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கொழும்பு தெற்கு போதனா வைத்தியசாலை
COLOMBO SOUTH TEACHING HOSPITAL

THE UNIVERSITY OF SYDNEY

Neonatal sepsis in a tertiary care hospital in Sri Lanka:

Reflections on rising antibiotic resistance over five years

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Background:

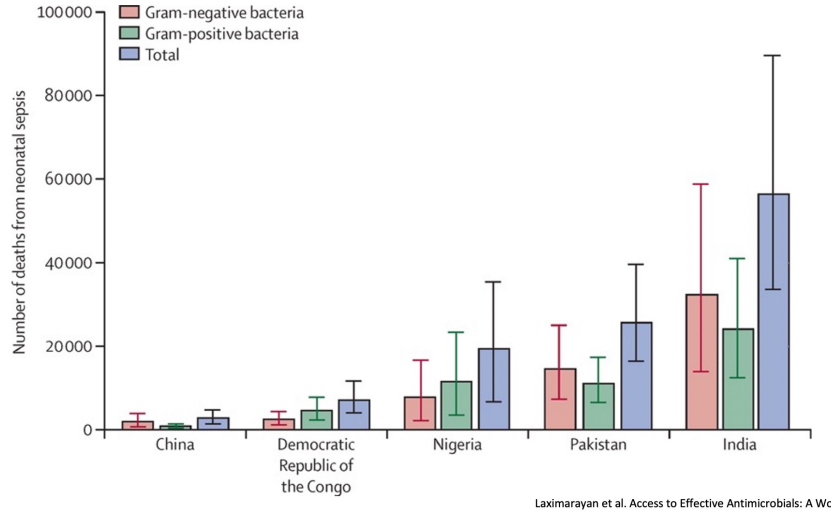
- High levels of antimicrobial resistance (AMR) are propagating deaths due to neonatal sepsis globally, particularly in Southeast Asia[1]

Why?

- Limited access to healthcare resources
- Lack of availability of newer antibiotics

- Scant published data pertaining to the epidemiology of neonatal sepsis within these regions results in:
  - Limited awareness on pathogen diversity
  - Difficulty in quantifying the burden of AMR

Estimated annual neonatal sepsis deaths caused by bacteria resistant to first-line antibiotics in 5 high-burden countries



Laximarayan et al. Access to Effective Antimicrobials: A Worldwide Challenge. *Lancet* 2016

[1]. GBD 2019 Antimicrobial Resistance Collaborators. Global mortality associated with 33 bacterial pathogens in 2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2022 Dec 17;400(10369):2221-2248. doi: 10.1016/S0140-6736(22)02185-7.Epub 2022 Nov 21. PMID: 36423648; PMCID: PMC9763654

Methods:

- To address the lack of published data pertaining to causes of neonatal sepsis and AMR rates in SE Asia, the NeoSEAP collaboration was launched in 2021, evaluating neonatal sepsis across 12 clinical settings in Southeast Asia and the Pacific
- The data presented today reflects that collated from Colombo South Teaching Hospital, Colombo, Sri Lanka as part of the 'NeoSEAP' project
- Data pertaining to blood culture isolates and their antibiotic susceptibilities were ascertained via review of hand-written laboratory logs from 1st January 2015 to 31st December 2020

  - Blood cultures were processed manually until 2017
  - Species identification available on limited isolates

- To evaluate the efficacy of currently-recommended empirical antibiotic regimens, a weighted incidence combination syndromic antibiogram (WISCA) model was built utilizing antimicrobial susceptibility data[2]

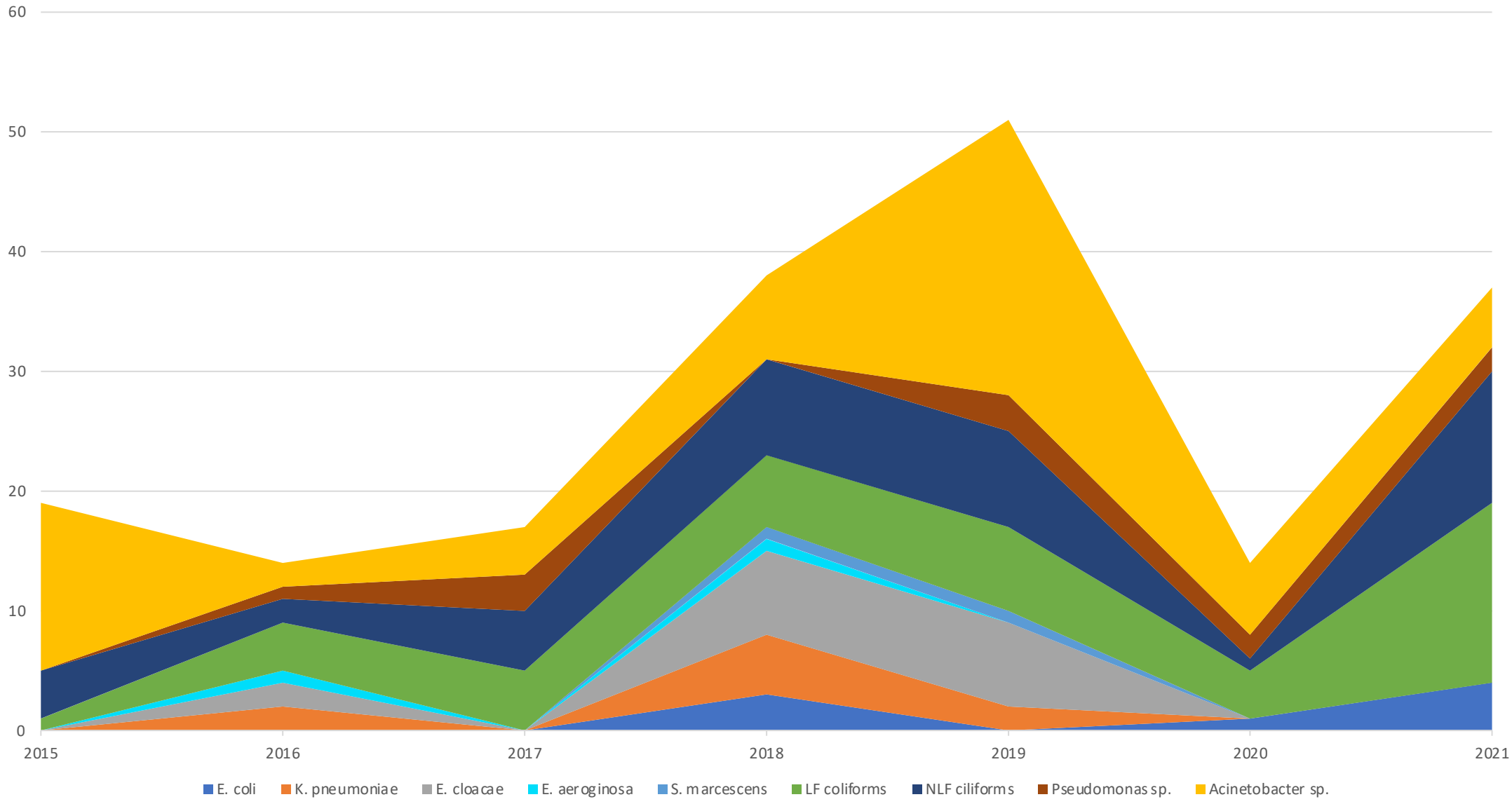
2 Bielicki et al, Antibiotic Resistance and Prescribing in European Children project. Selecting appropriate empirical antibiotic regimens for paediatric bloodstream I nfections: application of a Bayesian decision model to local and pooled antimicrobial resistance surveillance Antimicrob Chemother. 2016 Mar;71(3):794-802. doi: 10.1093/jac/dkv397. Epub 2015 Nov 30. PMID: 26626717.

Results:

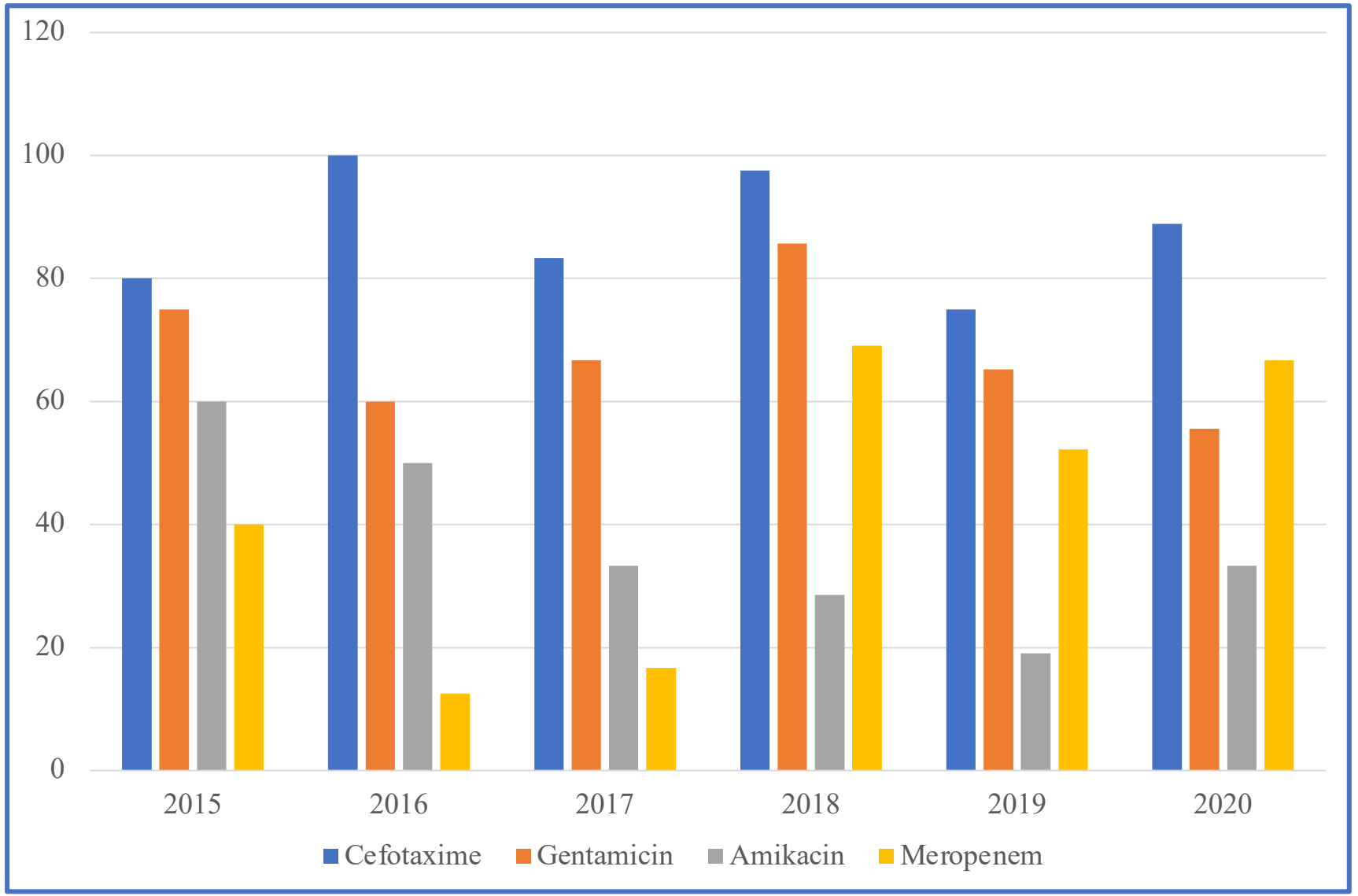
Year	2015	2016	2017	2018	2019	2020	2021	Total
Total live births	6,081	5,821	5,545	5,399	5,279	4,918	3,983	33,043
Total number of admissions to NICU	432	419	470	355	422	412	403	2,510
Total number of positive BC *excluding contaminants	**27**	**32**	**72**	**72**	**84**	**36**	**48**	323
Total number of gram-positive blood cultures	10 (37%)	10 (31%)	10 (13%)	10 (13%)	28 (33%)	15 (42%)	8 (17%)	83
Total number of gram-negative blood cultures	17 (74%)	16 (50%)	38 (53%)	51 (71%)	51 (61%)	18 (50%)	39 (81%)	191
Candida spp.	0	6 (19%)	18 (25%)	11 (15%)	2 (2%)	3 (8%)	1 (2%)	39

* Excluded contaminants included: Coagulase-negative Staphylococci *Corynebacterium (Diptheroids)* spp.. *Micrococcus* spp. *Propionibacterium spp.* and *Bacillus* spp.

Changing prevalence of pathogens causing gram-negative neonatal sepsis:



Antibiotic non-susceptibility of isolated Enterobacterales



Enterobacterale Outbreaks in the Neonatal Intensive Care Unit

Year	Total isolated	Incidence per 1000 live births
2015	05	0.82
2016	09	1.55
2017	11	1.98
2018	43	7.96
2019	25	4.74
2020	10	2.03

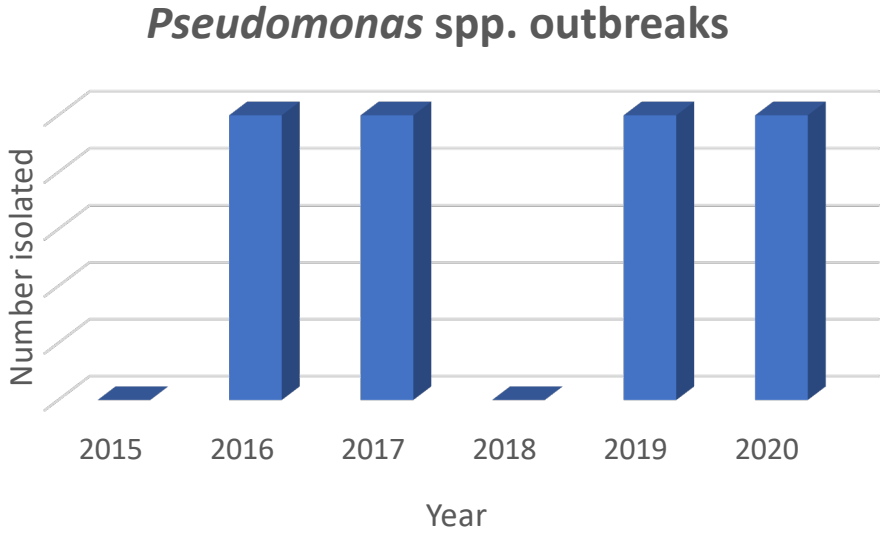
- An outbreak occurred due to *E. cloacae* between 11th June to 2nd July 2018
- Total of 6 babies were affected with 4 deaths
- The isolates were only susceptible to levofloxacin, amikacin and colistin
- All isolates harbored NDM-type MBL, plus CTX-M, OXA-1 and TEM extended-spectrum β-lactamases
- Affected neonates were treated with IV amikacin and colistin

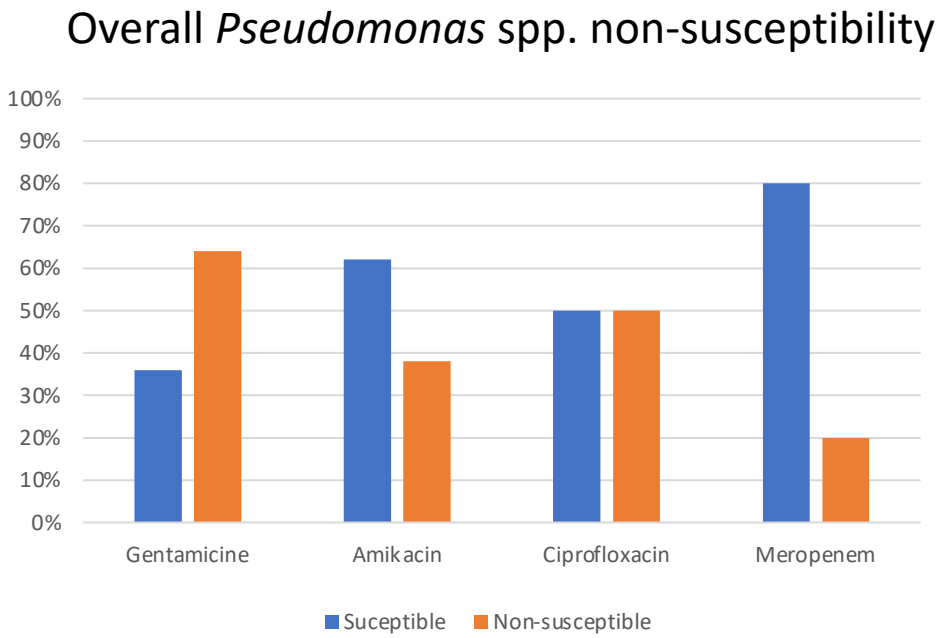
Other gram-negative outbreaks over the study period:

Rhizobium radiobacter:

- Between 3rd - 30th October 2017, 7 neonates with clinical sepsis had blood cultures positive for *Rhizobium radiobacter*
  - Total of 17 positive blood cultures
  - All isolates were susceptible to meropenem
- All the neonates were preterm
- 4 neonates (of 7) died

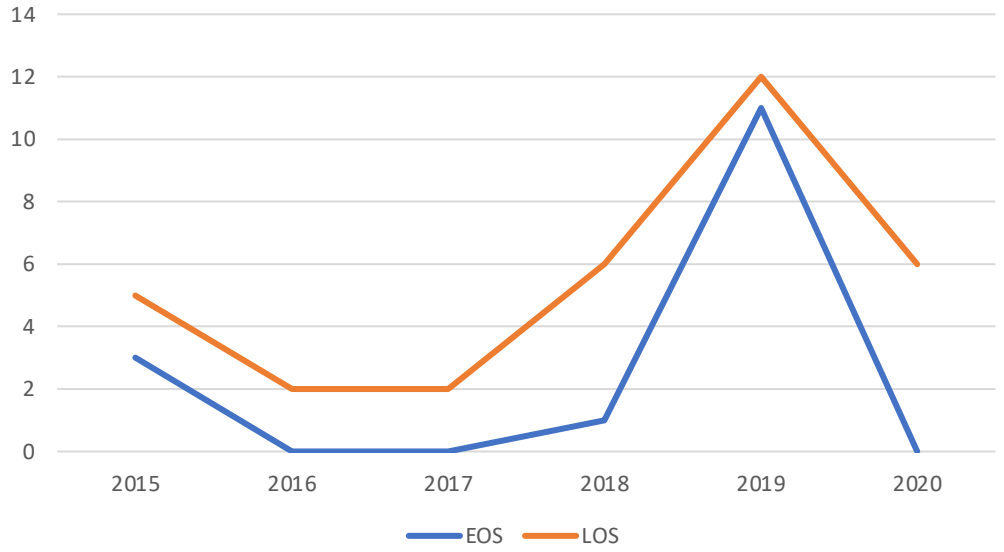
- Other outbreaks have included *Pseudomonas* spp., with high rates of aminoglycoside resistance and ~20% non-susceptibility to meropenem



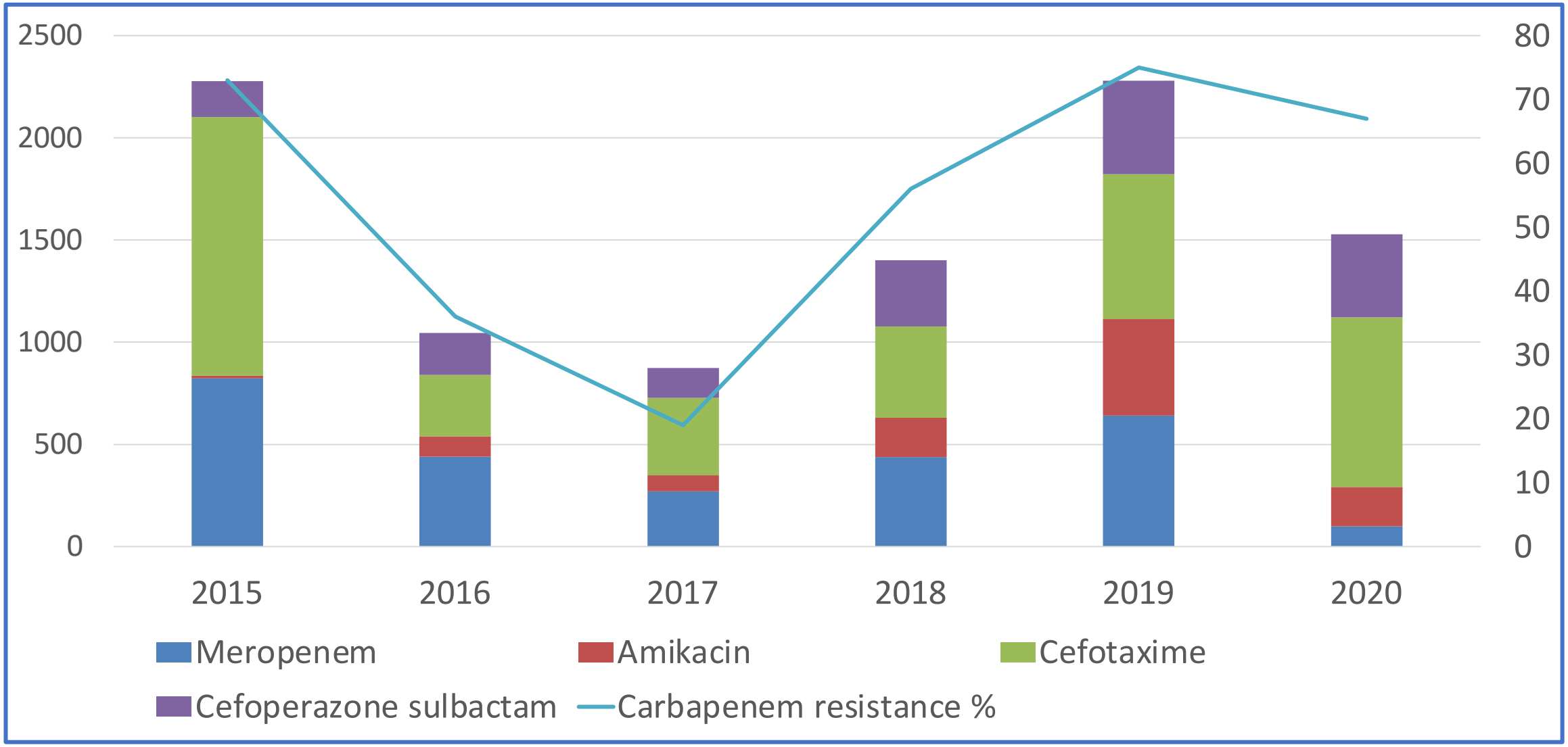


Acinetobacter spp. outbreaks

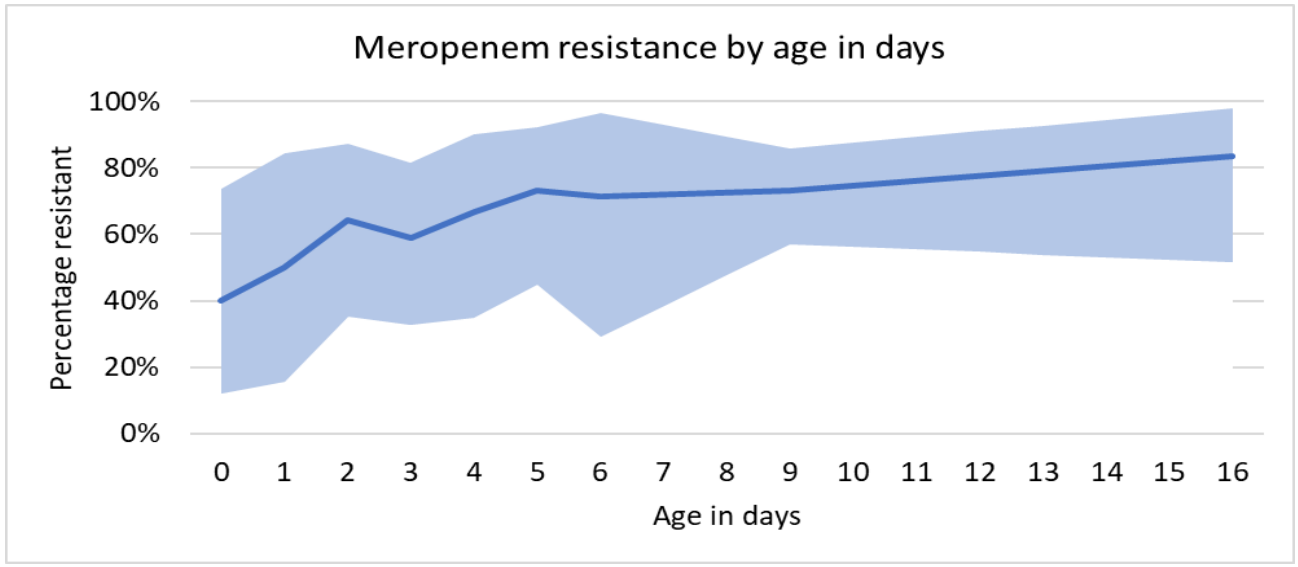
- Historically, this predominantly occurs in late-onset neonatal sepsis, though a 2019 outbreak also revealed this to be a predominant pathogen in early-onset sepsis, suggesting early horizontal acquisition
- Total of 19 babies were affected with *Acinetobacter* spp. sepsis in 2019
  - Birth weights were less than 1,500g in 11 babies
  - Ten were extreme premature (POA < 32 weeks)
- Many isolates were multidrug-resistant, including high rates of carbapenem-resistance
- 11 deaths resulted (/19, 58%)

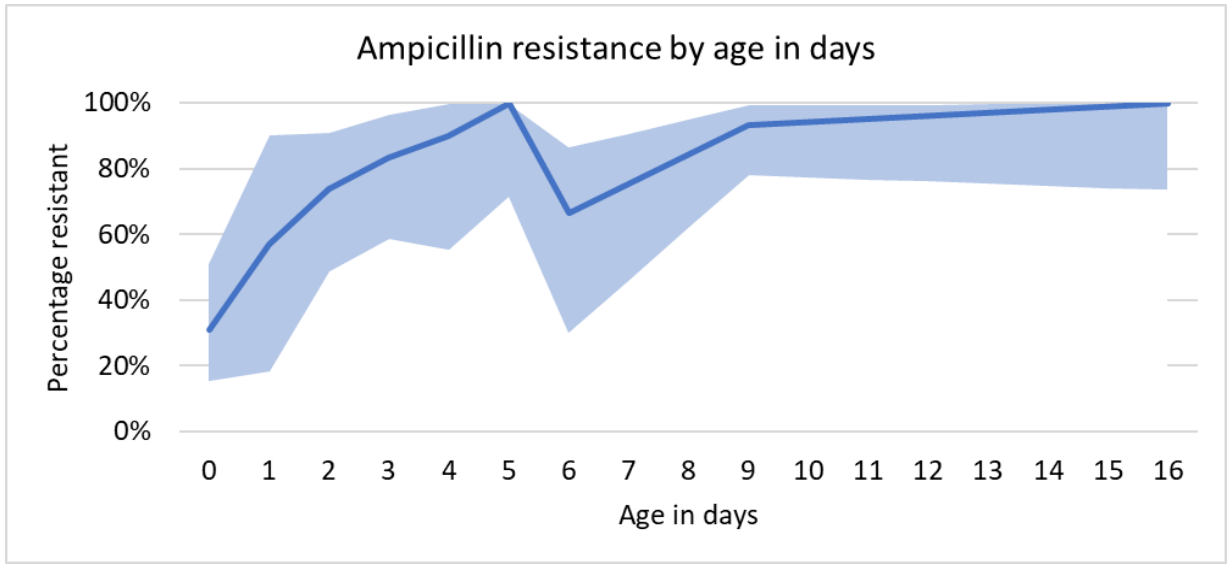


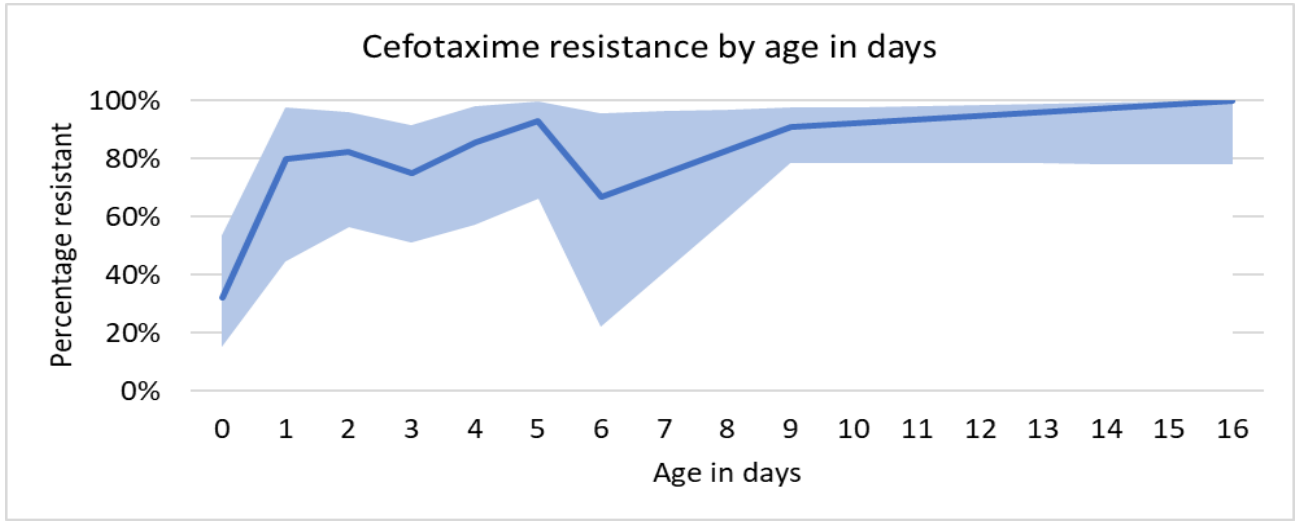
Correlation between antibiotic consumption & carbapenem resistance in gram-negative pathogens causing neonatal sepsis

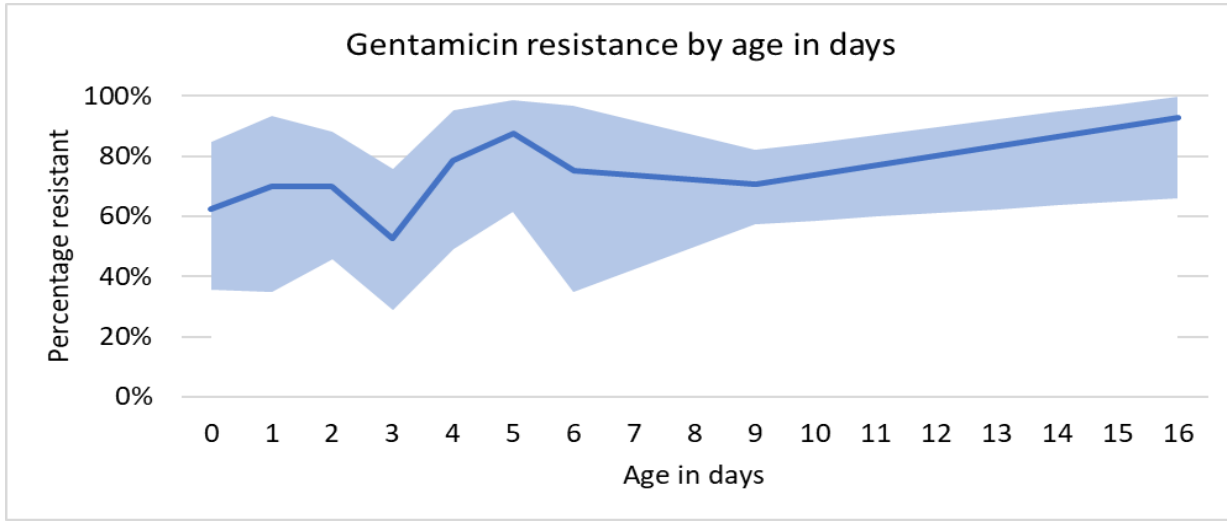


The likelihood of infection with an antibiotic-resistant pathogen increases with neonatal age









Neonatal sepsis due to gram-positive pathogens, 2015-2021:

Bacterial species	Total number isolated
Streptococcus agalactiae	31
Streptococcus pyogenes	3
Streptococcus pneumoniae	3
Other Streptococcus spp.	5
Enterococcus spp.	9
Staphylococcus aureus	19
Coagulase negative *Staphylococci**	6

* Clinically significant isolates only

Neonatal sepsis due to *Streptococcus agalactiae* (GBS):

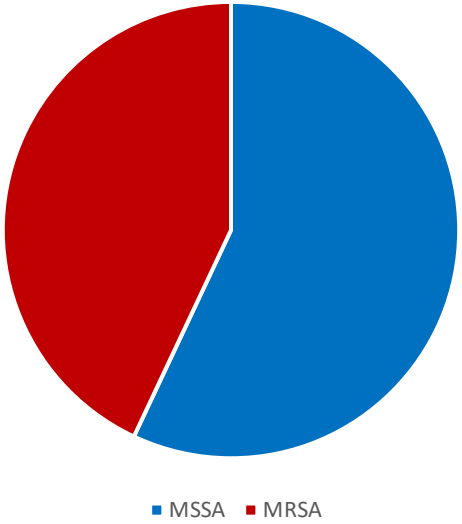
Year	Number of GBS isolated	GBS incidence per 1,000 live births
2015	5	0.66
2016	5	0.86
2017	5	0.90
2018	5	0.93
2019	7	1.33
2020	3	0.61
2021	1	0.25

Despite gram-negative pathogens predominating as a cause of neonatal sepsis in Sri Lanka, GBS incidence is still similar to that seen in high-income countries[3]

[3]Health *et al.* Group B Streptococcal disease in UK and Irish infants younger than 90 days Lancet 2004.

Staphylococcus as a pathogen of neonatal sepsis, 2015-2021:

Staphylococcus aureus



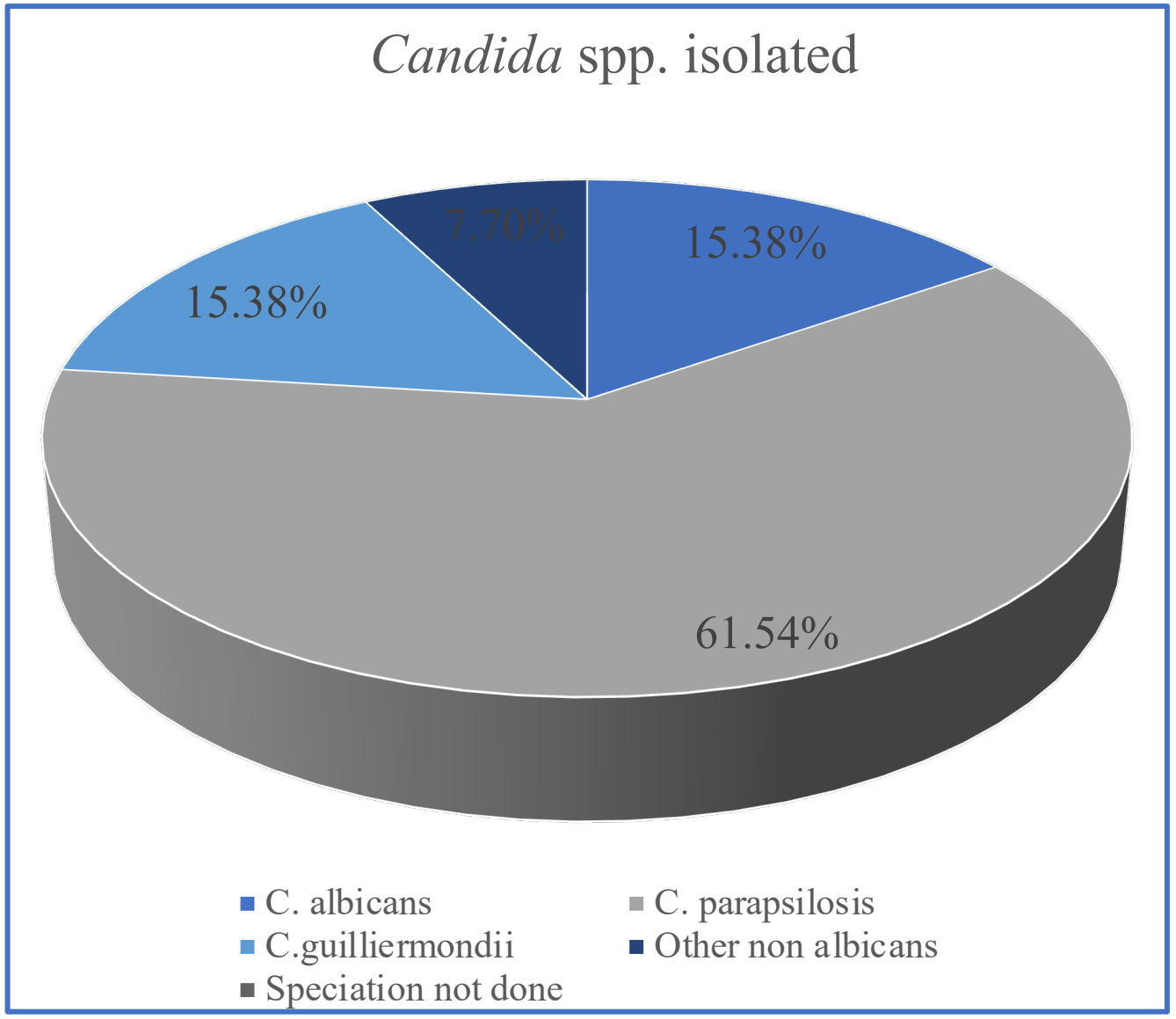
- Total of 19 blood cultures positive from 14 neonates for *Staphylococcus aureus*
- 3 neonates with multiple positive blood cultures had MRSA

Coagulase negative *Staphylococcus* species:

- 6 neonates had clinically significant CoNS bacteraemia
- 5 were late onset sepsis
- All the significant isolates were resistant to cefoxitin

Neonatal Candidaemia

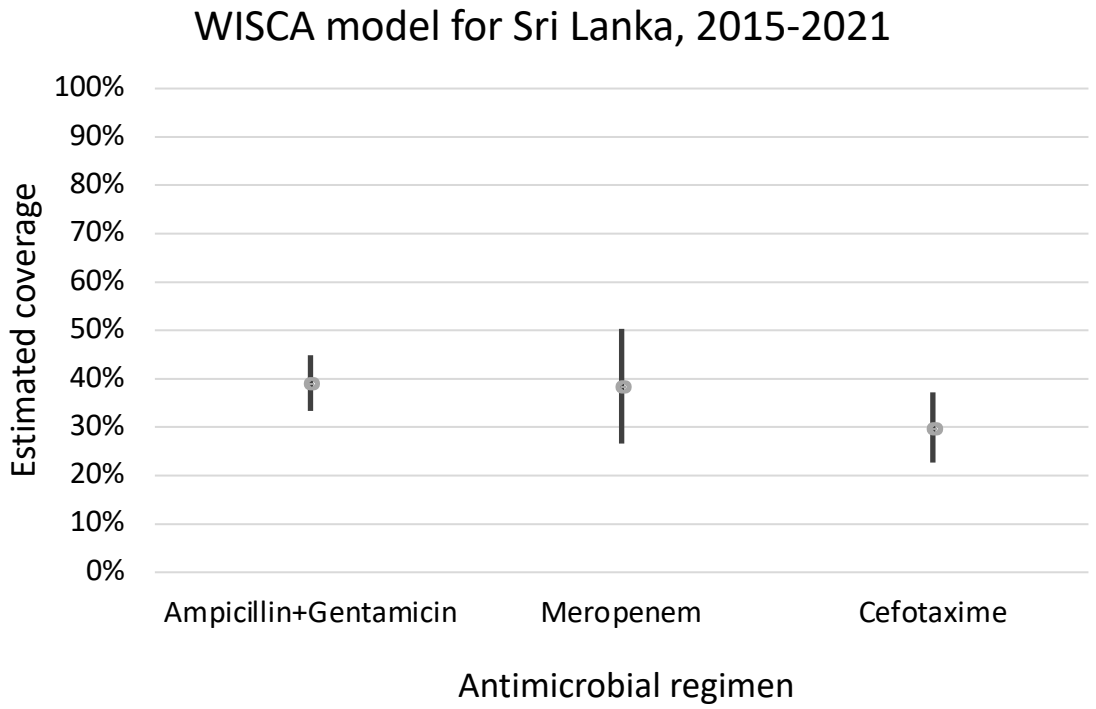
Year	Incidence of candidaemia per 1000 live births
2015	0
2016	0.48
2017	3.4
2018	1.41
2019	0.47
2020	0.48



How effective are currently-recommended antibiotics for neonatal sepsis in Sri Lanka?

- **Weighted incidence syndromic combination antibiogram (WISCA)** built to evaluate coverage provided by currently-recommended empirical regimens, utilising local susceptibility data (n=304 gram-negative and gram-positive pathogens)

- Currently recommended (or regularly prescribed) empirical regimens for neonatal sepsis are providing **limited coverage for neonates in Sri Lanka:**
  - Ampicillin-gentamicin: 39% (95% credible interval: 33 to 45%)
  - Cefotaxime: 30% (23 to 37%)
  - Meropenem: 30% (23 to 37%)

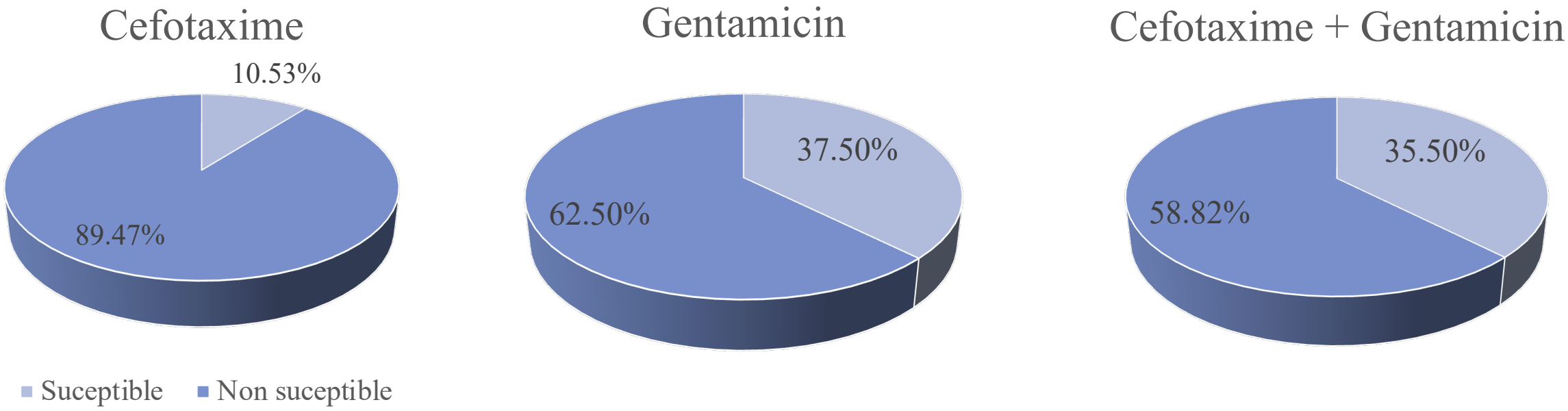


Conclusions

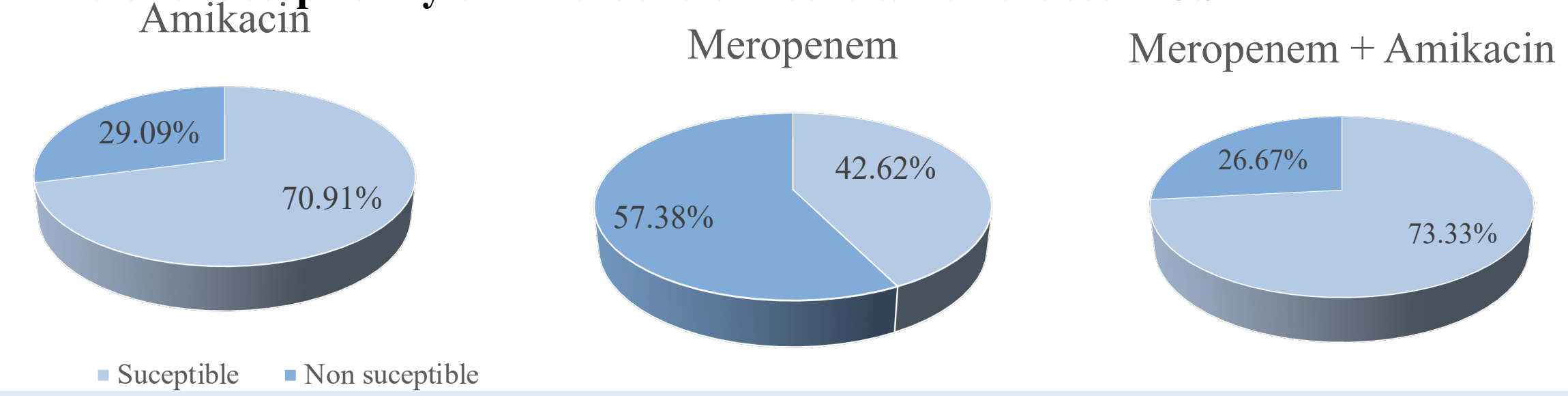
- High rates of neonatal multidrug-resistant infections highlight the urgent need in high-burden, resource-constrained settings for:
    1. Establishing antibiotic stewardship programs;
    2. Enhanced AMR surveillance;
    3. Delineating the time course of MDR pathogen colonisation and infection in neonates; and
    4. Enhancing access to more efficacious therapies to treat MDR infections in areas that need them most.

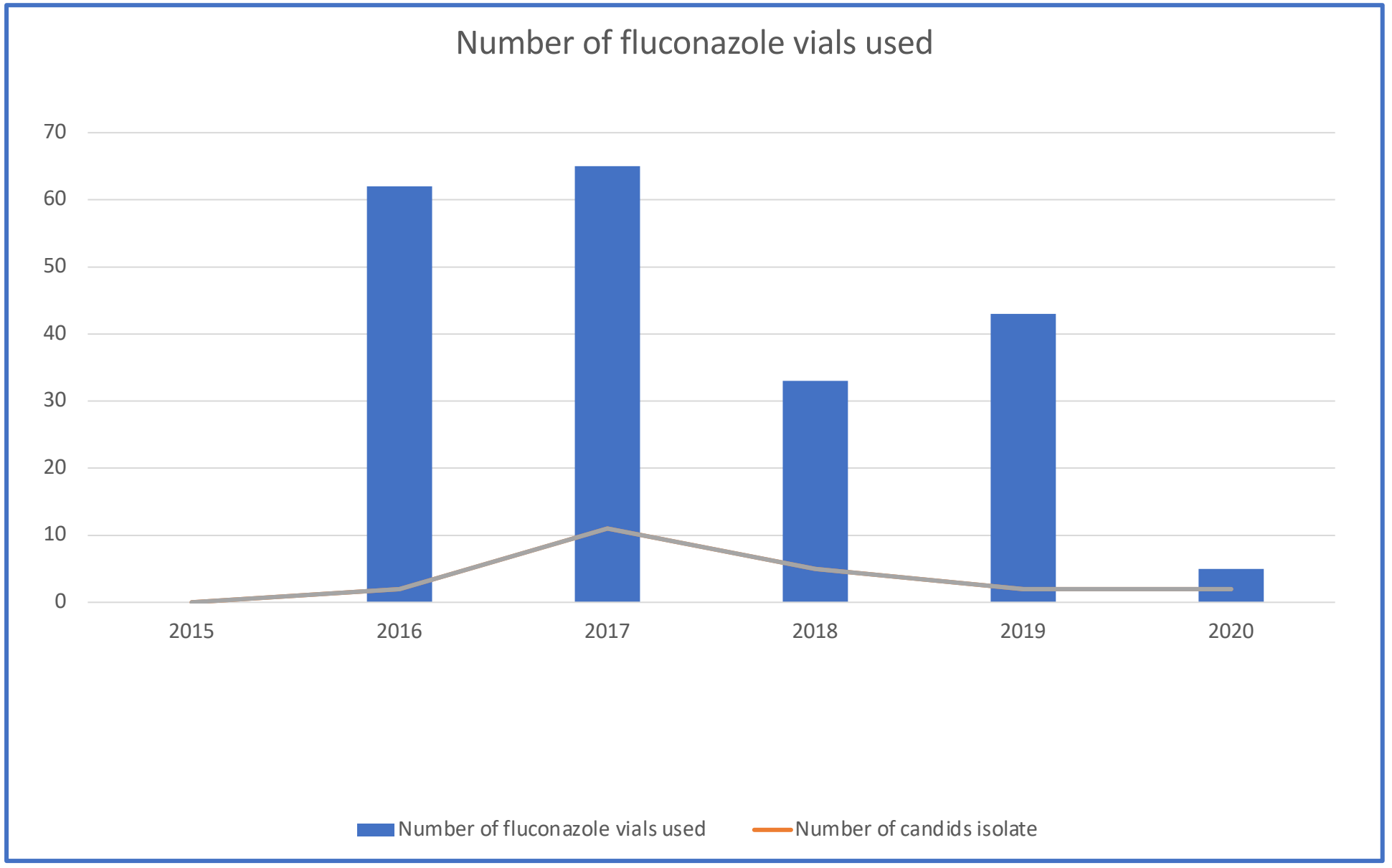
Spare slides (not to present)

Antibiotic susceptibility of Enterobacteriaceae which caused EOS:



Antibiotic susceptibility of Enterobacteriaceae which caused LOS:




Number of fluconazole vials used
70
60
50
40
30
20
10
0
2015
2016
2017
2018
2019
2020
Number of fluconazole vials used
Number of candids isolate