SciMedCentral

JSM Microbiology

Short Communication

Antimicrobial Resistance Surveillance of Sentinel Organisms over 20 Years in A Specialist Children's Hospital in The United Kingdom and Comparison to The ESPAUR Data

Luca Zombori[1]*, Stephane Paulus[2], Timothy Best[3], Mohsin A Shah[4] and James Hatcher[3]

[1]*Paediatric Intensive Care, Department of Heart and Lung, Great Ormond Street Hospital for Children, London WC1N 3JH, UK*

[2]*Paediatric Infectious Diseases, University of Oxford, Oxford OX1 4BH, UK*

[3]*Department of Microbiology, Great Ormond Street Hospital for Children, London WC1N 3JH, UK*

[4]*Digital Research Environment, Great Ormond Street Hospital for Children NHS Foundation Trust, DRIVE office, 40 Bernard Street London WC1N 1LE, UK*

***Corresponding author**

Luca Zombori, Great Ormond Hospital for Children, London WC1N 3JH, UK, Telephone: +44 20 7405 9200

Submitted: 18 April 2023

Accepted: 26 April 2023

Published: 27 April 2023

Keywords

- Antibiotic resistance
- *P.aeruginsa*
- Enterobacterales
- VRE
- MRSA
- paediatric intensive care unit

Abstract

Background: Following antibiotic resistance of sentinel organisms is a cornerstone of antimicrobial stewardship (AMS) activity.

Methods: We have monitored P.aeruginosa, Enterobacterales, Vancomycin resistant Enterococcus (VRE) and MRSA reported on clinical isolates of children on the intensive care units of a tertiary level paediatric hospital in London, United Kingdom over 20 years and compared it with the English Surveillance program for antimicrobial utilisation and resistance (ESPAUR) data.

Results: Resistance is higher in the examined hospital compared to ESPAUR. P.aeruginosa resistance against combined piperacillin-tazobactam+ciprofloxacin in 2011-12 reached 35.5%, although decreasing since; E.coli resistance against the same combination was 16.7% in 2005-6 also decreasing since; VRE was reported at 20% in 2017-8, comparable to ESPAUR data, but only 1% when calculated for the whole 20-year period. MRSA rates over the 20 years were of 13%, with a value in 2019-20 of 7.1% is comparable to ESPAURs 6%.

Conclusion: Monitoring resistance rates can help targeting AMS effort and informs infection control.Conclusions: This study confirmed the previously established donor selection criteria for total antibody level for convalescent plasma therapy; minimum level was 32 COI. Nevertheless, further rise in donor total antibody level did not improve the outcome of plasma recipient. Convalescent plasma therapy had significant effect on viral clearance; survivors cleared virus three times earlier than non-survivors. Neither donor total antibody level nor timing of plasma therapy influence their outcome.

INTRODUCTION

Antimicrobial resistance has been linked with the overuse of antimicrobials [1] and monitoring trends informs AMS and IPC. Six organisms commonly referred to as ESKAPE pathogens (*E. faecium, S. aureus, K.* pneumoniae, A.baumannii, *P. aeruginosa* and Enterobacter species) represent the clinically most relevant group as the most common causes of nosocomial infection with a high capacity to develop resistance against antibiotics [2]. This study aimed at monitoring rates of resistance in clinical isolates in four of the groups: Vancomycin resistant Enterococcus (VRE), Enterobacterales, *P. aeruginosa* and Methicillin Resistant *S. aureus* (MRSA) over 20 years at the intensive care units of Great Ormond Street Hospital (GOSH) for Children in London, United Kingdom. Great Ormond Street Hospital is a stand-alone children's hospital and a level 4 referral centre for specialist paediatric services with a 17-bed paediatric intensive care unit (PICU), a 21-bed cardiac intensive care unit (CICU) and a 10-bed neonatal intensive care unit (NICU).

METHODS

The data of antibiotic resistance was collected prospectively, but analysed retrospectively, using the electronic laboratory data records. All positive clinical isolates, with a separate analysis of blood cultures, from all four intensive care units from the past twenty years were analysed. Days between reportable specimens of the same patient was set to 365 days to avoid duplicate recording of the same episode. The organisms were defined as resistant if their resistance in the isolates was 50% or more. The results were plotted and compared with the English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) [3].

Blood culture resistance can be compared to the official national values published by English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) [3]. ESPAUR publishes resistance data collected from laboratories across the country. As the ESPAUR data consists of blood culture samples collected in all health care settings – although largely hospitals – and all age groups with likely a minority of samples collected from children, there is a limit of adaptability of the ESPAUR results to this sample. This study is conducted in a tertiary/quaternary level paediatric hospital where both the percentage of immunocompromised patients and the percentage of international patients might be higher than on a national level.

RESULTS AND DISCUSSION

P. aeruginosa

There has been 2351 clinical isolates of *P.aeruginosa* between 2001-2020 with the number of isolates ranging between 84-167 per year. Of this, there is a total of 90 blood cultures, equivalent to 3-7 per year. Resistance to amikacin, ceftazidime, ciprofloxacin, gentamicin, imipenem, meropenem and piperacillin-tazobactam is described.

For all clinical isolates over the period examined, resistance was stable with some peaks and troughs over the course of the study (see Appendix).

Resistance against combined antibiotics in *P.aeruginosa* in all clinical samples shows a steady and consistent decrease over the years with most combinations reaching resistance below 2% by the period of 2019-2020 with the exception of the combination piperacillin-tazobactam+ciprofloxacin with 3%, having started as high as 8% for piperacillin-tazobactam+gentamicin and between 6-7% for ciprofloxacin+gentamicin and piperacillin-tazobactam+ciprofloxacin [Graph 4].

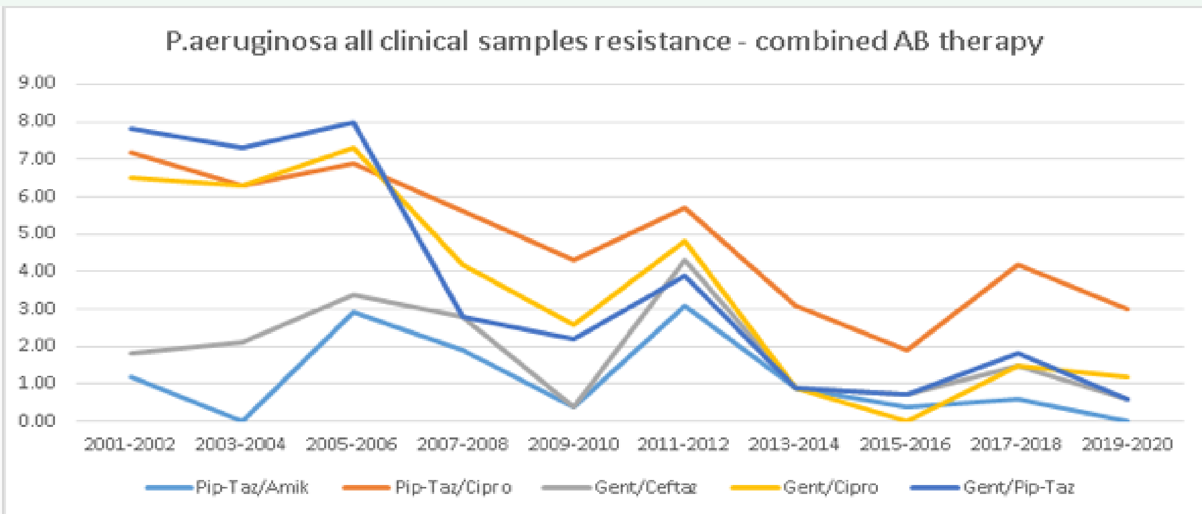
As for blood cultures, the value of analysis is limited by the small number of samples of an average of 4.5 per year. Resistance against all single agent antibiotics has been slightly decreasing over the years, except for ceftazidime, that shows a minimal increase [Graph 5]. In the past five years, the only detectable resistance is against piperacillin-tazobactam and meropenem, and both have decreased to 10% in 2019-2020.

Resistance of *P.aeruginosa* blood culture samples against combined antibiotic therapy has been decreasing, except for piperacillin-tazobactam+amikacin [Graph 1]. This increase is, however, due to a peak of resistance in 2011-12 of 25% that decreased to 10% by 2013-14 and to zero in all following years.

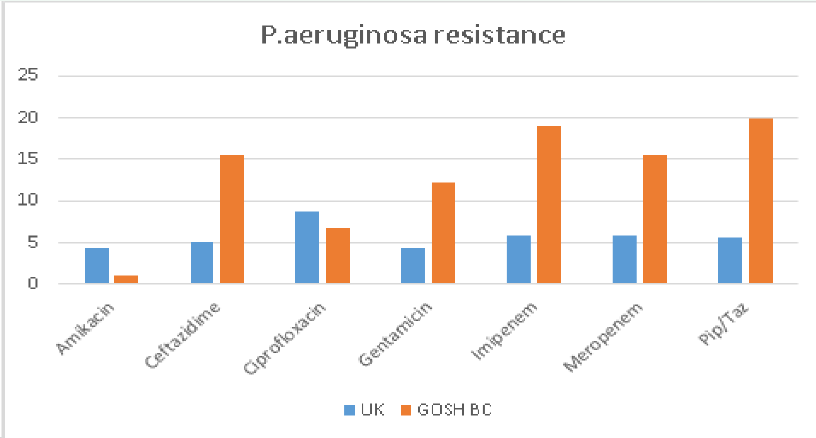
The highest resistance is against piperacillin-tazobactam+ciprofloxacin, that, following an initial drop from 22.2% to 7.7% increased to 37.5% in 2011-12 then gradually dropped to zero by the end of the study period. Of note, there is a peak of resistance against multiple antibiotics in the period of 2011-12, likely due to a few patients with multiresistant strains. The number of isolates in this period is not higher (8 in 2 years) than the average.

With the limitations of comparison in mind, there are some differences between the GOSH resistance data and that of ESPAUR (years of 2019-2020 for GOSH, 2019 for ESPAUR). Resistance is lower in GOSH than in the UK of *P.aeruginosa* blood culture isolates against amikacin, ciprofloxacin and gentamicin, but higher against ceftazidime, imipenem, meropenem and piperacillin-tazobactam [Graph 6]. These differences might reflect commonly used antibiotics in GOSH [Table1].

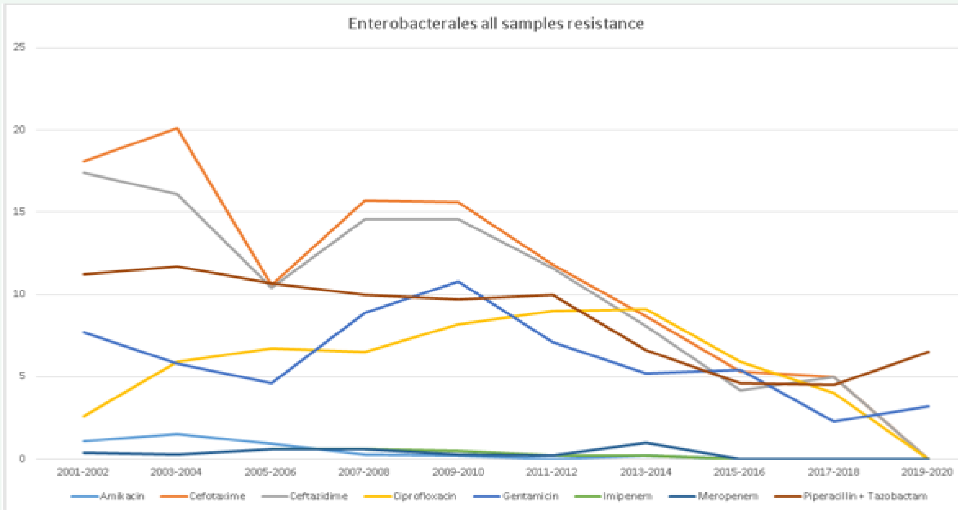
When comparing the ESPAUR 2019 data to the 20-year average resistance data of GOSH, GOSH has a higher resistance against all antibiotics, apart from amikacin and ciprofloxacin. Resistance against both antibiotics has disappeared altogether



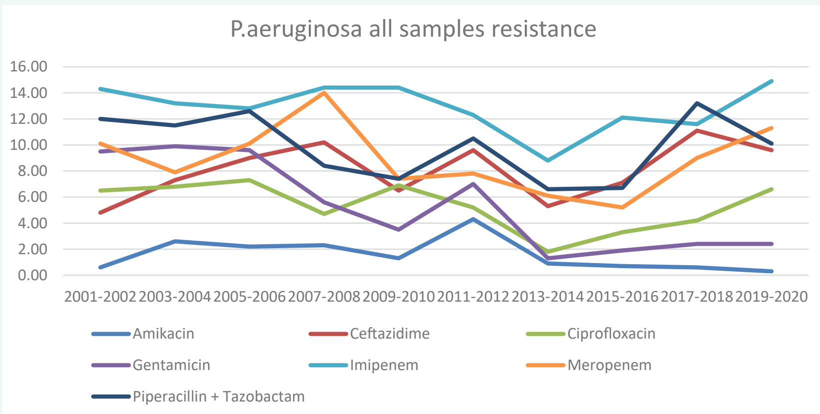
Graph 1: *P.aeruginosa* all clinical samples resistance against combined antibiotic therapy over 20 years



Graph 2: Comparison of *P.aeruginosa* BC resistance of Great Ormond Street Hospital (GOSH) and the United Kingdom (UK) as published by ESPAUR. GOSH data charted as the overall resistance of the study period of 20 years.



Graph 3: Enterobacterales all clinical samples resistance over the past 20 years



Graph 4: *P.aeruginosa* all clinical samples resistance against single agent antibiotics over 20 years

on the 2019 GOSH samples (see above), continuing a favourable trend. The average resistance of 12.5% against gentamicin has also disappeared on the 2019 samples. Resistance against the remaining antibiotics in 2019 are all lower than on the 20-year average [Graph 2].

ESPAUR measures resistance against the combination of 3 antibiotics, whereas the GOSH laboratories publish it against 2 antibiotics, making comparisons difficult. It can be said, however, that ESPAUR's 2-4% resistance against the 3 antibiotic combinations is much lower than GOSH's reaching as high as 35.5%.

Due to the multiple and highly adaptable resistance mechanisms of *P.aeruginosa* against many of the commonly used antibiotics in hospitals, treatment is challenging and the guidelines need frequent review based on newly emerging resistance patterns.

Enterobacterales

The group of Enterobacterales examined in this study consisted of *Citrobacter, Enterobacter, Erwinia, Escherichia, Hafnia, Klebsiell, Leclercia, Morganella, Pantoea, Pluralibacter gergoviae, Proteus, Raoultella* and *Serratia*. There have been 3661 clinical isolates of Enterobacterales on the intensive care units of our institution over the past 20 years [Graph 3], with samples between 16-260 per year, the highest number in 2013-14 and the lowest in 2019-20. Resistance is reassuringly decreasing against all antibiotics. The highest resistance was against cefotaxime in 2003-4 of 20% followed by 17.1% against ceftazidime in 2001-2, both decreased to zero by the end of the study period. Resistance against meropenem and imipenem is virtually non-existent throughout the period.

There were 451 Enterobacterales positive blood cultures (yearly average 22.5, range 19-33) [Graph 7]. All show a decreasing trend apart from resistance against ciprofloxacin, increasing from 7% to 12%. The highest initial resistance of cefotaxime (27.3%), ceftazidime (25.5%) and piperacillin-tazobactam (23.6%) decrease to 22.9%, 20.8% and 12.5% by 2019-20, respectively, although this trend is the sum of a dip of resistance against all antibiotics (except gentamicin) in 2015-16 followed by an increase.

As for antibiotic combinations, Gent/ceftaz, gent/Cipro, gent/piptaz, piptaz/amik all show a declining trend, while piptaz/Cipro is increasing.

Separate analysis of individual species enables comparison with the ESPAUR data:

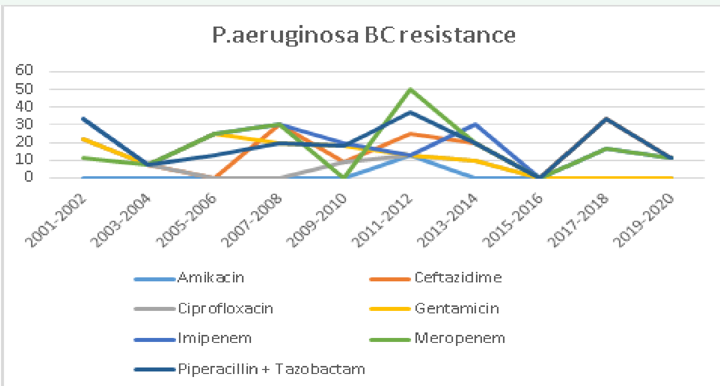
Escherichia coli

There are 95 *E. coli* positive blood cultures during the study period with a yearly average of 5 samples (range 3-7). Resistance goes as high as 42.9% against cefotaxime and ceftazidime, both in 2011-12, 30.8% against gentamicin and piperacillin-tazobactam in 2001-2 and 28.6% against ciprofloxacin between 2015-8. Resistance shows an increasing trend for ciprofloxacin (m=1.3945) cefotaxime (m=1.2248) ceftazidime (m=0.3958), while it is decreasing against piperacillin-tazobactam (m=-1.4055), amikacin (m=-0.4242) and gentamicin (m=-0.4085) and remains in essence zero for imipenem and meropenem throughout.

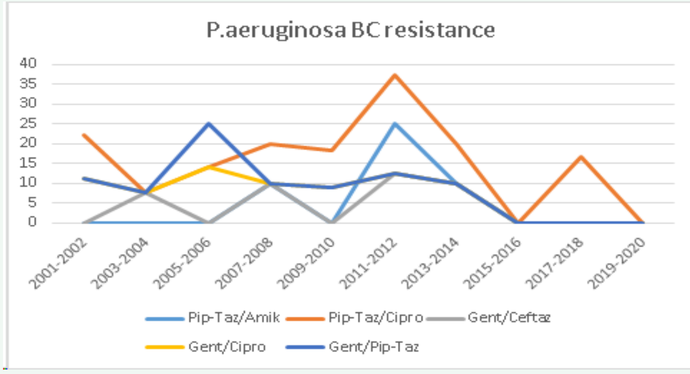
Resistance of *E. coli* grown from blood cultures against combination antibiotics is very high compared to the ESPAUR data [Graph 8]. While the latter reports 2-6% of the isolates over the past 5 years as resistant to a combination of antibiotics [2], the GOSH ICUs have as high as 15% of resistance in some of the years with the outlier of Gent/Ceftazidime combination in 2001 reported as 23.1%. Of note, ESPAUR reports resistance against combinations of 3 antibiotics, while the GOSH laboratory reports the same against combinations of 2 antibiotics. The small number of samples per year further limits the value of analysis.

Klebsiella pneumoniae

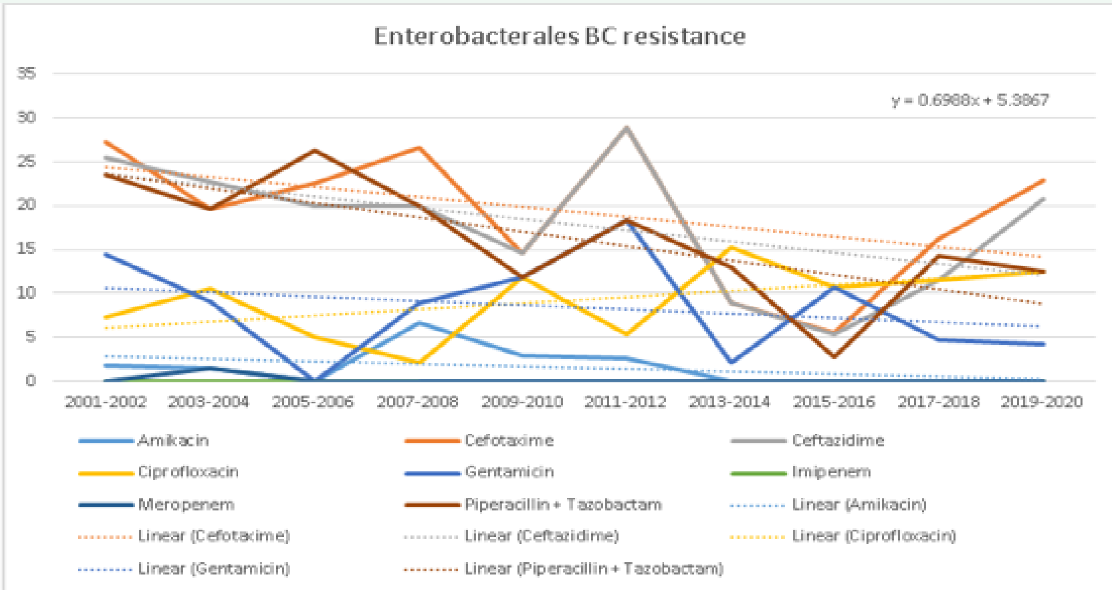
There are 47 samples of *K.pneumoniae* positive blood cultures during the study period, with a yearly average of 2.3, range 0-5. The highest resistance is 40% (of 5 samples) against



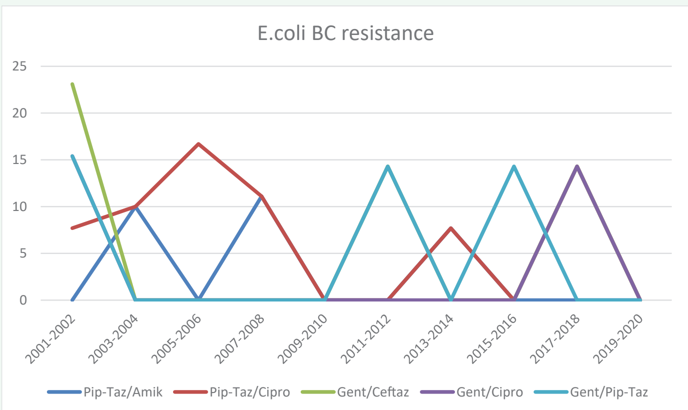
Graph 5: *P.aeruginosa* blood culture resistance against single agent antibiotic therapy over 20 years



Graph 6: *P.aeruginosa* blood culture resistance against combined antibiotic therapy over 20 years



Graph 7: Enterobacterales blood culture resistance trends over the past 20 years with trendlines.Trend equation of ciprofloxacin resistance displayed in the right upper corner.



Graph 8: E.coli blood culture resistance against combination antibiotics over the past 20 years

cefotaxime, ceftazidime and gentamicin in 2009-10, representing two patients with multiresistant chains [Graph 9]. Resistance of *K.pneumoniae* causing bloodstream infections shows a similar picture of resistance to those of E.coli to antibiotic combinations of up to 33.3% against piptaz/Cipro in 2019-20, gent/Cipro and gent/piptaz around 20%. Having had no resistant isolates at all up until 2009, resistance against all combinations have been rising throughout the 20 years. Although, if taken only the years when resistance first appeared, resistance trends have been declining, apart from piptaz/Cipro. Again, the small numbers of isolates each year limits value of the data.

Vancomycin resistant Enterococcus

There were 944 clinical isolates of *Enterococcus* in the study period, an average of 47 per year (range 34-60). Of the *E. faecalis* samples, none of them were vancomycin resistant. Vancomycin resistance of the *E. faecium* samples ranged between 0-80.4% with an overall 51.2% when counter for the whole 20-year period. Of other Enterococcus species (non-faecalis non-faecium) was 0-25%, overall, 1.6% for the whole period. Unfortunately, resistance of all species has been rising over the studied period.

As for blood culture isolates, of the –on average- yearly 10 samples (range 1-16), vancomycin resistance was 1% for the whole period. VRE faecium was isolated in only two periods, in 2003-2004 there was a 16.7% resistance, and in 2017-2018 a 2% resistance. There has been no VRE faecalis at any point [Graph 10].

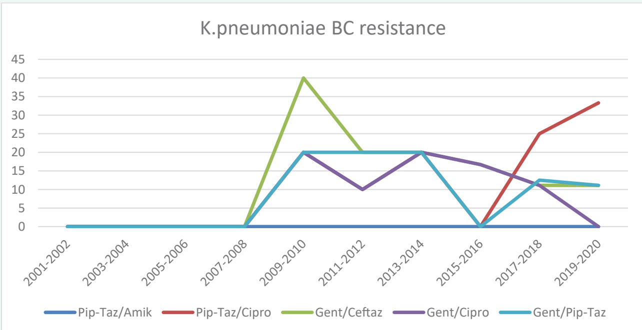
Glycopeptide resistance of blood culture isolates of Enterococci is high but has somewhat reduced in England between 2015 and 2019 from 17% to 15%, according to the ESPAUR data [3]. Although the blood cultures from the GOSH intensive care units have a much lower resistance, its sample size is very low with an average of only 10 *Enterococcus* positive blood cultures per year.

Methicillin-resistant Staphylococcus aureus (MRSA)

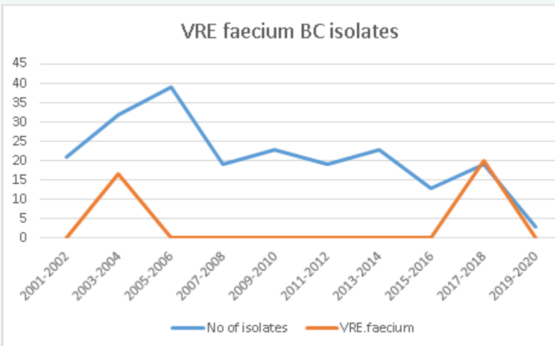
There were 3556 clinical isolates over the study period with a 178 samples per year on average (range 158-233) [Graph 12]. Flucloxacillin resistance is an average of 15.3% for the whole period, with a maximum of 25.4% in 2019-20 and a minimum of 12.6% in 2013-14. It shows a mildly increasing trend of m=0.2236.

Of the 185 blood culture isolates over the 20 years, overall resistance to flucloxacillin was 13% that is made up of a dip to 0% resistance in 2015-16 and a peak of 23% in 2017-18 [Graph 11].

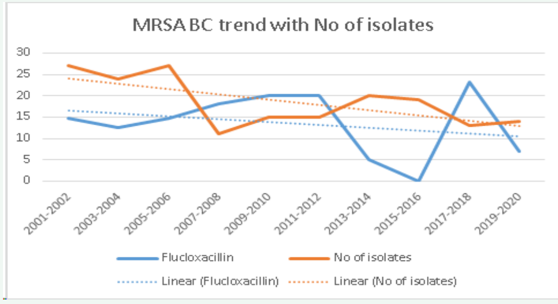
Resistance in 2019-20 was 7.1%. Over the years, resistance against all examined antibiotics (ciprofloxacin, flucloxacillin, gentamicin and amikacin) have decreased.



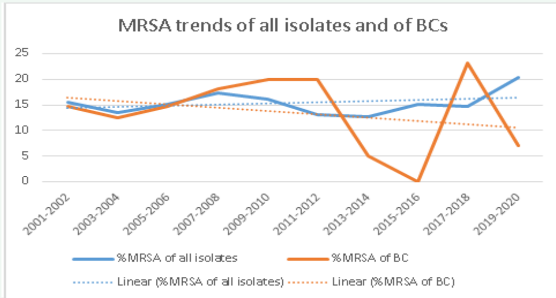
Graph 9: *K. pneumoniae* blood culture resistance



Graph 10: VRE faecium blood culture isolates. VRE faecalis not plotted as resistance zero throughout



Graph 11: MRSA positive blood cultures. Trend of the number of isolates and the percentage of MRSA of S.aureus positive blood cultures.



Graph 12: Trend of MRSA in all clinical isolates and in blood culture

Table 1: Comparison of *P.aeruginosa* BC resistance of Great Ormond Street Hospital (GOSH) and the United Kingdom (UK) as published by ESPAUR- 2019 data

	GOSH 2019	UK (ESPAUR) 2019
Amikacin	0	4.3
Ceftazidime	11.1	5
Ciprofloxacin	0	8.7
Gentamicin	0	4.3
Imipenem	11.1	5.9
Meropenem	11.1	5.9
Pip/Taz	11.1	5.6

The overall 13% methicillin resistance of blood cultures in our centre is higher than the nationally reported value [Graph 11]. However, the latest 2019-2020 value of 7.1% is comparable to the 6% of 2019 reported by ESPAUR [2]. The study results reflect the nationally reported increase in MRSA prevalence, as shown in all clinical isolates. ESPAUR calculated a 14% increase from a 20.5 per 100 000 population to 23.5 per 100 000 from 2015 to 2019 [2].

Despite the increasing prevalence, there is a decrease in the percentage of MRSA positive blood cultures, similarly to ESPAUR. This results likely reflect the work of the hospital infection control team that -following the detection of MRSA on an admission screen- notifies the care team, ensures isolation and elimination.

SUMMARY

Following antimicrobial resistance of sentinel pathogens is a cornerstone of antimicrobial stewardship. A 20-year retrospective study in the intensive care units of a tertiary level children's hospital in London, United Kingdom shows results overall comparable to those of ESPAUR with a few notable exceptions, likely reflecting international resistance due to overseas patients.

ACKNOWLEDGEMENT

This work was facilitated by the Project DRIVE Data Management Team at Great Ormond Street Hospital.

REFERENCES

1. Llor C, Bjerrum L. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. Ther Adv Drug Saf. 2014; 5: 229-241.

2. Rice LB. Federal Funding for the Study of Antimicrobial Resistance in Nosocomial Pathogens: no ESKAPE. J infect Dis. 2008; 197: 1079-1081.

3. English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR). 2022.