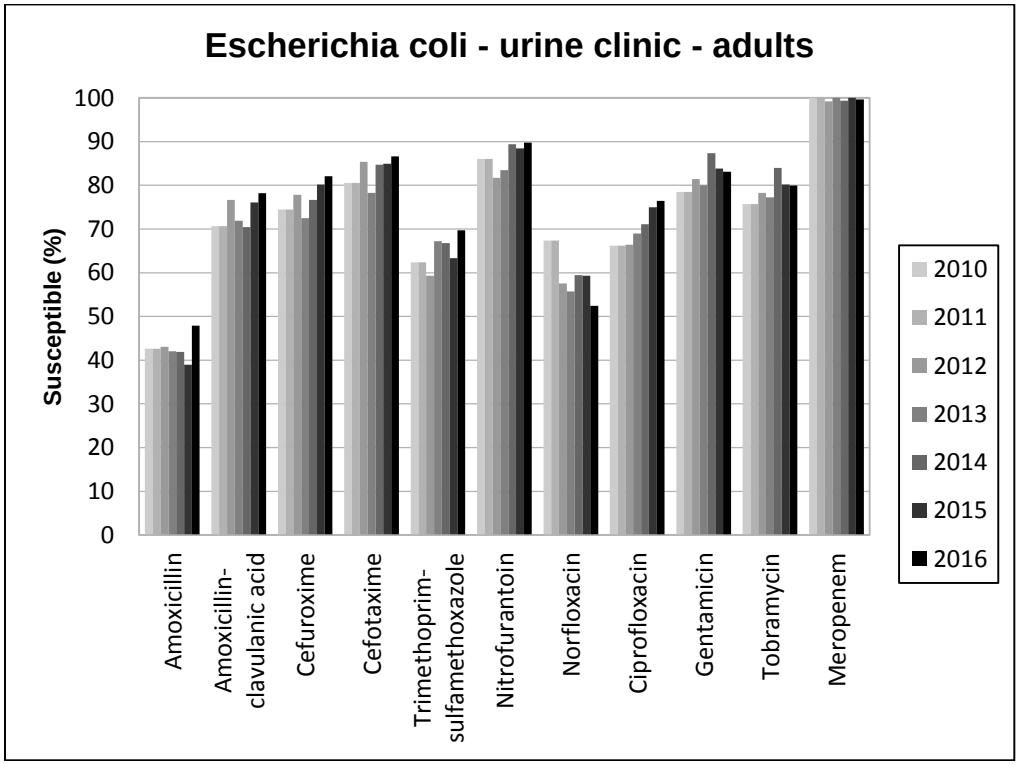
4.2. Results from urine cultures (clinic)

Clinical urine cultures represent rather routinely taken cultures as well as cultures from patients suspected or diagnosed with urosepsis and urinary tract infections. The most frequent uropathogens are *E. coli*, *K. pneumoniae*, *P. mirabilis* and *P. aeruginosa*. The various uropathogens showed quite similar distribution over the years reported.

	2012	2013	2014	2015	2016
E. coli	254	290	301	272	284
K. pneumoniae	145	135	155	147	135
P. mirabilis	56	51	62	52	50
P. aeruginosa	38	35	54	39	39

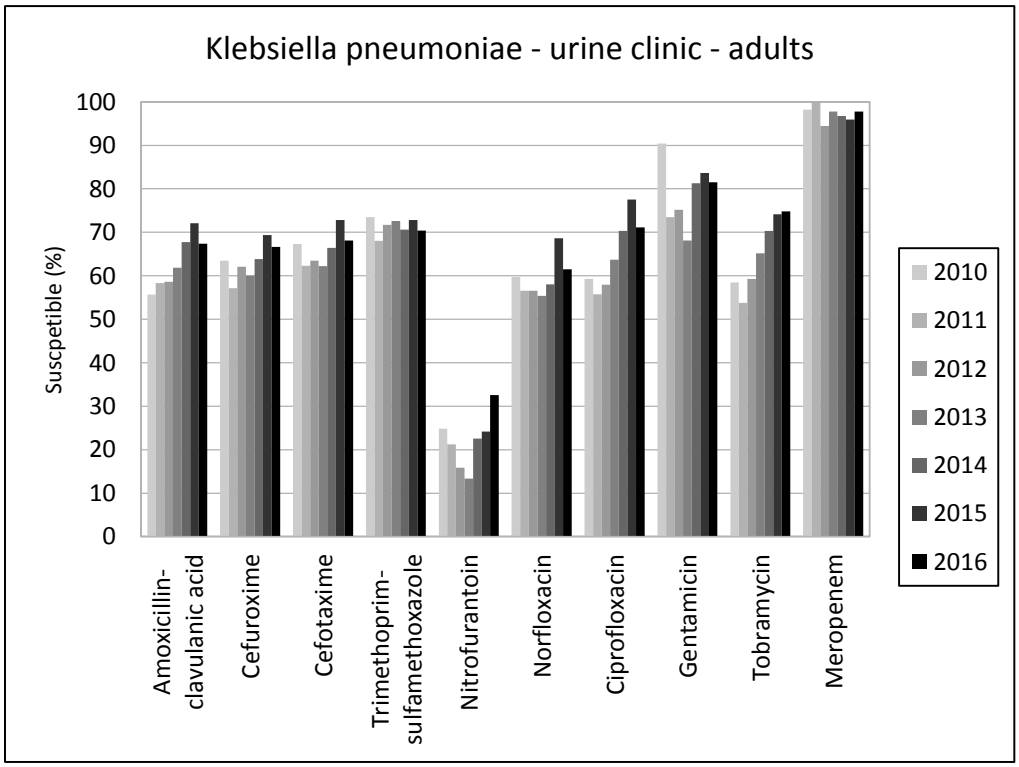
4.2.1. Results from urine culture (clinic), *E. coli*

Resistance to 3rd generation cephalosporins, indicative for the presence of ESBL enzymes, decreased further to 13% in 2016. Carbapenem susceptibility was 100% in reported isolates in 2015 and 2016. Other than meropenem, no single antibiotic was effective enough by itself. This warrants the use of cephalosporin plus aminoglycoside in empirical therapy for patients with severe urinary tract infection or urosepsis. Norfloxacin and ciprofloxacin show trends over time in opposing directions with norfloxacin susceptibility decreasing and ciprofloxacin susceptibility increasing.



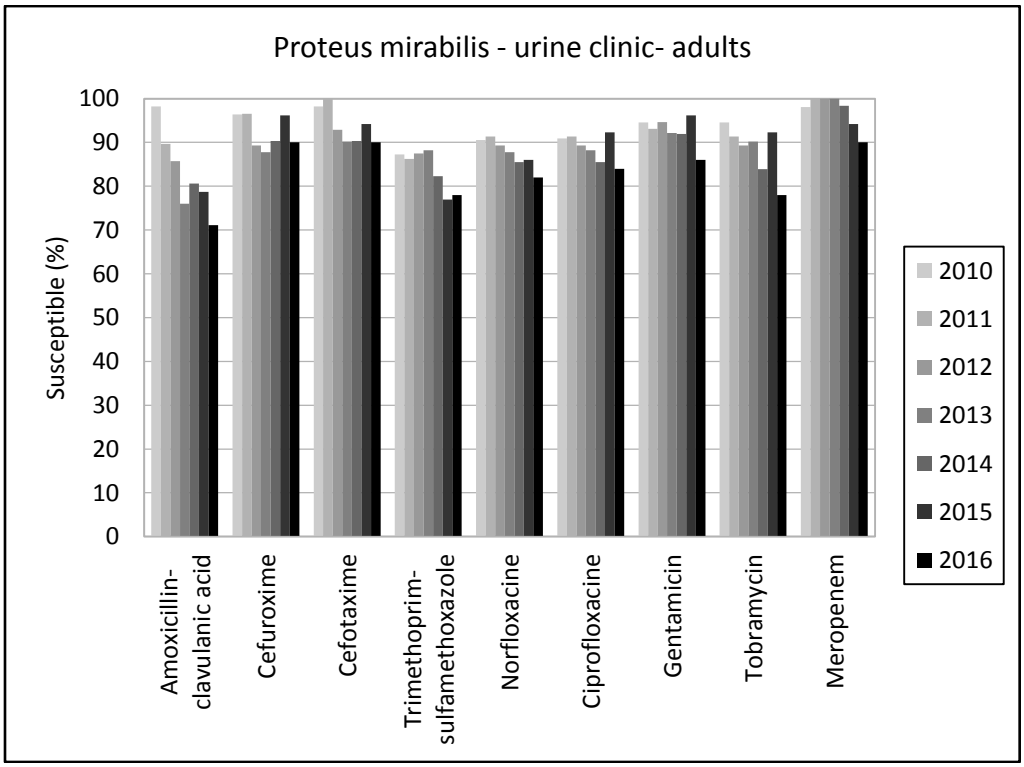
4.2.2. Results from urine cultures (clinic), *K. pneumoniae*

K. pneumoniae isolates from urine show similar patterns as in blood cultures with overall high levels of resistance. *K. pneumoniae* is overall more resistant than *E. coli*. Meropenem resistance is present in all the years, except 2011, indicating the continued circulation of carbapenemase-positive species. The majority of those are of the KPC genotype and, infrequently, of the NDM-1 genotype. Resistance to 3rd generation cephalosporins, indicative of ESBL enzymes, is over 30% in 2016.
K. pneumoniae is intrinsically resistant to amoxicillin which is not included in this report.



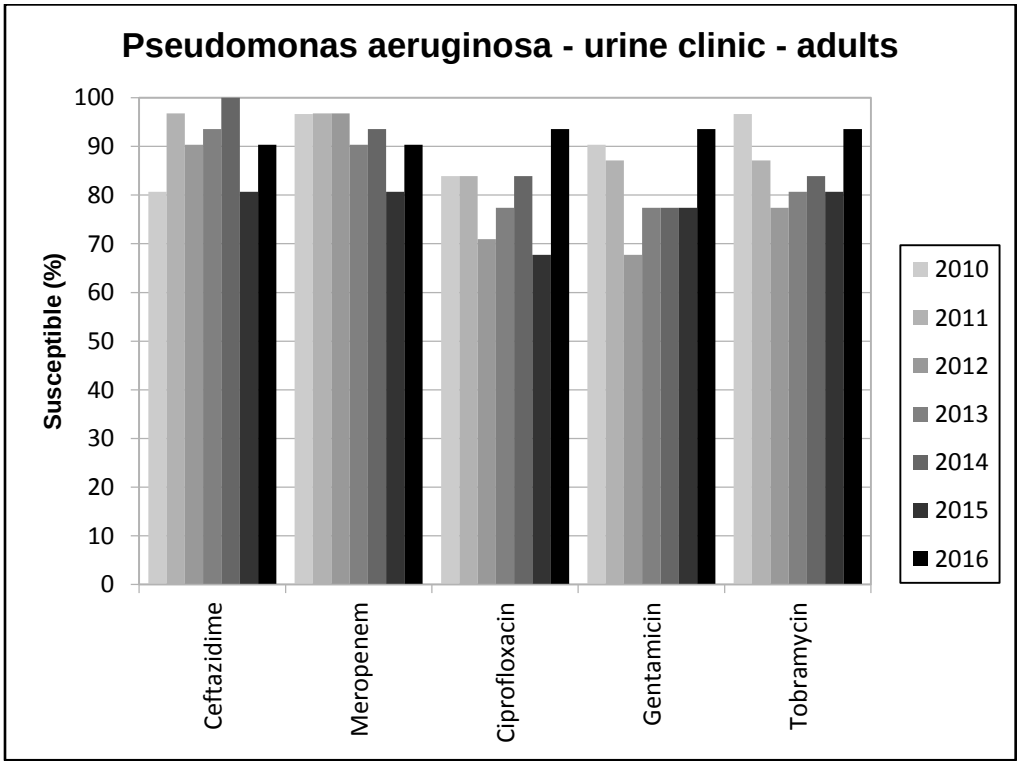
4.2.3. Results from urine cultures (clinic), *P. mirabilis*

Cultures of *P. mirabilis* showed far less resistance overall than *K. pneumoniae* and *E. coli*. Meropenem resistance increased notably in the years 2014 to 2016. In *P. mirabilis*, meropenem susceptibility testing with the VITEK II system requires confirmatory testing with e-testing and the carbapenem inhibition test (CIT) for the presence of carbapenemases. Except for the cephalosporins, all reported antibiotics showed marked decreases in susceptibility in 2016. This downward trend in susceptibility contrasts with the other uropathogens reported.



4.2.4. Results from urine cultures (clinic), *P. aeruginosa*

Isolates of *P. aeruginosa* from clinical urine cultures showed an increase of all reported antibiotics when compared to 2015. All antibiotics with antipseudomonal activity showed an increase of susceptibility to 90% or higher. Meropenem resistance in *P. aeruginosa* is frequently caused by other mechanisms than the activity of carbapenemases. The ADC has a procedure in place since 2016, for the detection of metallo-betalactamase type carbapenemases. These were not detected.



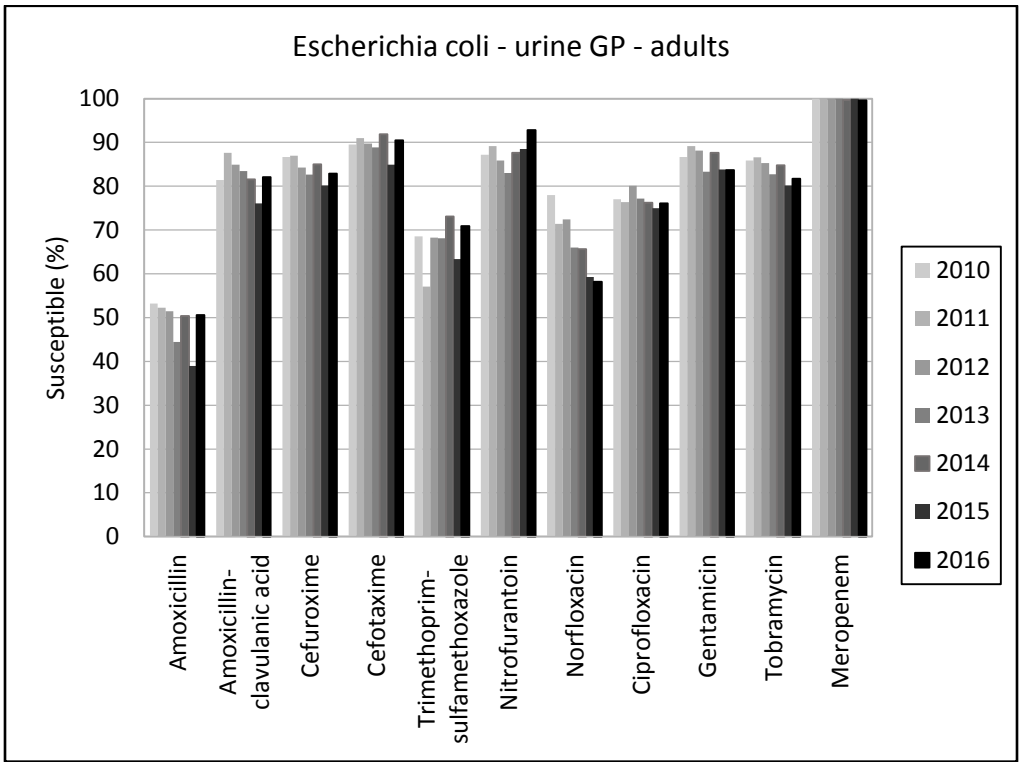
4.3. Results from urine cultures (general practice)

Cultures from general practice provide data on the resistance present in uropathogens. Numerically dominated by *E. coli*, other species like *K. pneumoniae*, *P. mirabilis* and *P. aeruginosa* are far less frequently encountered. Common uncomplicated cystitis is a frequent infectious entity in general practice and is often treated with empirical antibiotic therapy. The data presented in this section show the susceptibility data that determines the efficacy of empirical choices for antibiotic therapy. Nitrofurantoin remains highly effective for the number one pathogen *E. coli* but is ineffective for *P. mirabilis* and more than half of *K. pneumoniae* isolates. Fosfomycin susceptibility was tested for only a selection of isolates and is not included in this report.

	2012	2013	2014	2015	2016
E. coli	312	324	282	272	251
K. pneumoniae	76	72	65	60	55
P. mirabilis	37	40	51	24	35
P. aeruginosa	15	8	16	7	5

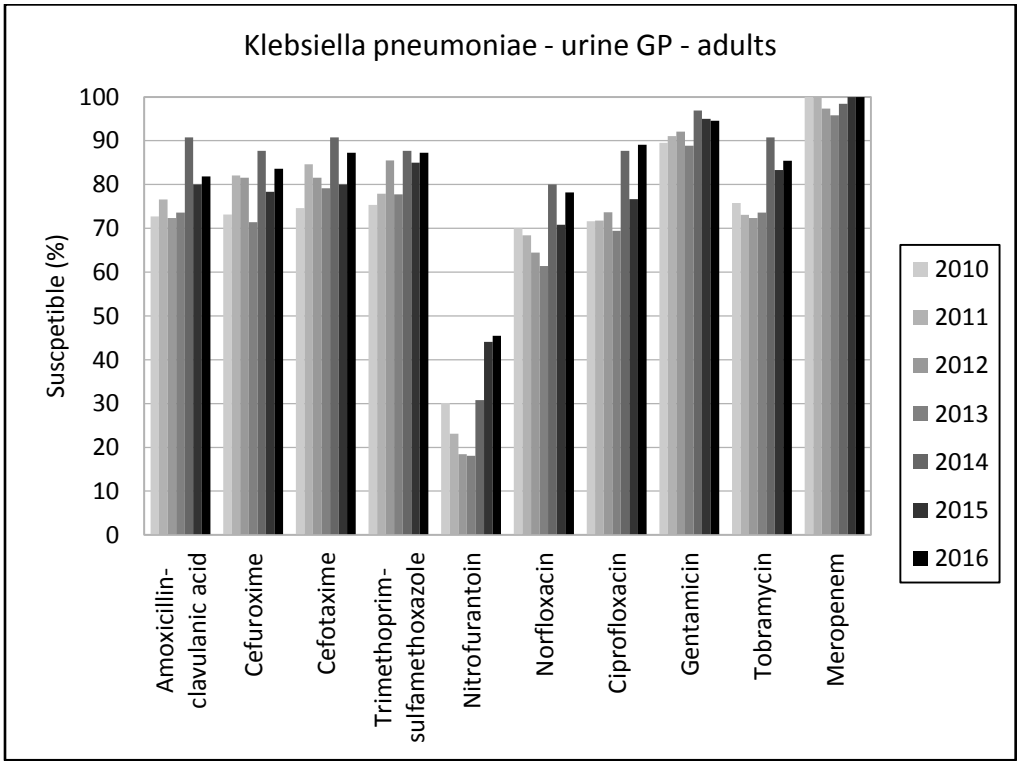
4.3.1. Results from urine cultures (general practice), *E. coli*

E. coli in general practice shows less resistance than the selection of clinical isolates. Nitrofurantoin susceptibility is just under 90% in 2015, with lower rates of susceptibility for amoxicillin-clavulanic acid and even lower rates for trimethoprim-sulfamethoxazole and ciprofloxacin. 3rd generation cephalosporin resistance is 10% in 2016, an improvement from 2015. Carbapenem resistance was detected in this population only in 2014. Norfloxacin showed a marked decrease in susceptibility with 58% of isolates testing susceptible. A notable decrease in norfloxacin susceptibility was also detected in *E. coli* derived from clinical urine cultures.



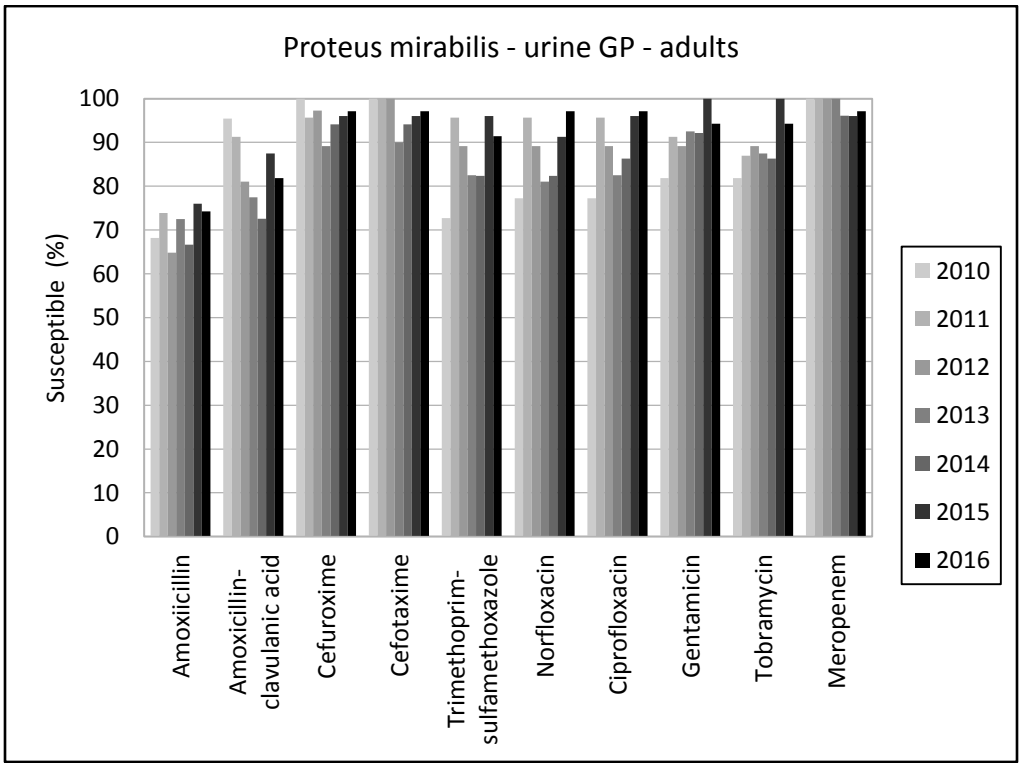
4.3.2. Results from urine cultures (general practice), *K. pneumoniae*

Appearing in less cultures than *E. coli*, *K. pneumoniae* has a smaller impact on the overall resistance in uropathogens. *K. pneumoniae* is intrinsically resistant to amoxicillin and in over half of the isolates resistant to nitrofurantoin. Combined with the intrinsic resistance of *P. mirabilis* to nitrofurantoin, this is a factor to consider for patients in whom nitrofurantoin for cystitis does not work. Meropenem susceptibility remained at 100% in 2015 and 2016.



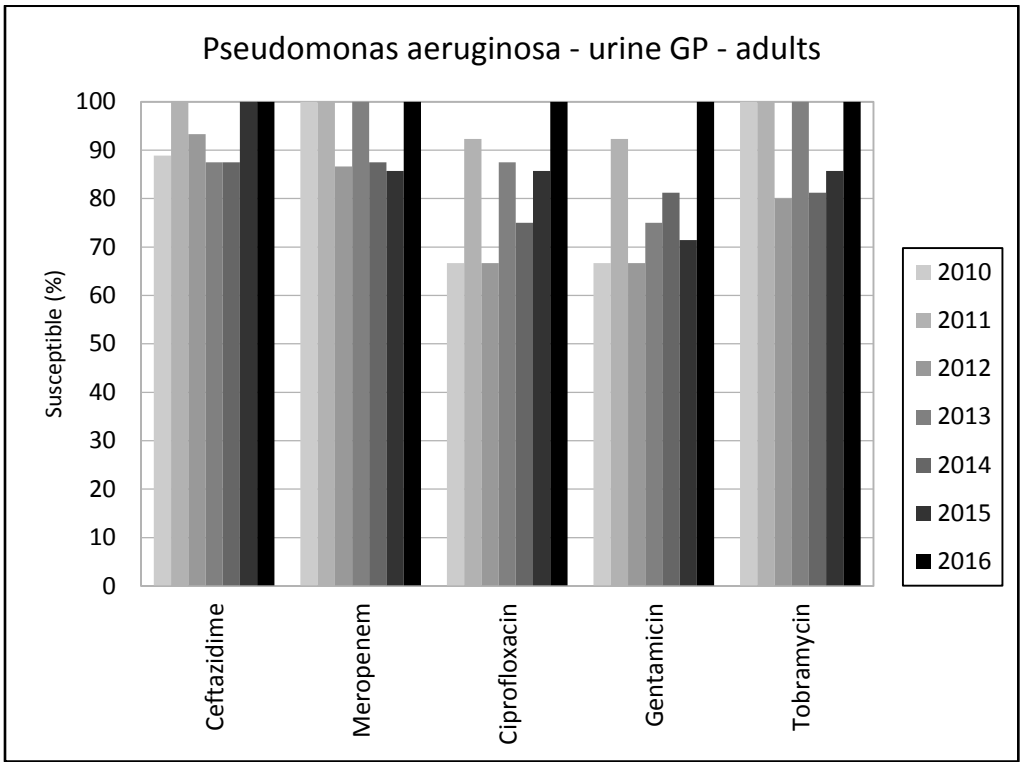
4.3.3. Results from urine cultures (general practice), *P. mirabilis*

Cultured less frequently than *E. coli*, *P. mirabilis* has a smaller share in the burden of antibiotic resistance in urinary tract infections. It is intrinsically resistant to nitrofurantoin and adds to the nitrofurantoin resistant infections together with *K. pneumoniae*. 2016 isolates of *P.* mirabilis showed an 82% susceptibility to amoxicillin-clavulanic acid and over 90% susceptibility to cotrimoxazole and ciprofloxacin. Resistance to meropenem was detected in 2014, 2015 and in 2016, indicating the circulation of carbapenemases in this population.



4.3.4. Results for urine cultures (general practice), *P. aeruginosa*

P. aeruginosa is infrequently cultured in urine samples in the general practice. Ciprofloxacin, the only oral antipseudomonal antibiotic was tested susceptible in all five isolates from 2016. The overall susceptibility was very similar to the isolates from clinical cultures. The number of included isolates is small and the results may be susceptible to the influence of chance.



4. Discussion

The 2016 report on antibiotic resistance shows concerning rates of resistance in the blood and urine cultures of Curaçao. MRSA was present in bloodcultures from three patients. 2015 and 2016 saw less MRSA than 2014 which is an encouraging trend. MRSA in bloodcultures can be regarded as the very tip of the iceberg of the total burden of MRSA in the population. The number of patients with MRSA in bloodcultures is vastly outnumbered by the asymptomatic MRSA carriers. Most of the control measures to contain the spread of MRSA in SEHOS concerns these numerous carriers in effort to prevent MRSA infections like the three patients in the 2016 data set. Despite significant efforts in SEHOS to isolate and eradicate MRSA carriers, some infections were still observed in 2016. Further decrease in MRSA infections seems possible and efforts to contain the spread of MRSA need to continue.

The rate of resistance in *E. coli* for 3rd generation cephalosporins relates to the presence of ESBL enzymes and is near 15% in the hospital isolates and near 10% in GP-derived isolates. In isolates of *K. pneumoniae*, the rate of ESBL is twice as high. ESBL carriership in admitted patients warrants isolation measures to control spread inside the institution. ESBL-carriers that present with infection in the clinic drive a large proportion of the intramural the meropenem prescriptions. Meropenem usage in turn invites the selective outgrowth of *K. pneumoniae* carbapenemase-positive (KPC) and other carbapenem resistant *Enterobacteriaceae*.

A constant threat is carbapenem resistance in the gram-negative bacteria of the *Enterobacteriaceae* family. Carbapenem-resistant isolates can spread within healthcare facilities and counter the efficacy of the last resort antibiotic meropenem. After the 2012 KPC outbreak, KPC transmission inside the hospital has largely been halted but KPC and other carbapenemases including NDM-1 are still detected among patients inside and outside SEHOS. Current carbapenemase screening and confirmation is aimed at the detection of two potent carbapenemases: KPC and NDM-1. Less potent carbapenemases of the OXA family are more difficult to detect. Updating of the carbapenemase screening and confirmation algorithm according to the guidelines of CSLI and NVMM complemented with meropenem and imipenem etesting as well as the Carbapenem Inhibition Test (CIT) took place in 2017. The CIT replaces the modified Hodge test for two reasons. The CIT has superior sensitivity, repeatability and CIT applies to non-fermenters like *Pseudomonas aeruginosa* as well. The carbapenem meropenem will remain the mainstay reserve antibiotic in infections with ESBL-positive *Enterobacteriaceae* and the AmpC-positive type II *Enterobacteriaceae*. Any lack of meropenem efficacy in gram-negative bacteria is always alarming and should trigger infection control measures for hospitalized patients.

KPC-positive isolates are susceptible to ceftazidime-avibactam (Avycaz) but not to aztreonam, whereas NDM-1 positive-isolates ought to be susceptible to aztreonam but not to ceftazidime-avibactam. PCR-based confirmation of the two enzymes is locally available but hardly ever requested. Neither of these two antibiotics are currently stocked because the number of patients that would require treatment with these drugs is (luckily) very small. Ad-hoc ordering usually takes longer than clinical relevancy lasts. Another option would be oral or intravenous fosfomycin which is supported by a growing base of evidence. Local fosfomycin susceptibility among the *Enterobacteriaceae* is unknown but will be included in the 2017 report.

Aminoglycosides like gentamicin, tobramycin and amikacin are obvious effective and cheap antibiotics to complement cephalosporins and carbapenems. Their use is restricted due to the lack of therapeutic drug monitoring (TDM) in Curaçao and the number of patients with renal disease. This situation puts patients at risk for toxicity resulting in severe and permanent side effects rendering patients deaf or dialysis dependent. TDM of gentamicin was introduced by ADC and SEHOS independently and facilitates the safe use of this aminoglycoside. Gentamicin resistance is considerable and some KPC-positive strains test only susceptible to amikacin and colistin.

The 2016 report on antimicrobial resistance both underscores and supports the continuing effort to counter antimicrobial resistance in Curaçao. The standardized periodic reporting of resistance in the most common bacterial pathogens is important to monitor effectiveness of current policies. It allows physicians to estimate the efficacy of empirical therapies. Although colistin and amikacin were not included in the 2016 report, resistance to both drugs was detected and will be included in the 2017 report.

The data presented in this report call for action to counter antimicrobial resistance. Resistance rates tend to decrease (except for *P. mirabilis*) or at least are stable which is a strong support to the ongoing efforts to control the spread of resistance. Some territories remain uncharted, notably the long-stay facilities in Curaçao. Expansion of antimicrobial stewardship inside and outside of SEHOS may further enhance the upward trend in susceptibility as noted in this report. The implementation of a National Action Plan on Antimicrobial Resistance (NAP-AMR) should further resolve gaps in surveillance and control in Curaçao. Failure to do so may result in regression in current trends and would likely require far more expensive antibiotic drugs to be introduced into the Curaçao healthcare system in the near future.