Annual report
Antimicrobial Resistance Surveillance Network
January 2018-December 2018

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Chapter 1 Summary of surveillance data

January 2018 to December 2018

Total number of isolates studied during the year 2018 was 60,497. The distribution of major groups of organisms in different specimens is shown in table 1.1 and figure 1.1. Members of Enterobacteriaceae were the commonest organisms in urine (82%), sterile body fluids (SS) (53%), deep infections (DI) (46%), superficial infections (SSI) (41%) and blood (38%). Non-fermenting gram-negative bacilli (NFGNB) were the predominant isolates in lower respiratory tract (LRT) (54%) and cerebrospinal fluid (CSF) (41%). Staphylococci constituted 32% of superficial infection isolates followed by blood (27%), CSF (21%) and deep infections (20%). Enterococci constituted 12% of isolates from sterile body fluids followed by deep infections (9%), urine (9%) and blood (6%). Yeast species were significant isolates in blood (6%) only.

The relative frequencies of various species isolated from patients presenting in OPDs and admitted to wards and ICUs are presented in table 1.2 and figures 1.2a & 1.2b. Overall, *Escherichia coli* was the commonest isolate (26%) followed by *Klebsiella pneumoniae* (15%), *Staphylococcus aureus* (12%) and *Pseudomonas aeruginosa* (12%). Gram negative organisms constituted 74 per cent of the isolates (44232 out of 59654 isolates). *E. coli*, *S. aureus* and *P. mirabilis* was more common in OPD isolates followed by ward and ICU. *K. pneumoniae*, *Acinetobacter* species and *E. faecium* were more common in ICU and least common in OPD isolates. *P. aeruginosa*, *E. faecalis* and coagulase negative staphylococci (CoNS) showed no such variation in distribution (Table 1.2, Figure 1.2a).

Enterobacteriaceae (other than salmonellae) constituted the major group (49%) of isolates overall (Table 1.1). Specimen wise distribution of major species of family Enterobacteriaceae is shown in table 1.3 and figures 1.3a & 1.3b. Overall, *Escherichia coli* was the commonest species (26%) followed by *Klebsiella pneumoniae* (15%), *Enterobacter cloacae* (1.5%) and *Proteus mirabilis* (1.8%) (Table 1.3, Figure 1.3 a,b). *E. coli* was the most predominant isolate from urine (58%), sterile body fluids (31%), blood (18%), superficial tissue infections (19%) and deep tissue infections (16%). Geographic area wise distribution (Table 1.4 and Figure 1.4) showed that isolates from eastern India had higher rates of *Klebsiella pneumoniae* than the rest of India. *Klebsiella* species were most predominant species in lower respiratory tract (21%) and CSF (11%). *Enterobacter cloacae* constituted 1.5% of CSF and 2.9% of deep tissue infections. *Proteus mirabilis* were common in 5% of deep and 2.8% of superficial tissue infections.

Salmonella Typhi constituted 78% of all *Salmonella* isolates and 1 % of all isolates, followed by *S.* Paratyphi A (14%) and other *Salmonella* species (8%) (Table

1.5a and Figure 1.5). There was no significant difference in distribution of *Salmonella* species in different geographical areas (Table 1.5b).

Nonfermenting Gram negative bacteria (NFGNB) constituted 23% of all isolates (table 1.1). Amongst the NFGNB, *Pseudomonas aeruginosa* was the commonest isolate (12%) followed by *Acinetobacter baumanii* (6%). *Stenotrophomonas maltophilia* and *Burkholderia cepacian* accounted for 0.5% and 0.3% of all isolates respectively. *P. aeruginosa* was grossly predominant in LRT (26%) followed by miscellaneous specimens (17%), superficial and deep tissue infections (13%). *A.baumanii* were predominant isolates from LRT (15%), deep infection (11%), CSF (8%), superficial infection (6%) and blood (5%) (Tables 1.6a, Figure 1.6). *Pseudomonas aeruginosa* was the predominant species of NFGNB amongst clinical isolates overall and in all geographical areas (Table 1.6b, Figure 1.7).

Out of the staphylococcus species, *S. aureus* was the predominant species in superficial infections (28%), deep infections (16%), LRT (5.9%), miscellaneous infections (16%), sterile body fluids (7%), blood (9%) and urine (0.7%) (Table 1.8a). CoNS were the predominant isolates in blood (18%) and CSF (14%) reflecting the high incidence of shunt infections and intravascular device associated infections respectively. In CSF and sterile body fluids, *S. epidermidis* was more frequent reflecting the ability of the species to form biofilms and the high incidence of shunt-associated and dialysis-associated infections. *S. saprophyticus* was most common in urine (table 1.8a). Among the coagulase negative staphylococcus species (CoNS), *S. haemolyticus* (25%) and *S. epidermidis* (24%) were the commonest species followed by *S. hominis* (Table 1.8b).

Enterococci constituted 6% of all isolates overall (Table 1.1). Among the *Enterococcus* species, *E. faecalis* and *E. faecium* accounted for 91% of the isolates. *E. faecalis* (67%) largely outnumbered *E. faecium* (24%). *E. faecium* was relatively more frequent in CSF (4%) and blood (3.5%) while *E.faecalis* was more frequent in deep infections (7%) and urine (5%) than other specimens (Table 1.9a). The relative frequencies of *E. faecalis* and *E. faecium* differed in different geographical areas. *E. faecium* was most frequent in eastern India (2.9%) and northern (2.4%) and *E. faecalis* was frequent in central part of India (2.3%) (Table 1.9b).

Table 1.1 Specimen wise distribution of major groups of organisms

	Blood n=11783 (%)	**Urine n=13658 (%)**	**LRT n =10058 (%)**	**SSI n=15208 (%)**	**DI n=351 1 (%)**	**SS n =1409 (%)**	**CSF n=390 (%)**	**Faeces n=536 (%)**	**Others n=3944 (%)**	**Overall n=60497 (%)**
Enterobacteriaceae	4430 (37.6)	11180 (81.9)	3522 (35)	6243 (41.1)	1607 (45.8)	746 (52.9)	112 (28.7)	156 (29.1)	1670 (42.3)	29666 (49)
Enteric *Salmonella*	620 (5.3)	4 (0)	0 (0)	13 (0.1)	2 (0.1)	3 (0.2)	0 (0)	120 (22.4)	2 (0.1)	764 (1.3)
NFGNB	1862 (15.8)	919 (6.7)	5392 (53.6)	3325 (21.9)	883 (25.1)	296 (21)	158 (40.5)	5 (0.9)	962 (24.4)	13802 (22.8)
Staphylococci	3153 (26.8)	144 (1.1)	617 (6.1)	4855 (31.9)	701 (20)	144 (10.2)	80 (20.5)	2 (0.4)	803 (20.4)	10499 (17.4)
Enterococci	677 (5.7)	1259 (9.2)	21 (0.2)	727 (4.8)	304 (8.7)	162 (11.5)	28 (7.2)	10 (1.9)	254 (6.4)	3442 (5.7)
Fungi	713 (6.1)	146 (1.1)	24 (0.2)	28 (0.2)	9 (0.3)	20 (1.4)	9 (2.3)	0 (0)	242 (6.1)	1191 (2)

Note:

1. **Blood** includes: Blood-central catheter, Blood-peripheral and Peripheral catheter-blood.
2. **LRT** (Lower Respiratory Tract) includes: BAL, Sputum, Lung aspirate, Endotracheal aspirate (ETA) and Lobectomy tissue (Lung tissue).
3. **SSI: Superficial Infection** includes: SST (Skin & Soft Tissue), Pus/exudate, Wound swab, Superficial Biopsy and Superficial Tissue.
4. **Deep Infection** includes: Abscess aspirate, Pus aspirate, Deep Biopsy and Deep Tissue.
5. **SS** (Sterile sites) includes: Fluid from sterile spaces, Abdominal fluid, Intracostal tube fluid, Pancreatic drain fluid, Pericardial fluid, Peritoneal fluid and Pleural fluid.

Table 1.2 Distribution of species of organisms in isolates from OPD, ward and ICU

	OPD n=19210	**Ward n=32046**	**ICU n=9241**	**Overall n=60497**
E. coli	5814 (30.3)	8436 (25.8)	1332 (14.4)	15582 (25.8)
K. pneumoniae	2442 (12.7)	4504 (14.1)	1837 (19.9)	8783 (14.5)
S. aureus	3285 (17.1)	3443 (10.7)	554 (6)	7282 (12)
P. aeruginosa	2441 (12.7)	3617 (11.3)	1215 (13.1)	7273 (12)
A. baumannii	504 (2.6)	2103 (6.6)	1262 (13.7)	3869 (6.4)
E. faecalis	501 (2.6)	1061 (3.3)	219 (2.4)	1781 (2.9)
A. calcoaceticus	325 (1.7)	572 (1.8)	533 (5.8)	1430 (2.4)
E. faecium	214 (1)	745 (2)	257 (3)	1216 (2)
Staphylococcus spp	258 (1.3)	765 (2.4)	160 (1.7)	1183 (2)
P. mirabilis	409 (2.1)	553 (1.7)	101 (1.1)	1063 (1.8)

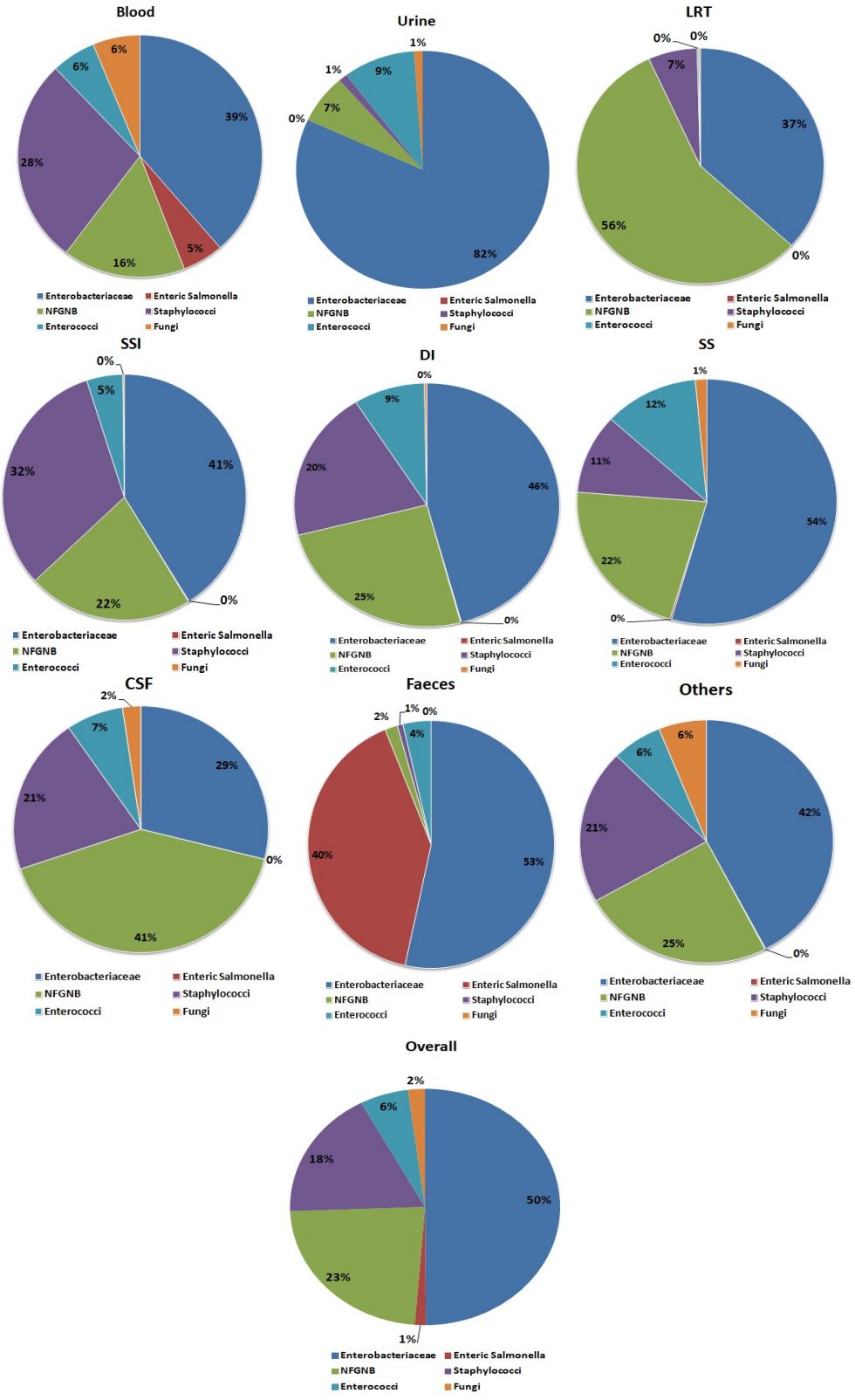


Figure 1.1 Specimen wise distribution of major groups of organisms

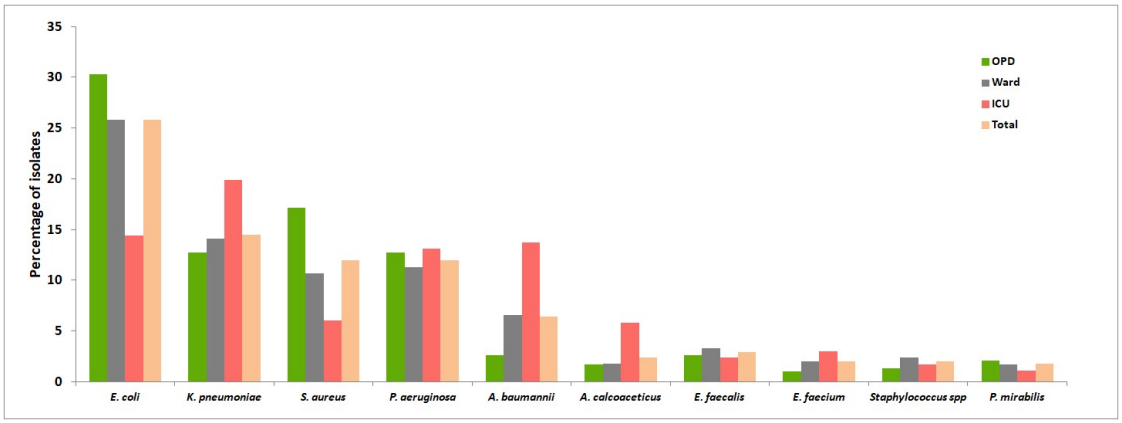


Figure 1.2a Distribution of species of organisms in isolates from OPD, ward and ICU

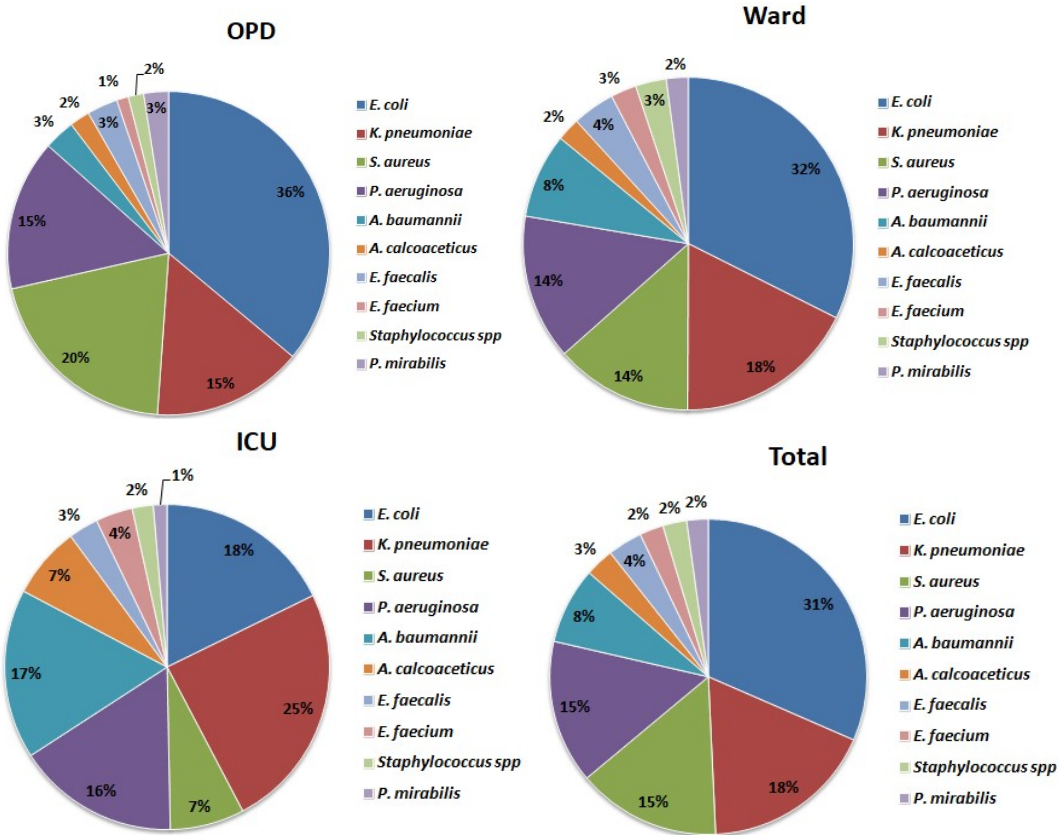


Figure 1.2b Distribution of species of organisms in isolates from OPD, ward and ICU

Table 1.3 Specimen wise distribution of major species of family Enterobacteriaceae

	Blood n=11783 (%)	**Urine n=13658 (%)**	**LRT n=10058 (%)**	**SI n=15208 (%)**	**DI n=3511 (%)**	**CSF n=390 (%)**	**SS n=1409 (%)**	**Others n=3944 (%)**	**Overall n=60497 (%)**
Escherichia coli	2134 (18)	7853 (58)	755 (8)	2899 (19)	572 (16)	40 (10)	432 (31)	784 (20)	15582 (26)
Klebsiella pneumoniae	1785 (15)	2065 (15)	2054 (21)	1653 (11)	456 (13)	42 (11)	185 (13)	514 (13)	8783 (15)
Enterobacter cloacae	203 (1.7)	142 (1)	96 (1)	277 (1.8)	103 (2.9)	6 (1.5)	21 (1.5)	67 (1.7)	920 (1.5)
Citrobacter koseri	16 (0.1)	179 (1.3)	29 (0.3)	156 (1)	39 (1)	2 (0.5)	2 (0.1)	20 (0.5)	444 (0.7)
Serratia marcescens	61 (0.5)	32 (0.2)	83 (0.8)	39 (0.3)	11 (0.3)	3 (0.8)	9 (0.6)	10 (0.3)	248 (0.4)
Proteus mirabilis	44 (0.4)	238 (1.7)	68 (0.7)	430 (2.8)	174 (5)	0 (0)	14 (1)	93 (2.4)	1063 (1.8)
Providencia rettgeri	2 (0)	33 (0.2)	20 (0.2)	44 (0.3)	42 (1.2)	0 (0)	4 (0.3)	2 (0.1)	148 (0.2)
Morganella morganii	29 (0.2)	63 (0.5)	17 (0.2)	135 (0.9)	59 (1.7)	1 (0.3)	3 (0.2)	16 (0.4)	323 (0.5)
Klebsiella spp.	31 (0.3)	236 (1.7)	268 (2.7)	197 (1.3)	6 (0.2)	7 (1.8)	29 (2.1)	54 (1.4)	828 (1.4)

Table 1.4 Geographical area wise distribution of major species of family Enterobacteriaceae

	North n=21403 (%)	**Central n=826 (%)**	**East n=2649 (%)**	**West n=16539 (%)**	**South n=27637 (%)**	**National n=69054 (%)**
Escherichia coli	4580 (21.4)	230 (27.8)	622 (23.5)	5193 (31.4)	7351 (26.6)	17954 (26)
Klebsiella pneumoniae	3274 (15.3)	117 (14.2)	543 (20.5)	2067 (12.5)	4228 (15.3)	10219 (14.8)
Enterobacter cloacae	278 (1.3)	21 (2.5)	11 (0.4)	165 (1)	553 (2)	1036 (1.5)
Proteus mirabilis	342 (1.6)	9 (1.1)	40 (1.5)	314 (1.9)	497 (1.8)	1242 (1.8)
Citrobacter koseri	43 (0.2)	4 (0.5)	16 (0.6)	248 (1.5)	193 (0.7)	483 (0.7)

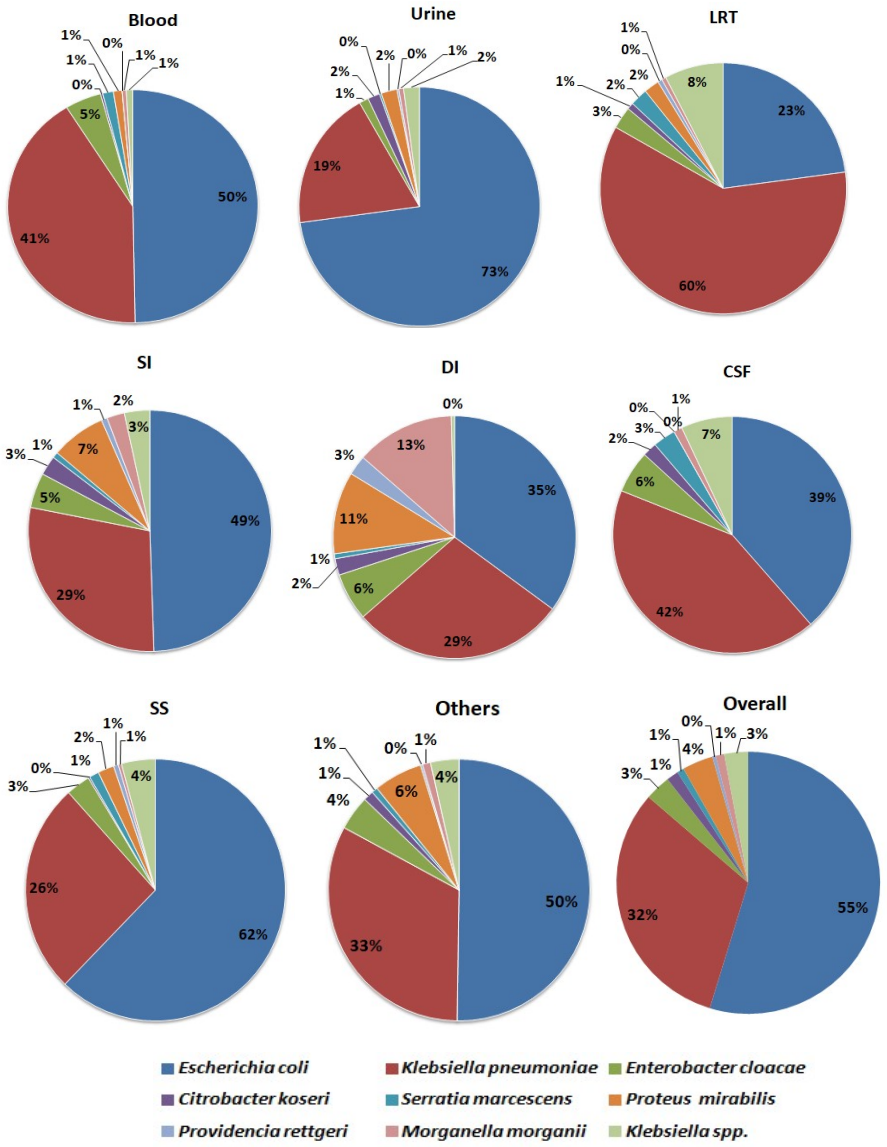


Figure 1.3a Specimen wise distribution of major species of family Enterobacteriaceae

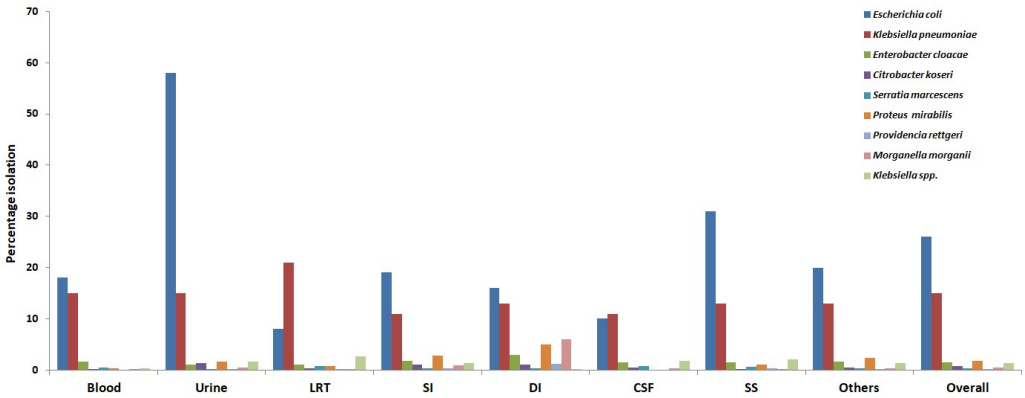


Figure 1.3b Specimen wise distribution of major species of family Enterobacteriaceae

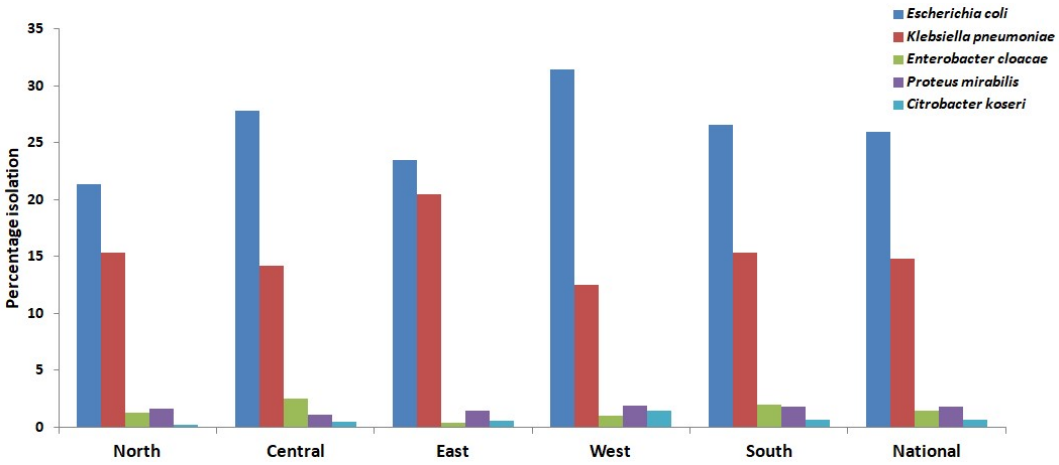


Figure 1.4 Geographical area wise distribution of major species of family Enterobacteriaceae

Table 1.5a Species wise distribution of Salmonella species

	Blood n=11783 (%)	**Faeces n=536 (%)**	**Others n=48178 (%)**	**Overall n=60497 (%)**
Total Salmonella	620 (5.3)	120 (22.4)	24 (0.05)	764 (1.3)
***Salmonella* Para A**	101 (0.9)	0 (0)	5 (0)	106 (0.2)
***Salmonella* Typhi**	489 (4.2)	98 (18.3)	11 (0)	598 (1)
***Salmonella* spp**	30 (0.3)	22 (4.1)	8 (0)	60 (0.1)

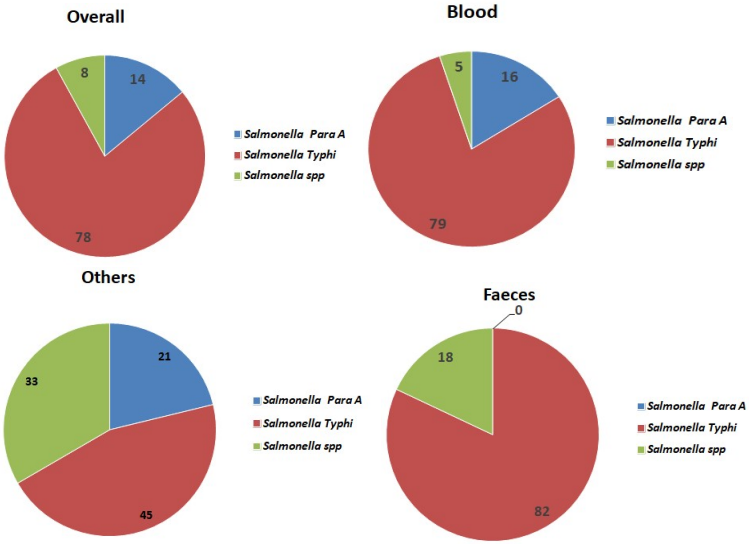


Figure 1.5. Species wise distribution of Salmonella species

Table 1.5b Geographical area wise distribution of Salmonella species

	North n= 4892	Central n= 92	East n=424	West n= 1750	South n=5660	Overall n=12818
Total Salmonella	310 (6.3)	7 (7.6)	1 (0.2)	116 (6.6)	204 (3.6)	638 (5)
Salmonella Typhi	225 (4.6)	7 (7.6)	1 (0.2)	98 (5.6)	175 (3.1)	506 (3.9)

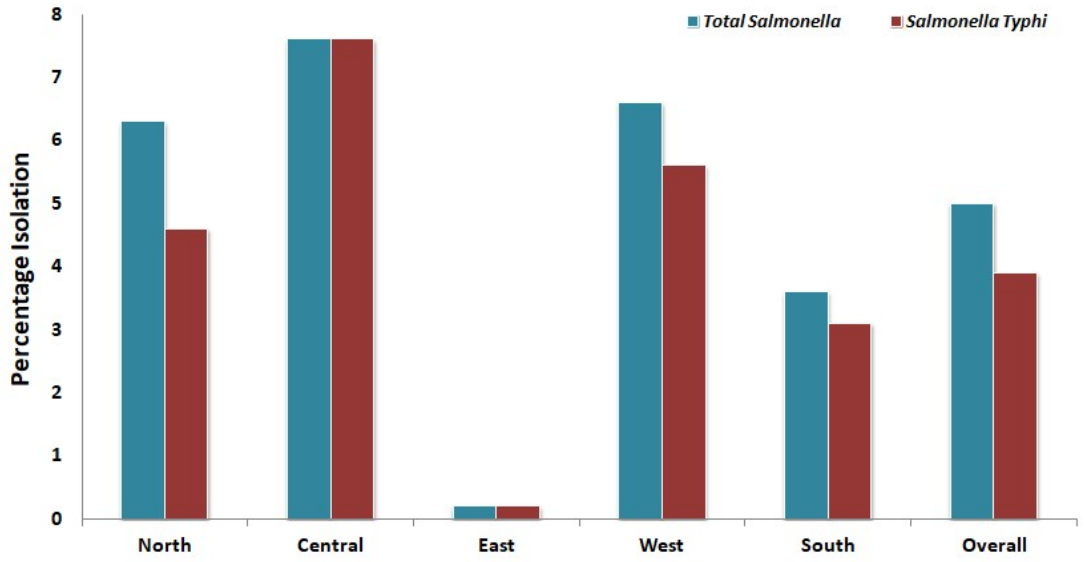


Figure 1.5b Geographical area wise distribution of Salmonella species

Table 1.6a Specimen wise distribution of NFGNB

	Blood n=11783 (%)	Urine n=13658 (%)	LRT n=10058 (%)	SI n=15208 (%)	DI n=3511 (%)	CSF n=390 (%)	SS n=1409 (%)	Others n=3944 (%)	Overall n=60497 (%)
Total NFGNB	1862 (15.8)	919 (6.7)	5392 (53.6)	3325 (21.9)	883 (25.1)	158 (40.5)	296 (21)	962 (24.4)	13802 (22.8)
P. aeruginosa	650 (5.5)	723 (5.3)	2632 (26.2)	1951 (12.8)	472 (13.4)	43 (11)	144 (10.2)	655 (16.6)	7273 (12)
A. baumannii	535 (4.5)	96 (0.7)	1539 (15.3)	980 (6.4)	369 (10.5)	30 (7.7)	51 (3.6)	268 (6.8)	3869 (6.4)
A. calcoaceticus	258 (2.2)	35 (0.3)	814 (8.1)	212 (1.4)	6 (0.2)	46 (11.8)	57 (4)	2 (0.1)	1430 (2.4)
S. maltophilia	110 (0.9)	15 (0.1)	114 (1.1)	20 (0.1)	3 (0.1)	2 (0.5)	19 (1.3)	10 (0.3)	293 (0.5)
B. cepacia	103 (0.9)	15 (0.1)	38 (0.4)	13 (0.1)	8 (0.2)	0 (0)	5 (0.4)	4 (0.1)	186 (0.3)

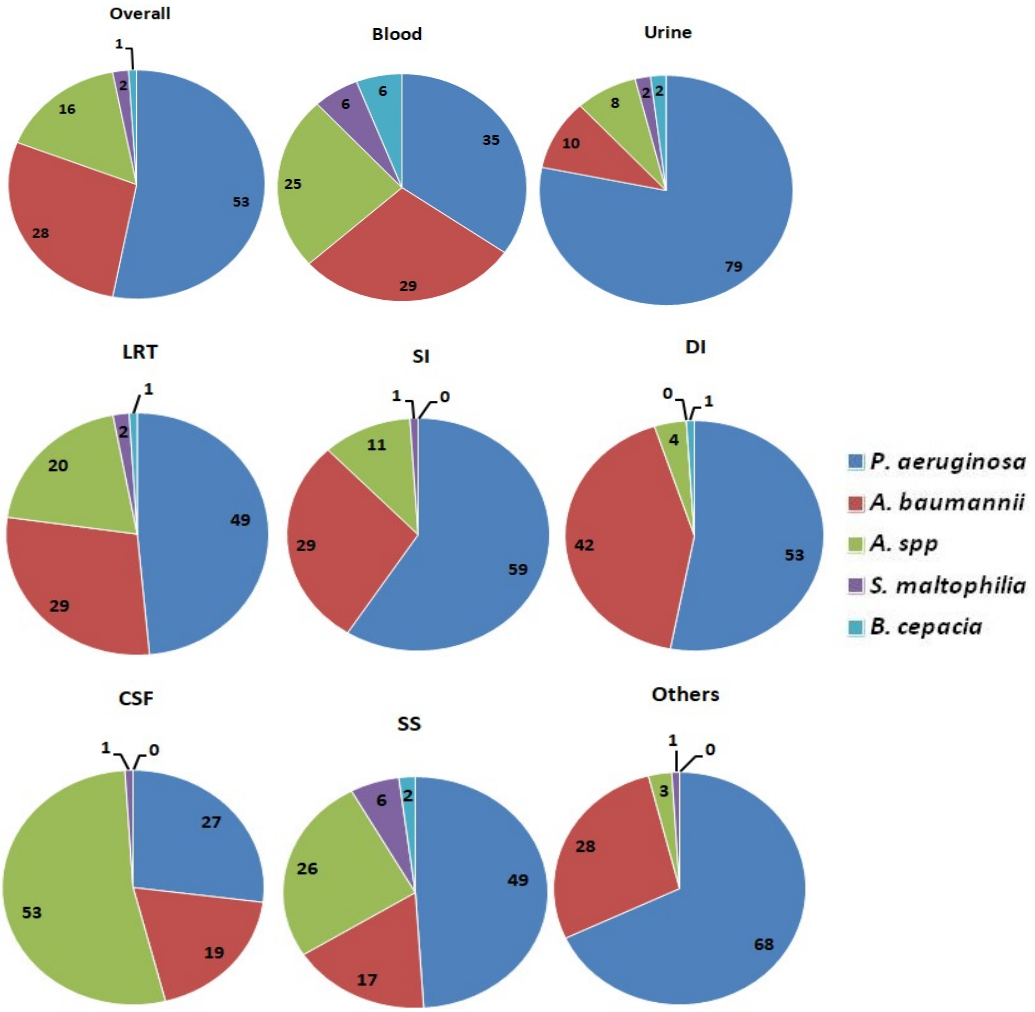


Figure 1.6 Specimen wise distribution of NFGNB

Table 1.6b Geographical area wise distribution of NFGNB in Total (except faeces)

	North (n=21403)	**Central (n=826)**	**East (n=2649)**	**West (n=16539)**	**South (n=27637)**	**Overall (n=69054)**
P. aeruginosa	2559 (12)	70 (8.5)	338 (12.8)	2180 (13.2)	3488 (12.6)	8635 (12.5)
A. baumannii	1530 (7.1)	45 (5.4)	139 (5.2)	850 (5.1)	1863 (6.7)	4427 (6.4)
A. calcoaceticus	1361 (6.4)	0 (0)	0 (0)	1 (0)	68 (0.2)	1430 (2.1)

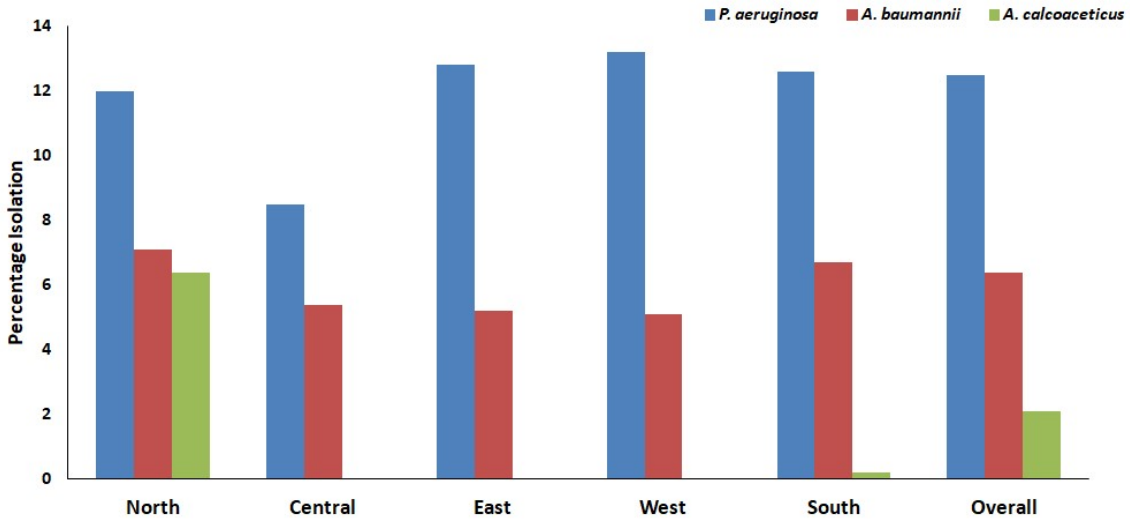


Figure 1.7 Geographical area wise distribution of NFGNB

Table 1.8a Specimen wise relative distribution of *S. aureus* and CoNS species

	Blood n=11783 (%)	**Urine n=13658 (%)**	**LRT n=10058 (%)**	**SI n=15208 (%)**	**DI n=3511 (%)**	**CSF n=390 (%)**	**SS n=1409 (%)**	**Others n=3944 (%)**	**Overall n=60497 (%)**
Total Staphylococci	3153 (26.8)	144 (1.1)	617 (6.1)	4855 (31.9)	701 (20)	80 (20.5)	144 (10.2)	803 (20.4)	10499 (17.4)
S. aureus	1046 (8.9)	98 (0.7)	597 (5.9)	4214 (27.7)	572 (16.3)	25 (6.4)	94 (6.7)	635 (16.1)	7282 (12)
MSSA	614 (5.2)	60 (0.4)	367 (3.6)	2461 (16.2)	380 (10.8)	9 (2.3)	57 (4)	437 (11.1)	4386 (7.2)
MRSA	423 (3.6)	38 (0.3)	228 (2.3)	1716 (11.3)	191 (5.4)	16 (4.1)	37 (2.6)	195 (4.9)	2844 (4.7)
CoNS	2107 (17.9)	46 (0.3)	20 (0.2)	641 (4.2)	129 (3.7)	55 (14.1)	50 (3.5)	168 (4.3)	3217 (5.3)
Staphylococcus haemolyticus	444 (3.8)	7 (0.1)	9 (0.1)	214 (1.4)	68 (1.9)	9 (2.3)	11 (0.8)	36 (0.9)	798 (1.3)
Staphylococcus epidermidis	465 (3.9)	8 (0.1)	3 (0)	182 (1.2)	26 (0.7)	26 (6.7)	14 (1)	36 (0.9)	760 (1.3)

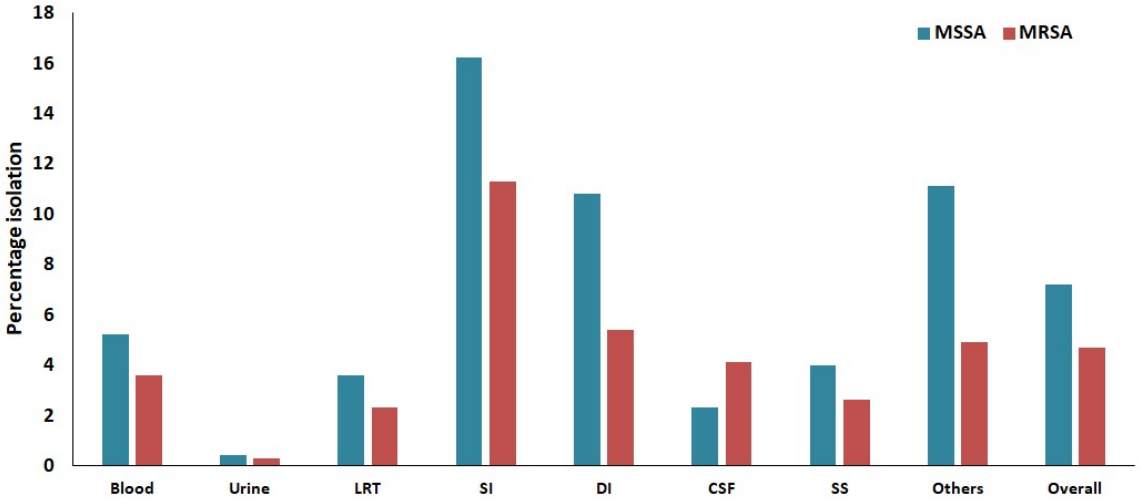


Figure 1.8a Specimen wise relative distribution of MSSA and MRSA

Table 1.8b Specimen wise relative distribution of CoNS species

	Blood n=2107 (%)	**Urine n=46 (%)**	**LRT n=20 (%)**	**SI n=641 (%)**	**DI n=129 (%)**	**CSF n=55 (%)**	**SS n=50 (%)**	**Faeces n= 1 (%)**	**Others n=168 (%)**	**Overall n=3217 (%)**
S.lugdenesis	13 (0.6)	3 (6.5)	0 (0)	24 (3.7)	4 (3.1)	2 (3.6)	1 (2)	0 (0)	10 (5.9)	57 (1.8)
S.haemolyticus	444 (21.1)	7 (15.2)	9 (45)	214 (33.4)	68 (52.7)	9 (16.4)	11 (22)	0 (0)	36 (21.4)	798 (24.8)
S.epidermidis	465 (22.1)	8 (17.4)	3 (15)	182 (28.4)	26 (20.2)	26 (47.3)	14 (28)	0 (0)	36 (21.4)	760 (23.6)
S.hominis	329 (15.6)	1 (2.2)	2 (10)	38 (5.9)	10 (7.6)	7 (12.7)	7 (14)	0 (0)	8 (4.7)	402 (12.5)
S.saprophyticus	3 (0.1)	5 (10.9)	0 (0)	4 (0.6)	3 (2.3)	1 (1.8)	0 (0)	1 (100)	0 (0)	17 (0.5)
Staphylococcus spp	853 (40.5)	22 (47.8)	6 (30)	179 (27.9)	18 (13.9)	10 (18.2)	17 (34)	0 (0)	78 (46.4)	1183 (36.8)

Table 1.8c Geographical area wise relative distribution of *S.aureus*, MSSA, MRSA and CoNS in Total (except faeces)

	North n=21403 (%)	**Central n=826 (%)**	**East n=2649 (%)**	**West n=16539 (%)**	**South n=27637 (%)**	**Overall n=69054 (%)**
Total *S. aureus*	2635 (12.3)	105 (12.7)	396 (14.9)	1562 (9.4)	3169 (11.5)	7867 (11.4)
MSSA	1194 (5.6)	60 (7.3)	222 (8.4)	806 (4.9)	2408 (8.7)	4690 (6.8)
MRSA	1400 (6.5)	45 (5.4)	174 (6.6)	749 (4.5)	756 (2.7)	3124 (4.5)
CoNS	1352 (6.3)	87 (10.5)	72 (2.7)	1037 (6.3)	1180 (4.3)	3728 (5.4)

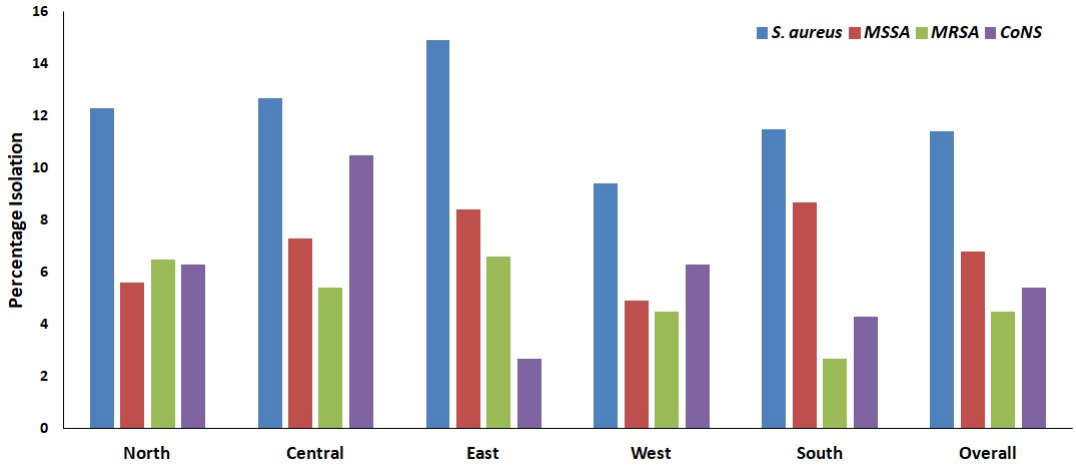


Figure 1.8c Geographical area wise relative distribution of MSSA and MRSA

Table 1.9a Specimen wise distribution of Enterococcus species

	Blood n=11783 (%)	**Urine n=13658 (%)**	**LRT n=10058 (%)**	**SI n=15208 (%)**	**DI n=3511 (%)**	**CSF n=390 (%)**	**SS n=1409 (%)**	**Others n=3944 (%)**	**Overall n=60497 (%)**
E. faecalis	217 (1.8)	676 (4.9)	4 (0)	459 (3)	235 (6.7)	8 (2.1)	42 (3)	138 (3.5)	1781 (2.9)
E. faecium	415 (3.5)	399 (2.9)	5 (0)	201 (1.3)	62 (1.8)	16 (4.1)	52 (3.7)	61 (1.5)	1216 (2)
Enterococcus spp	45 (0.4)	184 (1.3)	12 (0.1)	67 (0.4)	7 (0.2)	4 (1)	68 (4.8)	55 (1.4)	445 (0.7)

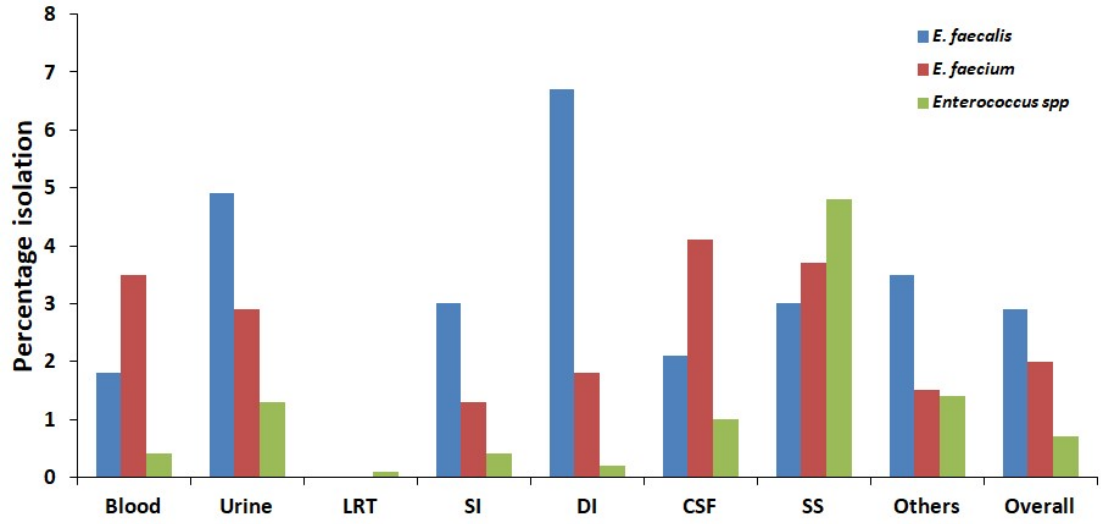


Figure 1.9a Specimen wise distribution of Enterococcus species

Table 1.9b Geographical area wise relative frequencies of the common species of enterococci

	North n=21403 (%)	**Central n=826 (%)**	**East n=2649 (%)**	**West n=16539 (%)**	**South n=27637 (%)**	**Overall n=69054 (%)**
E. faecalis	284 (1.3)	19 (2.3)	12 (0.5)	220 (1.3)	1381 (5)	1916 (2.8)
E. faecium	519 (2.4)	11 (1.3)	78 (2.9)	183 (1.1)	558 (2)	1349 (2)

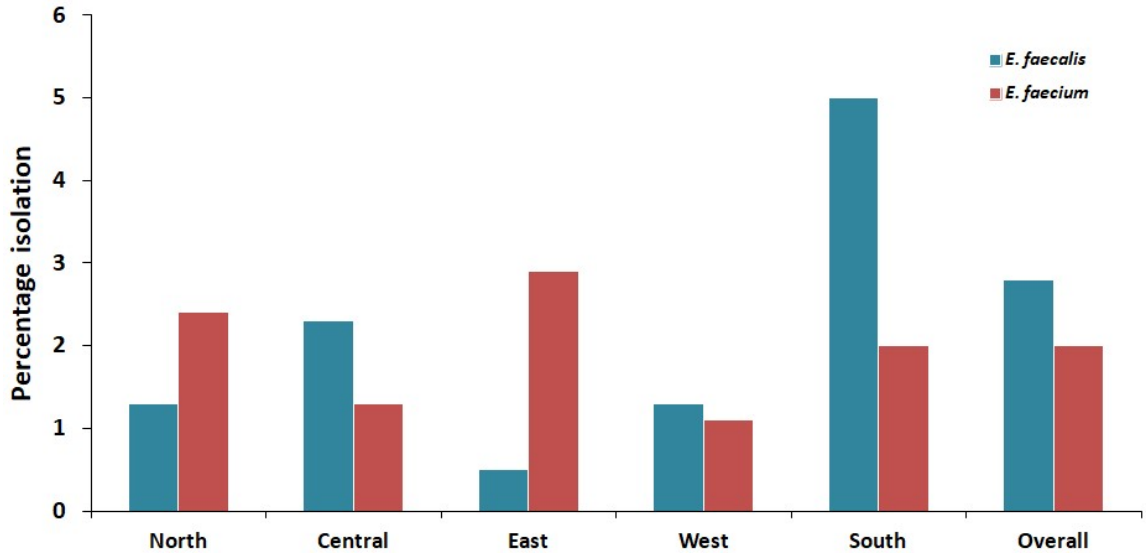


Figure 1.9b Geographical area wise relative frequencies of the common species of enterococci

Chapter 2 Enterobacteriaceae

Summary of results

All isolates of family Enterobacteriaceae were tested for susceptibility to amikacin, cefotaxime, ceftazidime, ciprofloxacin, levofloxacin, colistin, imipenem, meropenem, ertapenem and piperacillin-tazobactam.

Overall, maximum susceptibility was shown against colistin (92%) followed by amikacin (68%) and carbapenems (60-65%). Half (52%) of the isolates were susceptible to piperacillin-tazobactam. Colistin resistance was more frequent in *Klebsiella*spp (9%) and *Enterobacter* spp (7%) than *E. coli* (1%). Most isolates showed good (72-93%) susceptibility to amikacin except *Providencia* spp (53%) and *Klebsiella*spp (52%). *Klebsiella*spp showed poor susceptibility (48-53%) to carbapenems and piperacillin-tazobactam (41%) as compared to other species. The cephalosporins were moderately active against *Serratia*spp, *Proteus* spp and *Morganella*spp but poor against other species. The fluoroquinolones showed poor susceptibility (< 40%) in all species except *Serratia*spp and *Enterobacter* spp. *E. coli* showed far lower susceptibility to fluoroquinolones and 3G cephalosporins than *Klebsiella* spp and *Enterobacter* species. Urinary isolates showed overall poor susceptibility (< 40%) to 3G cephalosporins, fluoroquinolones and cotrimoxazole. *E.* coli showed good susceptibility to fosfomycin (90%) and nitrofurantoin (86%).Stratified data from OPD, Wards and ICUs consistently showed that the OPD isolates were the most susceptible and the ICU isolates were the most resistant.

A total of 369 *E. coli* and 374 *Klebsiella pneumoniae* isolates from 7 centres were subjected to multiplex PCR for 18 genes. TEM was most prevalent (54%) followed by OXA-1 (22%) and SHV (16%). AIIMS and PGI showed High prevalence of TEM, moderate prevalence of OXA-1 and low prevalence of SHV. Hinduja Hospital showed moderate prevalence of all three. TMC and SGRH showed high prevalence of OXA-1 followed by SHV and TEM. CMC showed high prevalence of TEM, moderate SHV and low OXA-1. JIPMER had moderate TEM and negligible SHV and OXA-1. In our isolates CTX M15 was most frequent (40%) followed by CTX M1, CTX M-8/25, CTX M-9 and CTX M-2.CTX M-15 was highly prevalent in isolates from AIIMS and Hinduja followed by PGIMER, CMC, JIPMER, SGRH and TMC.

NDM was the most prevalent (27%) carbapenemase followed by VIM (19%), IMP (15%) and KPC (15%). IMP and VIM was more prevalent in isolates from Hinduja and JIPMER and very low in SGRH, CMC and TMC. KPC was most common in AIIMS and Hinduja and least in SGRH, CMC and TMC. NDM was most prevalent in isolates from the north Indian centres including AIIMS followed by PGIMER and SGRH. It was relatively lower in the centres from southern and eastern India. *K. pneumoniae* isolates showed higher

prevalence of TEM, SHV, KPC and NDM and lower prevalence of OXA-1 and VIM than *E. coli* isolates. Prevalence of AmpC beta lactamases was below 10%.

Detailed analysis of results

All the isolates of family Enterobacteriaceae were tested for susceptibility to amikacin, cefotaxime, ceftazidime, ciprofloxacin, levofloxacin, colistin, imipenem, meropenem, ertapenem and piperacillin-tazobactam (Table 1 and Figure 1). Overall, maximum susceptibility was shown against colistin (92%) followed by amikacin (68%) and carbapenems (60-65%). Half (52%) of the isolates were susceptible to piperacillin-tazobactam. Colistin resistance was more frequent in *Klebsiella* spp (9%) and *Enterobacter* spp (7%) than *E. coli* (1%). Most isolates showed good (72-93%) susceptibility to amikacin except *Providencia* spp (53%) and *Klebsiella* spp (52%). There was a minor difference in susceptibility to imipenem (65%), meropenem (63%) and ertapenem (60%). *Klebsiella* spp showed poor susceptibility (48-53%) to carbapenems as compared to other species (63-94%). Susceptibility to piperacillin-tazobactam was good in *Proteus* spp (91%), *Morganella* spp (81%) and *Serratia* spp (76%) but poor in Klebsiella spp (41%). The cephalosporins were moderately active against *Serratia* spp, *Proteus* spp and *Morganella* spp but poor against other species. The fluoroquinolones showed poor susceptibility (< 40%) in all species except *Serratia* spp (~ 80%) and *Enterobacter* spp (~ 60%).

The susceptibility of the three major species of family Enterobacteriaceae, *E. coli*, *Klebsiella* spp and *Enterobacter* species are separately analyzed according to the specimen type, blood, lower respiratory tract, skin and superficial tissue infections and urine (Table 2-5, Figure 2-5).

Table 2.1 Results of susceptibility of Enterobacteriaceae to various antibiotics tested (results in %).

	Amikacin	Cefotax	Ceftazid	Cipro	Levoflox	Colistin	Imipen	Meropen	Ertapen	Pip-taz
	S	S	S	S	S	S	S	S	S	S
E. coli	80	17	24	23	15	99	75	69	65	54
Klebsiella	52	24	29	36	28	91	53	50	48	41
Enterobacter	73	33	40	60	59	93	74	73	72	61
Citrobacter	72	37	39	54	41	100	63	70	65	62
S. marcescens	86	59	54	82	78		89	94	90	76
Proteus	76	53	57	52	49		70	87	88	91
Providencia	53	30	34	40	30		69	69	70	64
M. morganii	93	50	55	42	35		72	81	82	81
Overall	68	24	30	34	30	92	65	63	60	52

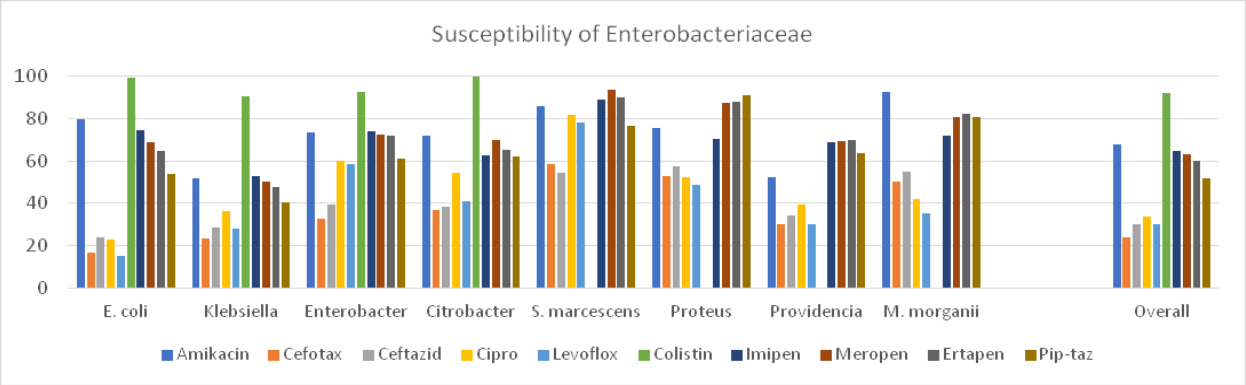


Figure 2.1 Results of susceptibility of Enterobacteriaceae to various antibiotics tested.

Table 2.2 Susceptibility of *E. coli*, *Klebsiella* spp and *Enterobacter* spp from blood.

	Amikacin	Cefotax	Ceftazid	Cipro	Colistin	Ertapen	Imipen	Levoflox	Meropen	Pip-taz
	S	S	S	S	S	S	S	S	S	S
E. coli	82	19	24	25	100	69	82	10	77	60
Klebsiella	45	19	22	30	89	37	48	22	42	34
Enterobacter	79	23	33	62	100	68	78	53	74	64
Overall	66	20	23	30	94	54	67	20	62	49

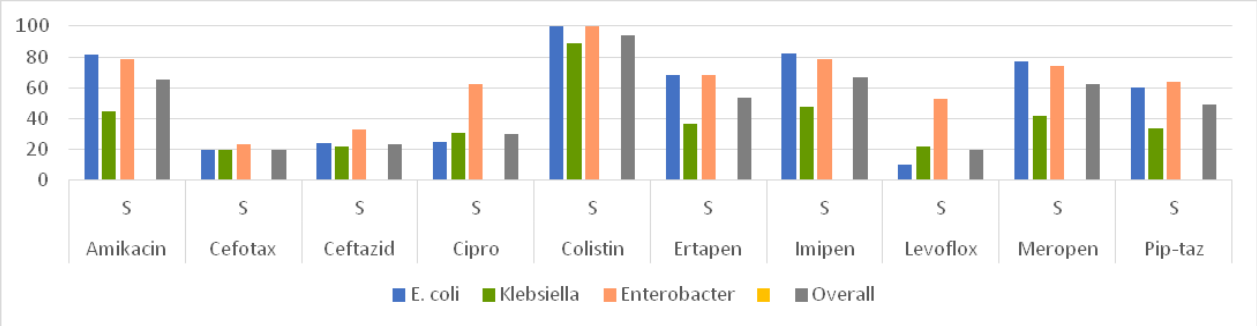


Figure 2.2 Susceptibility of *E. coli*, *Klebsiella*spp and *Enterobacter*spp from blood.

Table 2.3 Susceptibility of *E. coli*, *Klebsiella* spp and *Enterobacter* spp from lower respiratory tract.

	Amikacin	Cefotax	Ceftazid	Cipro	Colistin	Ertapen	Imipen	Levoflox	Meropen	Pip-taz
	S	S	S	S	S	S	S	S	S	S
E. coli	77	13	18	18	97	55	74	14	58	44
Klebsiella	53	26	33	40	92	51	55	29	52	43
Enterobacter	79	38	34	71	84	82	83	80	80	66
Overall	60	24	30	37	93	54	61	27	55	44

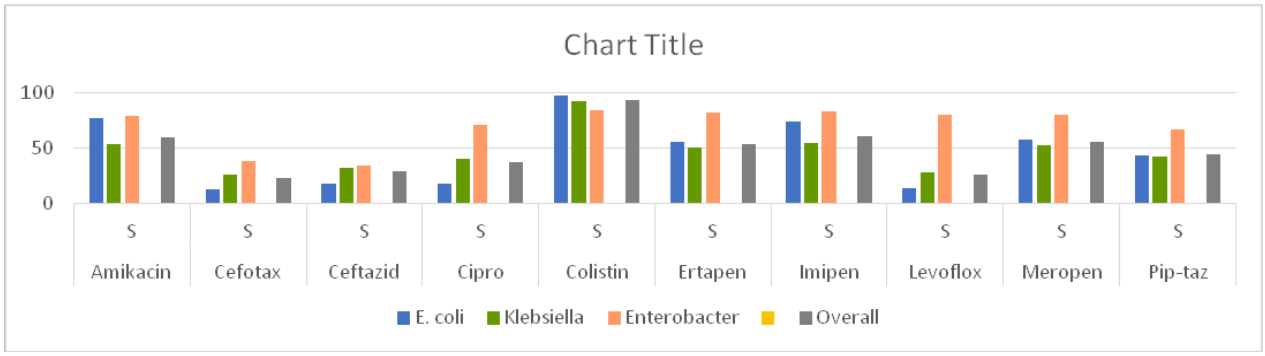


Figure 2.3 Susceptibility of *E. coli*, *Klebsiella* spp and *Enterobacter* spp from lower respiratory tract.

Table 2.4 Susceptibility of *E. coli*, *Klebsiella* spp and *Enterobacter* spp from skin and superficial infections.

	Amikacin	Cefotax	Ceftazid	Cipro	Colistin	Ertapen	Imipen	Levoflox	Meropen	Pip-taz
	S	S	S	S	S	S	S	S	S	S
E. coli	79	16	24	21	99	63	72	16	62	52
Klebsiella	55	24	30	36	94	52	55	32	53	43
Enterobacter	71	37	46	59	92	74	73	55	71	61
Overall	69	21	28	30	97	60	66	23	59	50

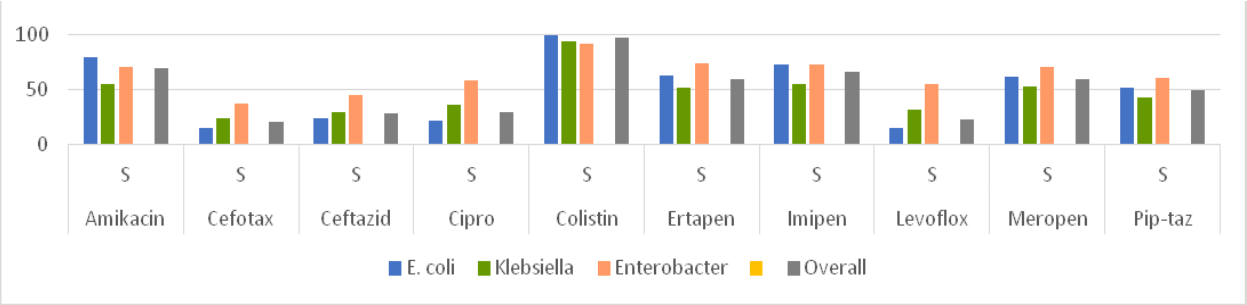


Figure 2.4 Susceptibility of *E. coli*, *Klebsiella* spp and *Enterobacter* spp from skin and superficial infections.

Table 2.5 Susceptibility of *E. coli*, *Klebsiella* spp and *Enterobacter* spp from urine.

	Amikacin	Cefotax	Cefazolin	Cipro	Colistin	Ertapen	Phospho	Imipen	Levoflox	Meropen	NFT	Pip-taz	Cotrimox
	S	S	S	S	S	S	S	S	S	S	S	S	S
E. coli	84	25	28	28	98	71	90	74	26	70	86	66	38
Klebsiella	67	34		47	81	65		71	49	66	49	57	54
Enterobacter	62	27	29	38	89	52		61	37	54	41	48	41
Overall	78	26	28	30	95	66		71	29	66	75	61	39

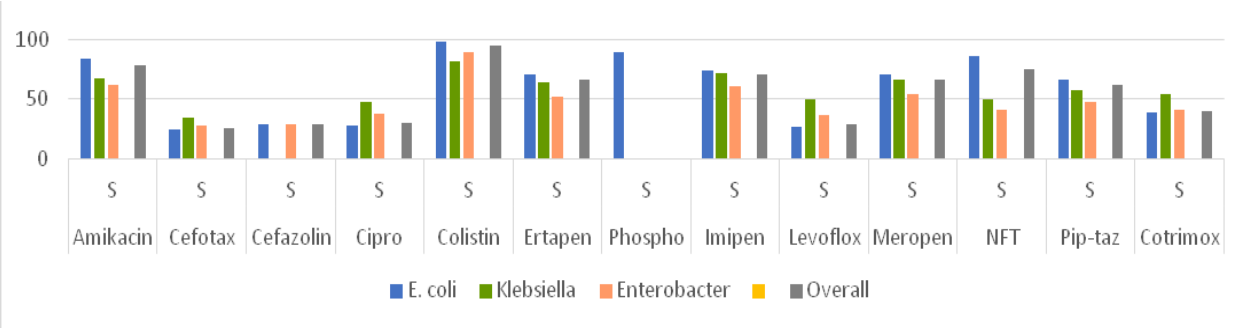


Figure 2.5 Susceptibility of *E. coli*, *Klebsiella* spp and *Enterobacter* spp from urine.

Of the three major species of Enterobacteriaceae, *E. coli* showed far lower susceptibility to fluoroquinolones and 3G cephalosporins than *Klebsiella* spp and *Enterobacter* species. For amikacin, carbapenems, piperacillin-tazobactam and colistin, Klebsiella species showed more resistance than the other two species.

Urinary isolates showed poor susceptibility (< 40%) to 3G cephalosporins, fluoroquinolones and cotrimoxazole. Fosfomycin, tested for urinary isolates of *E. coli* showed good efficacy of 90%. Nitrofurantoin also showed best efficacy for *E. coli* (86%). Most isolates were susceptible to colistin (95%) with Klebsiella spp being the least susceptible (81%) and E. coli the best results (98%). Amikacin showed an overall

susceptibility of 78 per cent followed by carbapenems (66-71%) and piperacillin-tazobactam (61%).

A comparative susceptibility of the major species from four major specimen sources showed that urinary isolates were most susceptible and blood and lower respiratory isolates were most resistant (Table 6, Figure 6). The difference was small and not statistically significant though consistent.

Table 2.6 Comparative susceptibility of major species from blood, lower respiratory tract infection, skin and soft tissues and urine.

	Amikacin	Cefazolin	Cefotax	Ceftazid	Cipro	Colistin	Ertapen	Imipen	Levoflox	Meropen	Pip-taz	NFT	Cotrimox
Blood	66		20	23	30	94	54	67	20	62	49		
LRT	60		24	30	37	93	54	61	27	55	44		
SSTI	69		21	28	30	97	60	66	23	59	50		
Urine	78	28	26		30	95	66	71	29	66	61	75	39

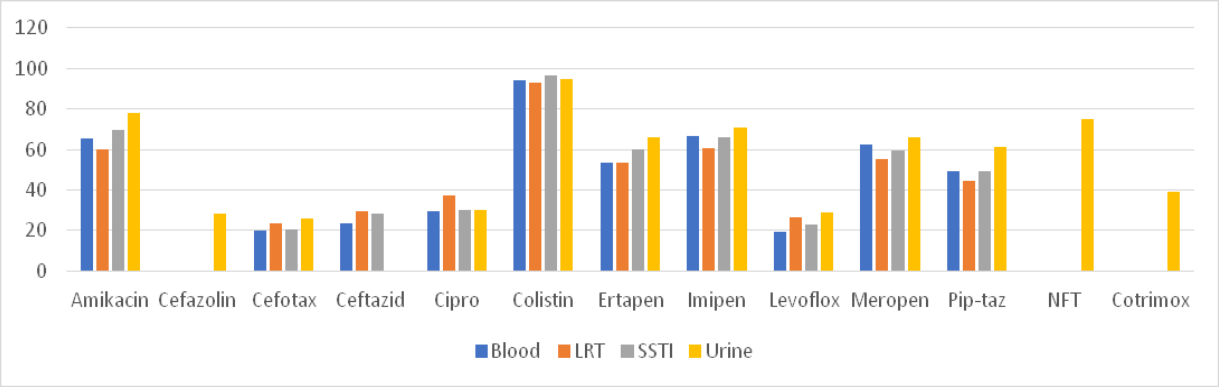


Figure 2.6 Comparative susceptibility of major species from blood, lower respiratory tract infection, skin and soft tissues and urine.

Comparative susceptibility of *E. coli*, *Klebsiella* spp, *Enterobacter* spp and *Citrobacter* spp showed similar patterns though *Klebsiella* spp were significantly less susceptible than the other three species by a factor of 25-30% for most of the effective antibiotics (Table 7-10, Figure 7-10). Stratified data from OPD, Wards and ICUs consistently showed that the OPD isolates were the most susceptible and the ICU isolates were the most resistant. *Enterobacter* spp were more susceptible to 3G cephalosporins and fluoroquinolones than *Klebsiella* spp while *E. coli* showed the worst susceptibility. Susceptibility of *Serratia* spp, *Proteus* spp, *Providentia* spp and *Morganella* spp showed that *Providentia* spp were the most resistant. The susceptibility of these species to fluoroquinolones and 3G cephalosporins was higher than that of *E. coli*. All the species showed highest susceptibility in OPD isolates followed by ward and ICU isolates (Table 11, Figure 11).

Table 2.7 Susceptibility of *E. coli* from OPD, ward and ICU.

	OPD	Ward	ICU	Total
	S	S	S	S
Amikacin	85	79	73	80
Cefotaxime	21	16	12	17
Ceftazidime	30	24	16	24
Ciprofloxacin	26	23	18	23
Levofloxacin	19	15	12	15
Colistin	99	100	99	99
Imipenem	85	72	70	75
Meropenem	74	69	61	69
Ertapenem	72	63	59	65
Pip-taz	61	53	45	54

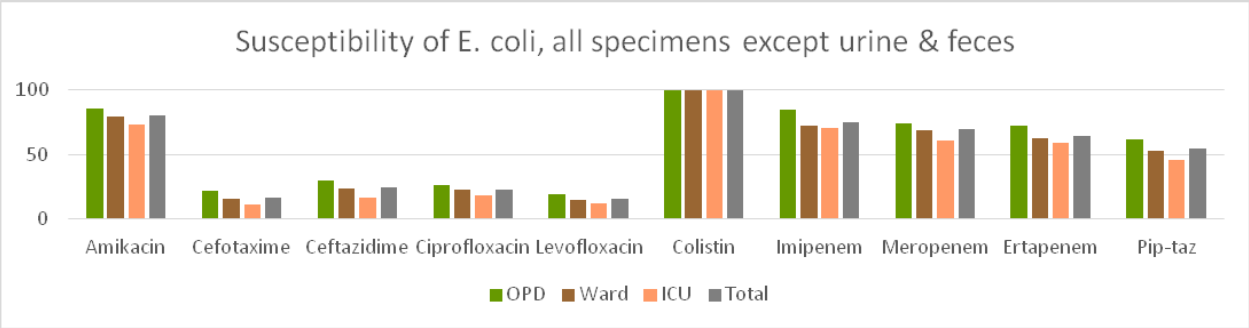


Figure 2.7 Susceptibility of *E. coli* from OPD, ward and ICU.

Table 2.8 Susceptibility of *Klebsiella pneumoniae* from OPD, ward and ICU.

	OPD	Ward	ICU	Total
	S	S	S	S
Amikacin	67	50	40	51
Cefotaxime	38	21	13	23
Ceftazidime	48	26	16	28
Ciprofloxacin	50	33	25	35
Levofloxacin	33	23	17	23
Colistin	91	91	90	91
Imipenem	69	51	43	53
Meropenem	65	48	38	50
Ertapenem	63	46	36	48
Pip-taz	57	38	28	40

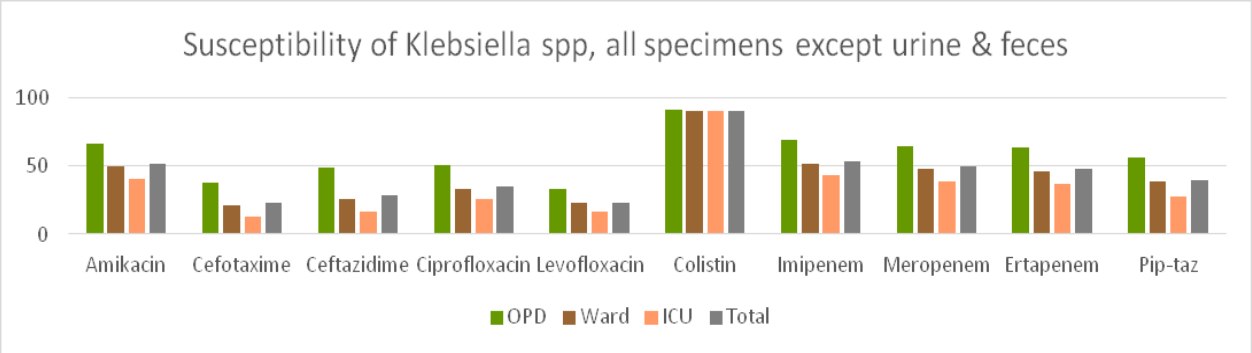


Figure 2.8 Susceptibility of Klebsiella pneumoniae from OPD, ward and ICU.

Table 2.9 Susceptibility of Enterobacter spp from OPD, ward and ICU.

	OPD	Ward	ICU	Total
	S	S	S	S
Amikacin	84	70	63	73
Cefotaxime	42	29	24	33
Ceftazidime	54	36	25	40
Ciprofloxacin	72	55	51	60
Levofloxacin	66	53	61	59
Colistin	97	90	83	93
Imipenem	84	69	68	74
Meropenem	82	69	63	73
Ertapenem	84	68	60	72
Pip-taz	74	57	46	61

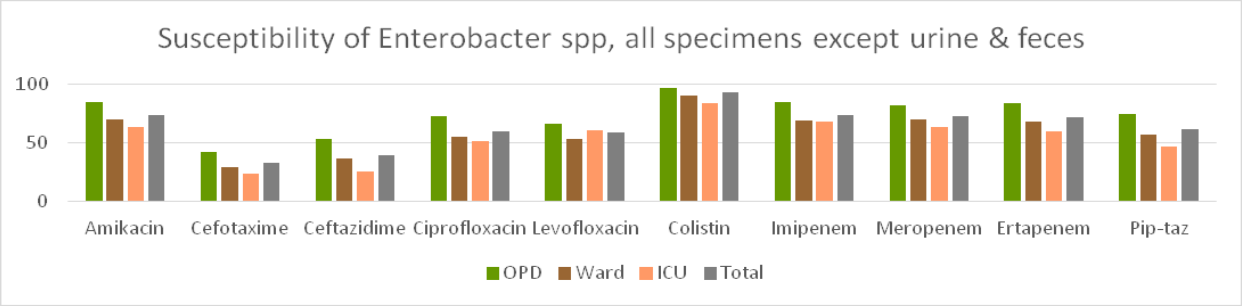


Figure 2.9 Susceptibility of Enterobacter spp from OPD, ward and ICU.

Table 2.10 Susceptibility of Citrobacter spp from OPD, ward and ICU.

	OPD	Ward	ICU	Total
	S	S	S	S
Amikacin	83	66	77	72
Cefotaxime	47	30	43	36
Ceftazidime	59	32	36	39
Ciprofloxacin	74	45	54	54
Levofloxacin	54	38	35	41
Colistin	100	100	100	100
Imipenem	79	56	66	63
Meropenem	82	66	61	70
Ertapenem	79	60	67	65
Pip-taz	77	56	59	62

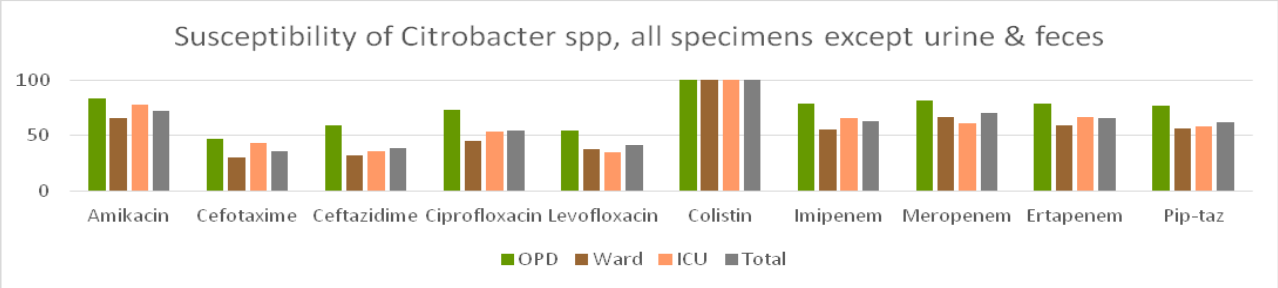


Figure 2.10 Susceptibility of Citrobacter spp from OPD, ward and ICU.

Table 2.11 Susceptibility of Serratia spp, Proteus spp, Providencia spp and Morganella spp.

	Amika			Cefotax			Ceftazid			Cipro			Erta			Imipen			Levo			Meropen			Pip-taz		
	OPD	Ward	ICU	OPD	Ward	ICU	OPD	Ward	ICU	OPD	Ward	ICU	OPD	Ward	ICU	OPD	Ward	ICU	OPD	Ward	ICU	OPD	Ward	ICU	OPD	Ward	ICU
	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
S. marcescens	96	83	83	69	55	57		52	50	89	80	79	92	84	97	82	87	96		68		98	88	99	81	80	68
P. mirabilis	81	72	63	62	49	35	66	54	36	56	49	41	92	87	79	78	69	59	59	42		92	86	79	96	89	84
P. vulgaris		81			59			63			62			82			61						83			93	
P. rettgeri		45			16			26			31			59			62						61			52	
P. stuartii		56			40			31			44			66			65						64			63	
M. morganii	93	93		57	46		67	50		46	40		89	76		79	66			42		88	76		89	76	
Overall	84	75	69	60	47	42	67	49	39	58	50	51	91	81	85	79	69	73	60	48	50	91	81	84	92	82	76

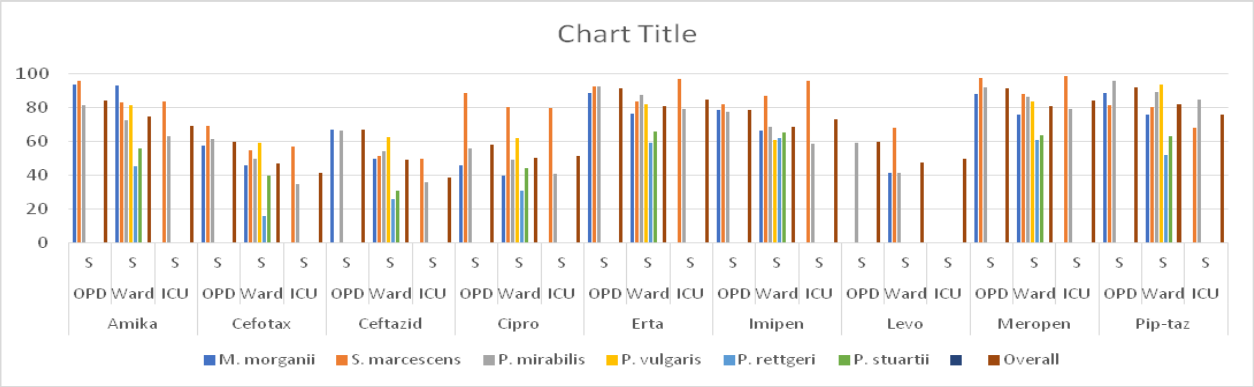


Figure 2.11 Susceptibility of Serratia spp, Proteus spp, Providencia spp and Morganella spp.

Table 2.12 Susceptibility of Enterobacter species from all specimens (Except urine & feces) OPD/Ward/ICU wise

Organism	E. cloacae				(now Klebsiella) aerogen				Enterobacter spp				Overall			
Antibiotic	Total	OPD	Ward	ICU	Total	OPD	Ward	ICU	Total	OPD	Ward	ICU	Total	OPD	Ward	ICU
	773	267	424	82	139	41	65	33	309	75	195	39	1221	383	684	154
Amikacin	78	84	76	77	72	90	69	55	61	84	56	41	73	84	70	63
Cefotaxime	36	41	34	42	31	48	23	27	26	43	22	8	33	42	29	24
Ceftazidime	43	51	41	31	39	61	33	30	34	56	30	13	40	54	36	25
Ciprofloxacin	65	72	61	57	57	76	44	61	50	72	46	31	60	72	55	51
Colistin	93	97											93	97	90	
Ertapenem	77	84	73	71	78	89	75	71	58	80	55	0	72	84	68	60
Imipenem	78	84	74	78	77	88	72	72	62	83	58	44	74	84	69	68
Levofloxacin	57	61	53						60	76	53		59	66	53	
Meropenem	77	81	74	77	76	87	74	67	61	83	59	32	73	82	69	63
Pip-taz	65	75	61	55	60	78	55	48	52	69	50	28	61	74	57	46

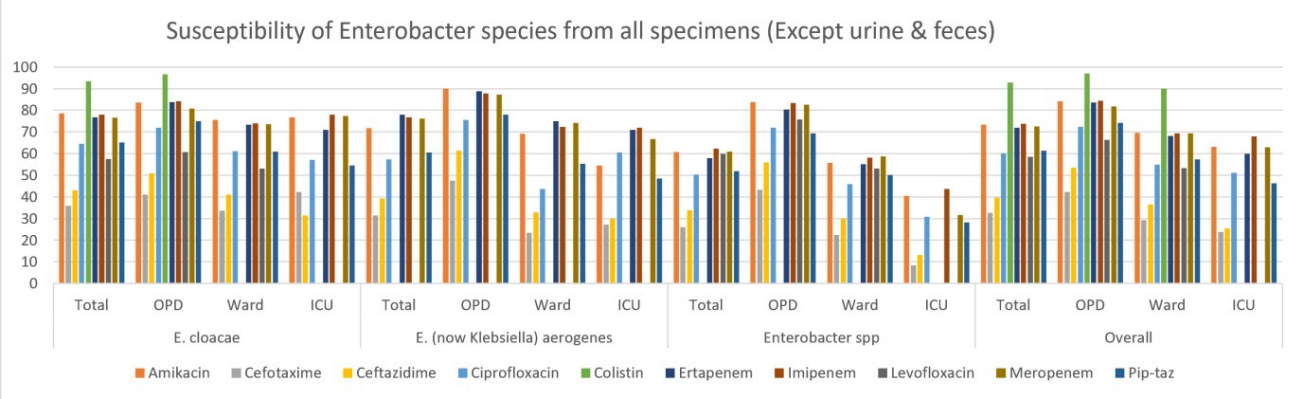


Figure 2.12 Susceptibility of Enterobacter species from all specimens (Except urine & feces) OPD/Ward/ICU wise

Table 2.13 Susceptibility of Citrobacter species from all specimens (Except urine & feces) OPD/Ward/ICU wise

Organism	C. freundii				C. koseri				Citrobacter spp				Overall			
Antibiotic	Total	OPD	Ward	ICU	Total	OPD	Ward	ICU	Total	OPD	Ward	ICU	Total	OPD	Ward	ICU
	196	47	138	11	264	77	154	33	42	20	22		507	144	314	49
Amikacin	69	83	63		77	90	69	79	59				72	83	66	76
Cefotaxime	31	39	28		43	63	34	45	20				37	50	30	41
Ceftazidime	37	55	31		42	69	34		18				39	59	32	34
Ciprofloxacin	51	68	44		57	81	46	55	57	81	46	55	54	74	45	52
Colistin	100												100			
Ertapenem	59	79	52		72	88	66	70	72	88	66	70	65	79	60	65
Imipenem	60	84	51		66	85	57	67	66	85	57	67	63	79	56	65
Levofloxacin	43		38		42		40		42		40		41	54	38	33
Meropenem	66	81	62		77	92	71	67	77	92	71	67	70	82	66	59
Pip-taz	59	76	53		67	84	59	61	67	84	59	61	62	77	56	56

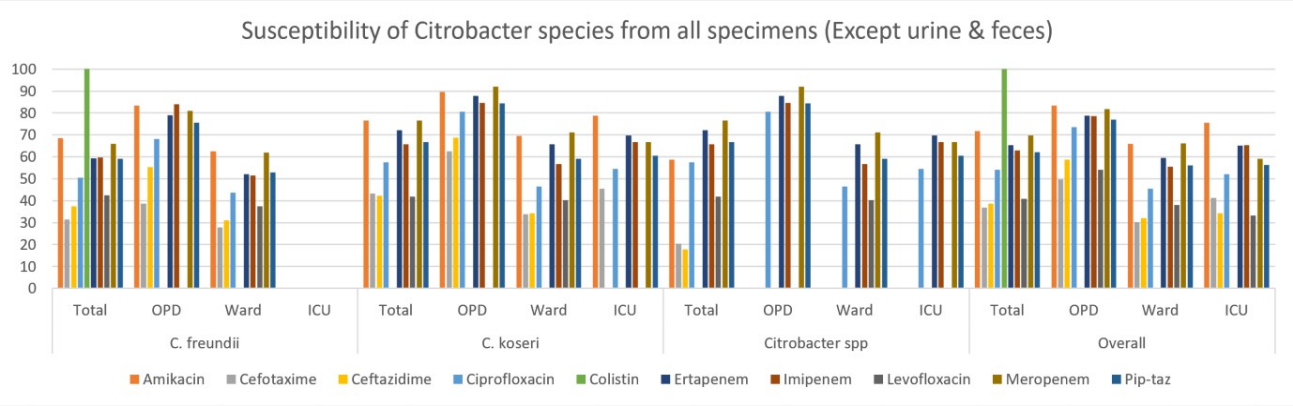


Figure 2.13 Susceptibility of Citrobacter species from all specimens (Except urine & feces) OPD/Ward/ICU wise

Molecular detection of resistance genes: *E. coli* and *K. pneumoniae*

A total of 369 *E. coli* and 374 *Klebsiella pneumoniae* isolates from 7 centres (Table 12) were subjected to multiplex PCR for 18 genes (Table 13).

Table 2.14 Number of isolates tested centre wise and species wise.

	AIIMS	PGIMER	Hinduja	JIPMER	TMC	SGRH	CMC	Total
E. coli	60	60	48	60	21	60	60	369
K. pneum	60	60	53	60	21	60	60	374

Table 2.15 Gene targets and amplicon sizes for molecular analysis

	Gene target	Amplicon (bp)
Multiplex 1	TEM	800
	SHV	713
	OXA-1	564
Multiplex 2	CTX M1	668
	CTX M2	404
	CTX M9	651
	CTX M8/25	326
Multiplex 3	ACC	346
	FOX	162
	MOX	895
	DHA	997
	CIT	538
	EBC	683
Multiplex 4	IMP	139
	VIM	390
	KPC	538
Monoplex	NDM	
Monoplex	CTX M15	

Comparison between *E. coli* and *K. pneumoniae*. *K. pneumoniae* isolates showed higher prevalence of TEM, SHV, KPC and NDM and lower prevalence of OXA-1 and VIM than *E. coli* isolates (Table 14-17).

Table 2.16 Overall prevalence of β-lactamase genes in *E. coli* and *K. pneumoniae.*

	TEM (%)	SHV (%)	OXA-1 (%)
E. coli	49	11	26
K. pneum	59	22	19

Table 2.17 Overall prevalence of extended spectrum β-lactamase genes in *E. coli* and *Klebsiella pneumoniae.*

	CTX M1 (%)	CTX M2 (%)	CTX M9 (%)	CTX M8/25 (%)	CTX M-15 (%)
E. coli	26	10	15	16	44
K. pneum	25	8	13	14	42

Table 2.18 Overall prevalence of AmpC β-lactamase genes in *E. coli* and *Klebsiella pneumoniae.*

	ACC (%)	FOX (%)	MOX (%)	DHA (%)	CIT (%)	EBC (%)
E. coli	2	2	8	8	12	8
K. pneum	0	2	9	6	5	4

Table 2.19 Overall prevalence of carbapenemase genes in *E. coli* and *Klebsiella pneumoniae.*

	IMP (%)	VIM (%)	KPC (%)	NDM (%)
E. coli	14	22	6	23
K. pneum	17	15	24	31

Comparison between centres. As shown in Table 18, out of TEM, SHV and OXA-1, TEM was most prevalent (54%) followed by OXA-1 (22%) and SHV (16%). AIIMS and PGI showed High prevalence of TEM (87% and 65%), moderate prevalence of OXA-1 (21% and 14%) and low prevalence of SHV (<10%). Hinduja Hospital showed moderate prevalence of all three (TEM 42%, OXA-1 30% and SHV 23%). TMC and SGRH showed

high prevalence of OXA-1 (43% and 40%) followed by SHV (33% and 24%) and TEM (33% and 15%). This may have significant impact on therapeutics because of inhibitor resistance of OXA-1. CMC showed high prevalence of TEM (51%), moderate SHV (34%) and low OXA-1 (19%). JIPMER had moderate TEM (29%) and negligible SHV and OXA-1 (2% and 3%).

Table 2.20 Prevalence of β-lactamase genes centre wise.

	TEM (%)	SHV (%)	OXA-1 (%)
AIIMS	87	7	21
PGIMER	65	4	14
Hinduja	42	23	30
JIPMER	29	2	3
TMC	33	33	43
SGRH	15	24	40
CMC	51	34	19
Overall	54	16	22

Table 2.21 Prevalence of extended spectrum β-lactamase genes centre wise.

	CTX M1 (%)	CTX M2 (%)	CTX M9 (%)	CTX M8/25 (%)	CTX M-15 (%)
AIIMS	56	13	11	8	69
PGIMER	57	3	3	0	37
Hinduja	8	19	26	27	58
JIPMER	1	3	8	23	28
TMC	14	17	5	2	21
SGRH	11	8	28	3	22
CMC	23	0	2	4	36
Overall	24	10	15	15	40

As shown in Table 19, CTX-M β-lactamases are considered a paradigm in the evolution of a resistance mechanism. Incorporation of different chromosomal *bla*$_{CTX-M}$ related genes from different species of *Kluyvera* has derived in different CTX-M clusters. *In silico* analyses have shown that this event has occurred at least nine times; in CTX-M-1 cluster (3), CTX-M-2 and CTX-M-9 clusters (2 each), and CTX-M-8 and CTX-M-25 clusters (1 each). In our isolates CTX M15 was most frequent (40%) followed by CTX M1 (24%), CTX M-8/25 (15%), CTX M-9 (15%) and CTX M-2 (10%). Overall there was not much difference in prevalence of the CTX M genes between *E. coli* and *K. pneumoniae*. CTX M-1 was more frequent in PGIMER isolates (57%) and AIIMS isolates (56%) than CMC (23%), TMC, Kolkata (14%), SGRH, Delhi (11%), Hinduja Hospital (7%) and JIPMER (0.8%). CTX M-8/25 was most prevalent in isolates from Hinduja Hospital (27%) and JIPMER (23%) but less than 10 percent at other centres. CTX M-9 was most prevalent in SGRH (28%) and Hinduja Hospital (26%) but 11% or less at other centres.

Within the CTX-Menzymes, the CTX-M-15, and CTX-M-14 are by far the most important ones, virtually invading all human and animal compartments as well as the environment all over the world. CTX M-15 was highly prevalent in isolates from AIIMS (69%) and Hinduja (58%) followed by PGIMER (37%), CMC (36%), JIPMER (28%), SGRH (22%) and TMC (21%).

Table 2.22 Prevalence of carbapenemase genes centre wise.

	IMP (%)	VIM (%)	KPC (%)	NDM (%)
AIIMS	13	18	28	40
PGIMER	12	9	13	29
Hinduja	30	42	28	13
JIPMER	21	27	13	12
TMC	0	0	0	17
SGRH	9	13	6	22
CMC	5	3	1	18
Overall	15	19	15	27

As shown in Table 20, overall, NDM was the most prevalent (27%) carbapenemase followed by VIM (19%), IMP (15%) and KPC (15%). IMP and VIM was more prevalent in isolates from Hinduja (30% and 42%) and JIPMER (21% and 27%) and very low in SGRH (9% and 13%), CMC (5% and 3%) and TMC (0 and 0). KPC was most common in

AIIMS (28%) and Hinduja (28%) and least in SGRH, CMC and TMC. NDM was most prevalent in isolates from the north Indian centres including AIIMS (40%) followed by PGIMER (29%) and SGRH (22%). It was relatively lower in the centres from southern and eastern India.

AmpC beta lactamases As shown in Table 21, overall, prevalence of AmpC beta lactamases was below 10%. Except for JIPMER with a moderate prevalence of MOX (26%), DHA (24%) and EBC (23%), other centres showed low prevalence of each gene.

Table 2.23 Prevalence of AmpC β-lactamase genes centre wise.

	ACC (%)	FOX (%)	MOX (%)	DHA (%)	CIT (%)	EBC (%)
AIIMS	0	0	2	1	12	0
PGIMER	0	0	7	0	20	0
Hinduja	5	0	17	9	0	14
JIPMER	0	0	26	24	0	23
TMC	10	17	0	0	0	0
SGRH	0	2	0	0	1	0
CMC	0	4	0	5	21	0
Overall	1	1	9	6	6	6

Chapter 3- Typhoidal Salmonella

Summary of results

Antimicrobial resistance in typhoid fever is a cause of concern because this is a community acquired blood stream infection responsible for high morbidity and mortality if not treated with appropriate drug. The increasing resistance to ciprofloxacin which has been used as first line drug for the last two decades, has made ceftriaxone/cefiximeas the drug of choice at present. With increasing use of ceftriaxone, MIC to ceftriaxone has now started showing increasing trend and is responsible for clinical non response. Absolute resistance is also emerging in isolated cases. Therefore, there is a need for continuous monitoring of antimicrobial resistance in *Salmonella* Typhi and *S.* Paratyphi A.

During the study period of 2018, total 62 Salmonella Spp. were isolated from AIIMS. Out of which 16 were *Salmonella* Paratyphi A and 46 were *Salmonella* Typhi while one strain was salmonella group C. We received 273 *Salmonella* strains from other centers like JIPMER Puducherry, PGI Chandigarh, CMC Vellore, Hinduja Mumbai, Apollo Chennai and Sir Gangaram Delhi hospital as nodal centre.

Antimicrobial susceptibility was determined by Kirby Bauer disk diffusion method according to the Clinical Laboratory Standards Institute (CLSI) guidelines 2018 for amoxicillin (10µg), co-trimoxazole (1.25/23.75µg), ciprofloxacin (5µg), nalidixic acid (30µg), chloramphenicol (30µg), ceftriaxone (30µg) and cefixime (5µg).

Strains showing multiple resistant to ampicillin, chloramphenicol and co-trimoxazole were defined as MDR while NAR (nalidixic acid resistant) and NAS (nalidixic acid sensitive) were defined based on susceptibility to nalidixic acid. MIC for ciprofloxacin, levofloxacin, ofloxacin and ceftriaxone was determined by E-Test. For ceftriaxone or cefixime resistant isolates, screening for ESBLs enzymes was done by PCR for the presence of CTX-M genes.

Selected strains from each center were characterized for molecular studies, which included molecular mechanism of fluoroquinolone resistance and molecular typing by MLST and PFGE. In *Salmonella* Typhi, MDR was 2- 3% and lesser in *Salmonella* Paratyphi A. Ciprofloxacin susceptibility was 7-12% in *Salmonella* Typhi, 1% in *Salmonella* Paratyphi A and 13% in *Salmonella* Spp. We found pefloxacin susceptibility was 19% in *S.* Typhi and 7% in *S.* Paratyphi A and can be used as surrogate marker for fluoroquinolone like levofloxacin and ofloxacin. The discordant results between ciprofloxacin and pefloxacin needs further study. All the isolates were ceftriaxone /cefixime sensitive except 8 ceftriaxone resistant *S.* Typhi from Hinduja Mumbai hospital. A creeping increase in MIC pattern was observed for ceftriaxone from 0.047 to 0.094 µg/ml in *S.* Typhi followed by 0.064 to 0.094µg/ml in *S.* Paratyphi A over years. But none of the strain was found ESBL +ve or carried CTX-M genes.

Fluoroquinolone resistance at molecular level was studied in 102 typhoidal isolates. The most common mutation was S83 to F/Y followed by D87 to N/G/Y. Par C mutation was detected in three isolates only. No mutations were detected in *gyrB* and *parE* genes. Strains with more than one mutation in *gyrA* gene had higher MIC. Efflux pump was not responsible for resistance. Qnr B was found in two *Salmonella* Typhi isolates one each from Hinduja, Mumbai and AIIMS. Further characterization for molecular typing was done by MLST (Multiple locus Sequence Type) and PFGE (Pulse Field Gel Electrophoresis) to study the clonality. By using MLST, *Salmonella* Typhi grouped in ST1 and ST2 and *Salmonella* Paratyphi A was grouped in ST85 by MLST in concordance with other studies. PFGE was done in 27 typhoidal Salmonella from all the centers. Similarity coefficient was calculated and two types of PFP (pulsed field profile) were observed.

To summarize *S*. Typhi is the most common etiological agent followed by *S.* Paratyphi A in India. The ciprofloxacin susceptibility is only7-12%. Resistance in *S*. Paratyphi A is higher as compared to *S*. Typhi. MDR is decreasing. Fluoroquinolone resistance was associated with DNA gyrase mutations. So, it is no longer empirical choice. Third generation cephalosporins are most commonly used for the treatment. But MIC_{50} and MIC_{90} showed increasing trend. No significant change was observed in molecular mechanism. The molecular typing shows clonal dissemination of *Salmonella* Typhi.

Detailed analysis of data

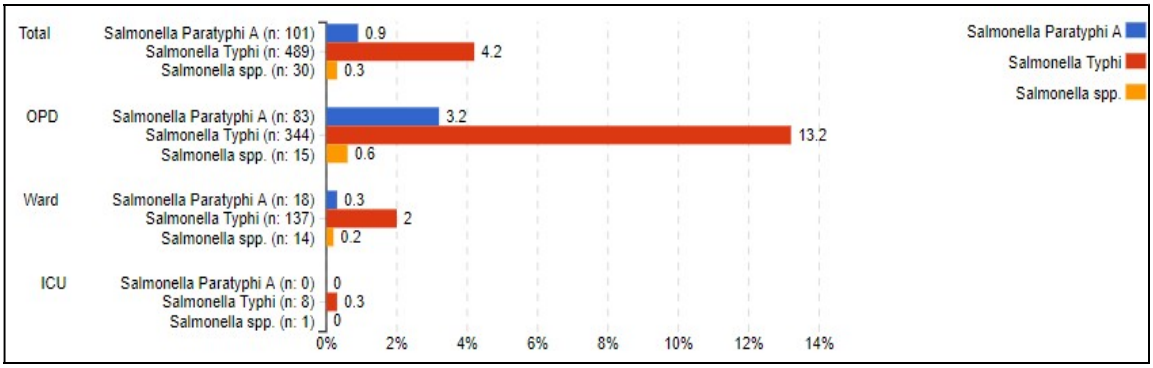
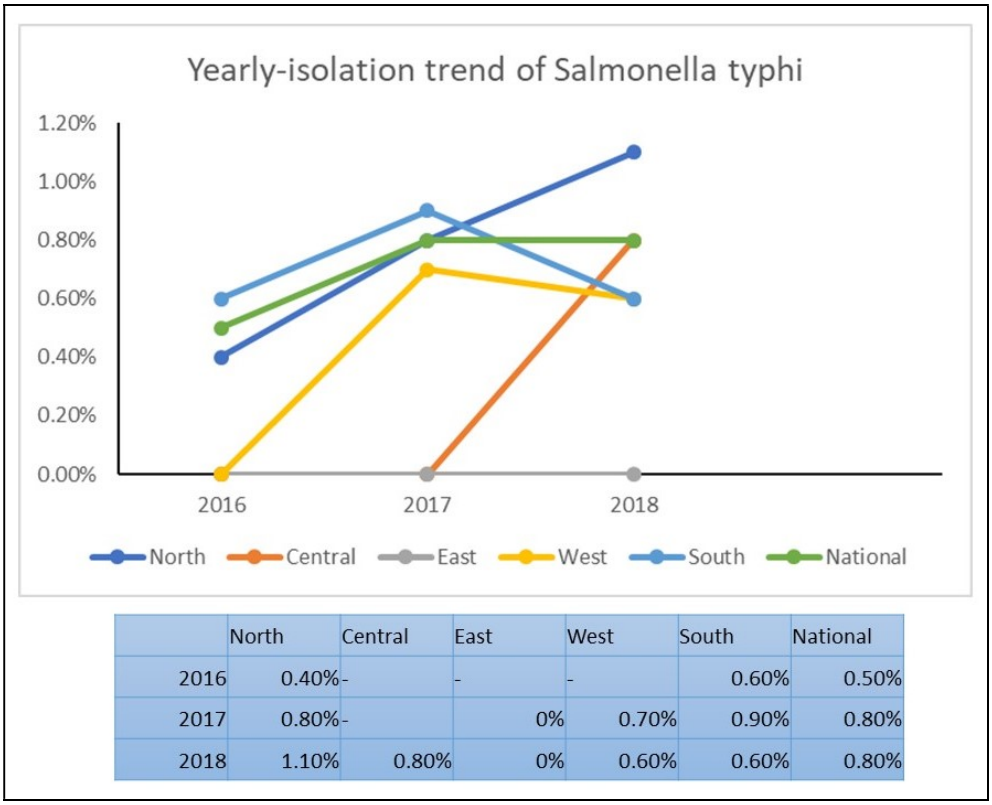


Figure 3.1 Location-wise Isolation pattern of Salmonella species isolated from Blood across OPD, Ward and ICU

Figure 3.1 shows that total 620 Salmonella were isolated from OPD, Ward and ICU. Out of 442 Salmonella isolated from OPD, 344 were *Salmonella* Typhi followed by 101 Paratyphi A and 30 other Salmonella spp. While from ward, out of 169 Salmonella, 137 were *Salmonella* Typhi followed by 18 Paratyphi A and 14 Salmonella spp. In case of isolation from ICU, total 8 *Salmonella* Typhi were isolated followed by only one Salmonella spp.

Over all maximum number of Enteric fever patients (442) were enrolled from OPD. The admission was required for 178 cases.

Out of 489 *Salmonella* Typhi maximum numbers were isolated from OPD followed by ward and ICU. While out of 101 *Salmonella* Paratyphi A 83 were isolated from OPD followed by 18 from ward while no *Salmonella* Paratyphi A were isolated from ICU. Overall the most common etiological agent for enteric fever was *S.*Typhi followed by *S.* Paratyphi A.



	North	Central	East	West	South	National
2016	0.40%	-	-	-	0.60%	0.50%
2017	0.80%	-	0%	0.70%	0.90%	0.80%
2018	1.10%	0.80%	0%	0.60%	0.60%	0.80%

Figure 3.2 Yearly-isolation trend of Salmonella Typhi from All Samples (except Faeces)

Figure 3.2 presents yearly isolation trend of *Salmonella* Typhi which shows that in 2016, 0.4% *Salmonella* Typhi was isolated from North India followed by 0.6% isolation from South India. Overall 0.5% *Salmonella* Typhi was isolated from India during 2016. While in 2017, total isolation from India was 0.8%. Out of which, 0.8% Typhi was isolated from North India followed by 0.7% and 0.9% isolation from West and South India respectively. In 2018, from North India total isolation of *Salmonella* Typhi was 1.1% followed by 0.8% from Central part of India and 0.6% from west and south India respectively as additional centers participated from these regions.Overall isolation of *Salmonella* Typhi increased from 0.5% in 2016 to 0.8% in 2017 and 2018. No isolation of *Salmonella* Typhi was observed from East India during study period.

Table 3.1: Susceptibility pattern of Salmonella species isolated from Blood

AMA	Blood		
	Salmonella Paratyphi A n=101	*Salmonella* Typhi n=489	Salmonella Spp. n=30
Ampicillin	98/101 (97)	465/486 (96)	28/30 (93)
Azithromycin	0/0	418/426 (98)	0/0
Cefixime	88/88 (100)	300/304 (99)	15/17 (88)
Ceftriaxone	101/101 (100)	296/304 (97)	25/29 (86)
Chloramphenicol	98/98 (100)	445/474 (94)	29/29 (100)
Ciprofloxacin	1/97 (1)	27/385 (7)	3 /24 (13)
Pefloxacin	1 /14 (7)	38/196 (19)	0/0
Trimethoprim-sulfamethoxazole	99/99 (100)	469/485 (97)	28/28 (100)

Table 3.1 represents antibiotic susceptibility pattern of all Salmonella species isolated from blood which shows overall 97% *Salmonella* Typhi were sensitive to ampicillin, Chloramphenicol and Co-trimoxazole. Ampicillin susceptibility was less than Chloramphenicol and Co-trimoxazole. 98% isolates were susceptible to azithromycin and 97 % to ceftriaxone respectively. Ciprofloxacin susceptibility has decreased to 7% only while pefloxacin susceptibility was seen in 19%.

In *Salmonella* Paratyphi A, no MDR has beenfound while ampicillin susceptibility was 97%. Ciprofloxacin susceptibility is decreasing as reported only 1%. Ceftriaxone and cefixime were 100% susceptible. In Salmonella spp., out of all the isolates, total 93% were susceptible to ampicillin while no MDR was found. Ciprofloxacin susceptibility was12% followed by 86% for ceftriaxone.

Salmonella Paratyphi A

Table 3.2 Susceptibility pattern of *Salmonella* Paratyphi A from Blood across different regions of India

Antibiotic	National (n=101)		North (n=80)		Central (n=0)		East (n=0)		West (n=11)		South (n=10)	
	n= (%)	% Range	n= (%)	% Range	n= (%)	% Range	n= (%)	% Range	n= (%)	% Range	n= (%)	% Range
Ampicillin	98/101 (97)	98	77/80 (96)	100	0/0 (-)	-	0/0 (-)	-	11/11 (100)	100	10/10 (100)	100
Cefixime	88/88 (100)	100	80/80 (100)	100	0/0 (-)	-	0/0 (-)	-	1/1 (100)	100	8/8 (100)	100
Ceftriaxone	101/101 (100)	100	80/80 (100)	100	0/0 (-)	-	0/0 (-)	-	11/11 (100)	100	10/10 (100)	100
Chloramphenicol	98/98 (100)	100	77/77 (100)	100	0/0 (-)	-	0/0 (-)	-	11/11 (100)	100	10/10 (100)	100
Ciprofloxacin	1/97 (1)	-	1/80 (1)	-	0/0 (-)	-	0/0 (-)	-	0/11 (-)	-	0/6 (-)	-
Pefloxacin	1 /14 (7)	-	1/11 (9)	-	0/0 (-)	-	0/0 (-)	-	0/0	-	0/3 (-)	-
Trimethoprim-sulfamethoxazole	99/99 (100)	100	79/79 (100)	100	0/0 (-)	-	0/0 (-)	-	11/11 (100)	100	9/9 (100)	100

Table 3.2 shows antibiotic susceptibility pattern of *Salmonella* Paratyphi A from blood and it shows that *Salmonella* Paratyphi A become completely resistant to ciprofloxacinas the susceptibility to the drug was 1% only.

No MDR was found in Paratyphi A. Ampicillin susceptibility was 97% while chloramphenicol and cotrimoxazole was 100% susceptible form North India. Third generation cephalosporin's (Ceftriaxone and cefixime) were 100% susceptible.

Table 3.3: Yearly susceptibility trends of *Salmonella* Paratyphi A from Blood

AMA	Year 2017	year 2018
	Total n=41	Total n=101
	S%	S%
Ampicillin	38/40 (95)	98/101 (97)
Cefixime	26/27 (96)	88/88 (100)
Ceftriaxone	40/40 (100)	101/101 (100)
Chloramphenicol	30/30 (100)	98/98 (100)
Ciprofloxacin	4/40 (10)	1/97 (1)
Pefloxacin	4/7 (57)	1/14 (7)
Trimethoprim-sulfamethoxazole	41/41 (100)	99/99 (100)

Table 3.3 shows yearly susceptibility trend of *Salmonella* Paratyphi A. Cases of typhoid fever caused by *Salmonella* Paratyphi A has increased from 41 in 2017 to 101 in 2018. It shows that ampicillin susceptibility has increased from 95 % in 2017 to 97% in 2018 while ciprofloxacin susceptibility has decreased from 10% in 2017 to 1% in 2018. Ceftriaxone and cefixime were 100% susceptible.

Salmonella Typhi

Table 3.4: Susceptibility pattern of *Salmonella* Typhi from Blood

Antibiotic	National (n=489)		North (n=217)		Central (n=0)		East (n=1)		West (n=96)		South (n=175)	
	n= (%)	% Range	n= (%)	% Range	n= (%)	% Range	n= (%)	% Range	n= (%)	% Range	n= (%)	% Range
Ampicillin	465/486 (96)	100	207/214 (97)	100	0/0 (-)	-	1/1	-	88/96 (92)	93	169/175 (97)	98
Azithromycin	418/426 (98)	98	179/184 (97)	98	0/0 (-)	-	1/1	-	93/93 (100)	100	145/148 (98)	100
Cefixime	300/304 (99)	100	212/213 (99.5)	100	0/0 (-)	-	1/1	-	6/6 (100)	100	81/84 (96)	100
Ceftriaxone	445/453 (98)	100	214/214 (100)	100	0/0 (-)	-	1/1	-	88/96 (92)	92	142/142 (100)	100
Chloramphenicol	459/474 (97)	100	202/209 (97)	100	0/0 (-)	-	1/1	-	85/92 (92)	92	171/172 (99)	100
Ciprofloxacin	27/385 (7)	-	10/200 (5)	-	-	-	0/1	-	0/40	-	17/144 (12)	-
Pefloxacin	38/196 (19)	-	5/48 (10)	-	-	-	0/1	-	0/0	-	33/147 (12)	-
Trimethoprim-sulfamethoxazole	469/485 (97)	100	206/216 (95)	100	0/0 (-)	-	1/1	-	90/95 (95)	95	171/172 (99)	100

Table 3.4 represents antibiotic susceptibility pattern of *Salmonella* Typhi from blood which shows that ampicillin susceptibility was 96% from India which include 97% susceptibility from North and South India respectively while 92% from West India. Overall 3% *Salmonella* Typhi were MDR (Resistant to ampicillin, chloramphenicol and co-trimoxazole). Azithromycin susceptibility was 98% from North and South India. While overall ceftriaxone susceptibility was 98% from India which includes 92% susceptibility from West India because all ceftriaxone resistant isolates were isolated from single site. Ciprofloxacin susceptibility was 7% from India which includes 5% from North India and 12% from South India while *Salmonella* Typhi was completely resistant to ciprofloxacin from west India.

Table 3.5 Yearly susceptibility trends of *Salmonella* Typhi from Blood

AMA	Year 2017	year 2018
	Total n=344	Total n=489
	S%	S%
Ampicillin	304/331 (92)	465/486 (96)
Azithromycin	266/278 (96)	418/426 (98)
Cefixime	221/223 (99)	300/304 (99)
Ceftriaxone	328/333 (98)	445/453 (98)
Chloramphenicol	266/277 (96)	459/474 (97)
Ciprofloxacin	35/302 (12)	27/385 (7)
Pefloxacin	36/178 (20)	38/196 (19)
Trimethoprim-sulfamethoxazole	322/341 (94)	469/485 (97)

Table 3.5 shows yearly susceptibility trend of *Salmonella* Typhi. Overall isolation of *Salmonella* Typhi has increased form 344 in 2017 to 489 in 2018. The antibiotic susceptibility pattern shows that ampicillin susceptibility has increased from 92% in 2017 to 96% in 2018 and also azithromycin susceptibility has increased from 96% in 2017 to 98% in 2018. While ciprofloxacin susceptibility has decreased from 12% in 2017 to 7% in 2018. Third generation cephalosporin's (ceftriaxone and cefixime) susceptibility was 98.5%.

Molecular data and its relevance: *Salmonella* Typhi & S. Paratyphi A

Mechanism of fluoroquinolone resistance at molecular level was studied in 102 Typhoidal isolates. The Mutations in DNA gyrase was the most common cause with mutations at S83 to F/Y followed by D87 to N/G/Y. *ParC* mutation was detected in three isolates only. No mutation was detected in *gyrB* and *pare* genes. Strains with more than one mutation in gyrase A gene had higher MICs. Efflux pump was not responsible for resistance. *Qnr*B was found in two *Salmonella* Typhi isolates one each from Hinduja and AIIMS. None of the isolate was positive for ESBL genes.

Therefore, gyr A mutation is mainly responsible for ciprofloxacin resistance while presence of qnr is very rare. No efflux pump mutation has been detected. Ceftriaxone resistance is found in Salmonella Typhi but no ESBL gene has been detected. Molecular typing was done by MLST (multiple locus sequence typing) and PFGE (Pulse field gel electrophoresis). By MLST, *Salmonella* Typhi was grouped in ST1 and ST2 sequence types and confirm the predominance of two sequence types and *Salmonella* Paratyphi A was grouped in ST85 and ST129.PFGE was done in representative typhoidal Salmonellae from all the centers. Similarity coefficient was calculated and two types of PFP (Pulsed Field Profile, PEP-I and PEP-II) were observed in the studied isolates. There is no significant change or trend observed in molecular mechanism of resistance. The molecular typing shows clonal dissemination of *Salmonella* Typhi and *S.* Paratyphi A in India.

Chapter 4- NFGNB

Summary of results

The overall isolation rate of Non-fermenters among the culture positives was 22.8% for the year 2018. NFGNB was commonly isolated from LRT (53.6%) followed by CSF (40.5%), superficial infection (22%), sterile sites (21%), blood (15.8%) and 24.4% in other specimens. Among NFGNB, *P. aeruginosa* was predominantly isolated (12%) followed by *Acinetobacter spp* (10%). *A. baumannii* was identified in 6.4% of the isolates. Other NFGNB's such as *Stenotrophomonas maltophilia* and *Burkholderia cepecia* was identified only in 0.5% and 0.3% respectively. The isolation rate was higher in LRT than in other specimens. These pathogens were mostly seen in North India (29%).

Pseudomonas aeruginosa: *Pseudomonas aeruginosa* is the fourth most common organism (12%) isolated from all specimens with 12% prevalence among NFGNB reported. Antimicrobial susceptibility revealed lowest susceptible rates in isolates from ICU settings (50-60%), followed by Wards (60-70%) and OPD (80-90%) respectively. Notably, isolates from CSF and Urine were highly resistant compared to other specimens such as LRTI, Blood, SI and DI. Among the anti-pseudomonal agents, low susceptible rates for fluoroquinolones (~60%) were observed, followed by cephalosprorins (~65%), carbapenems (~69%), aminoglycosides (~70%) and colistin (91%). No significant differences in susceptibility were observed between different specimens except for CSF and urine. Overall, of all the anti-pseudomonal agents, piperacillin/tazobactam, tobramycin and colistin could be of better choice to choose as an empirical therapy with moderate susceptibility profile. Carbapenem based combinations could be preferred with either aminoglycoside or colistin for patients admitted in ICU settings, where drug resistant rates are high.

Acinetobacter baumannii: A total of 3869 clinical isolates of *A. baumannii* were collected from various specimens across OPD, ward and ICU. Decreased susceptibility rates were observed for Cephalosporins like cefepime and ceftazidime across all the specimens followed by piperacillin-tazobactam, amikacin, and levofloxacin. Among carbapenems, imipenem shows susceptibility rate of <15% whereas meropenem shows 20%. Therefore, carbapenem monotherapy is not a choice of treatment for *Acinetobacter* infections. Susceptibility to minocycline is found to be around 57% and combination therapy with colistin, meropenem and rifampicin can be considered. In addition, susceptible rates of different classes of antibiotics against isolates collected between 2016 and 2018 were lower for ceftazidime followed by piperacillin-tazobactam, imipenem, meropenem and amikacin.

P. aeruginosa has little variation across specimens from OPD (13%), Wards (11%) and ICU (13%) settings. Isolation rates were found higher in LRT (36%) and SI (27%) followed by Urine (10%), blood (9%) and DI (7%) respectively. A total of 3869 clinical

isolates of *A. baumannii* were collected from various specimens across OPD, ward and ICU. Isolation of *A. baumannii* was more from ICU (13.7%) followed by ward (6.6%) and OPD (2.6%). The numbers isolated for *S. maltophilia* and *Burkholderia cepacia* is less 0.5% and 0.3% respectively.

Detailed analysis of data

Trend analysis over the years has shown decline in the isolation rates of *P. aeruginosa* in 2018. The year wise isolation trend of *A. baumannii* collected in 2016, 2017 & 2018 was 5%, 7% and 6% respectively. Isolates of *A. baumannii* collected from ICU showed reduced susceptibility rates (<10%) to all the tested antibiotics compared to isolates from ward and OPD. Among the various specimens tested against different classes of antibiotics, susceptible rates are less among specimens like LRT and blood (<10%) followed by specimens from deep infection (<15%).

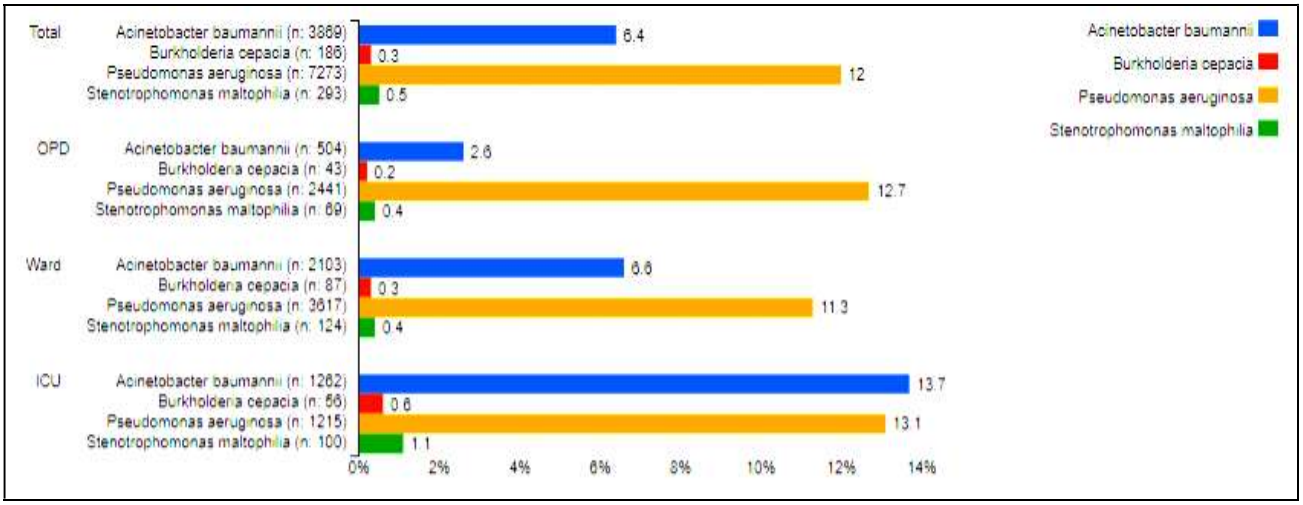


Figure 4.1: Location-wise Isolation pattern of *P aeruginosa*, *Stenotrophomonas maltophilia*, *A baumanii* and *Burkholderia cepacia* isolated from all samples across OPD, Ward and ICU.

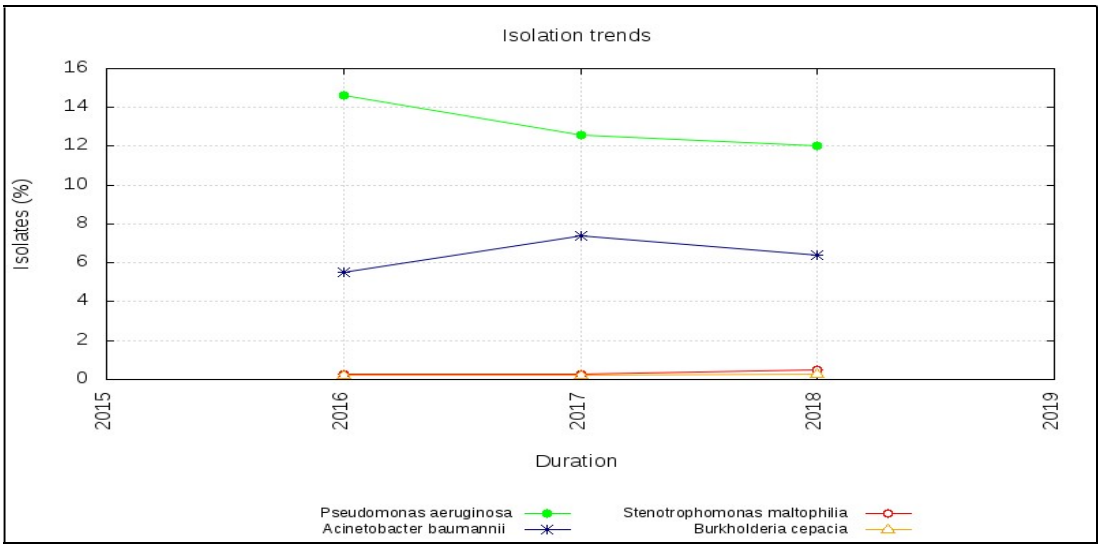


Figure 4.2: Yearly Isolation trend of *P aeruginosa*, *Stenotrophomonas maltophilia, Abaumanii* and *Burkholderia cepacia* isolated from all samples.

Acinetobacter baumanii: Isolates of *A. baumannii* collected from ICU showed reduced susceptible rates (<10%) to all the tested antibiotics compared to isolates from ward and OPD (Table 4.1), whereas minocycline showed susceptible rate of 60.9%. Among OPD, amikacin showed comparatively increased susceptibility of 45% than inwards and ICU (<23%). Among the various specimens tested against different classes of antibiotics, susceptible rates are less among specimens like LRT and blood (<10%) followed by specimens from deep infection (<15%) (Table 4.2). Susceptibility profile of different classes of antibiotics against isolates collected between 2016 and 2018 were less for ceftazidime followed by piperacillin-tazobactam, imipenem, meropenem and amikacin. There has been reduced susceptibility to all these antibiotics from 2016 to 2017, whereas this trend is not observed in 2018 (Table 4.3: Figure 4.3).

Table 4.1: Location-wise susceptible percentage of *A. baumanii* isolated from all samples across OPD, Ward and ICU.

AMA	Total n=4507	OPD n=571	Ward n=2477	ICU n=1459
	(S %)	(S %)	(S %)	(S %)
Amikacin	869/3768 (23.1)	212/479 (44.3)	471/2069 (22.8)	186/1220 (15.2)
Cefepime	581/4417 (13.2)	160/557 (28.7)	305/2426 (12.6)	116/1434 (8.1)
Ceftazidime	568/4124 (13.8)	140/500 (28)	306/2262 (13.5)	122/1362 (9)
Colistin	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)
Imipenem	809/4476 (18.1)	195/564 (34.6)	463/2461 (18.8)	151/1451 (10.4)
Levofloxacin	951/4007 (23.7)	183/506 (36.2)	568/2179 (26.1)	200/1322 (15.1)
Meropenem	943/4137 (22.8)	202/543 (37.2)	567/2236 (25.4)	174/1358 (12.8)
Minocycline	2371/3693 (64.2)	312/459 (68)	1330/1999 (66.5)	729/1235 (59)
Piperacillin-tazobactam	753/4452 (16.9)	191/565 (33.8)	417/2443 (17.1)	145/1444 (10)

Table 4.2: Sample-wise susceptible percentage of *A.baumanii*

AMA	Blood	LRT	Superficial Infection	Deep Infection	CSF	Urine
	n=691	n=1770	n=1105	n=381	n=49	n=123
Amikacin	166/589 (28.2)	238/1363 (17.5)	226/967 (23.4)	77/367 (21)	12/40 (30)	56/112 (50)
Cefepime	122/671 (18.2)	150/1751 (8.6)	143/1085 (13.2)	46/375 (12.3)	10/49 (20.4)	48/118 (40.7)
Ceftazidime	114/646 (17.6)	158/1599 (9.9)	145/1022 (14.2)	43/372 (11.6)	4/41 (9.8)	45/107 (42.1)
Colistin	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)
Imipenem	171/688 (24.9)	189/1763 (10.7)	236/1093 (21.6)	60/379 (15.8)	12/49 (24.5)	62/119 (52.1)
Levofloxacin	175/602 (29.1)	231/1642 (14.1)	298/939 (31.7)	98/349 (28.1)	12/45 (26.7)	53/109 (48.6)
Meropenem	176/592 (29.7)	240/1647 (14.6)	286/991 (28.9)	65/370 (17.6)	12/45 (26.7)	68/119 (57.1)
Minocycline	350/576 (60.8)	839/1480 (56.7)	679/906 (74.9)	277/360 (76.9)	14/23 (60.9)	45/65 (69.2)
Piperacillin-tazobactam	161/678 (23.7)	182/1748 (10.4)	196/1097 (17.9)	58/379 (15.3)	12/49 (24.5)	65/120 (54.2)

Table 4.3: Yearly susceptible trend of *A. baumannii* isolated from all samples.

AMA	Year-2016	Year-2017	Year-2018
	Total n=396	Total n=3361	Total n=4508
	(S%)	(S%)	(S%)
Amikacin	102/347 (29.4)	638/3314 (19.3)	869/3769 (23.1)
Cefepime	67/318 (21.1)	369/3302 (11.2)	581/4418 (13.2)
Ceftazidime	56/328 (17.1)	356/3204 (11.1)	568/4125 (13.8)
Colistin	*0/0	*0/0	*0/0
Imipenem	104/334 (31.1)	502/3348 (15)	809/4477 (18.1)
Levofloxacin	104/312 (33.3)	887/3042 (29.2)	951/4008 (23.7)
Meropenem	100/331 (30.2)	616/3289 (18.7)	943/4138 (22.8)
Minocycline	*0/0	926/1380 (67.1)	2371/3694 (64.2)
Piperacillin-tazobactam	94/335 (28.1)	485/3189 (15.2)	753/4453 (16.9)

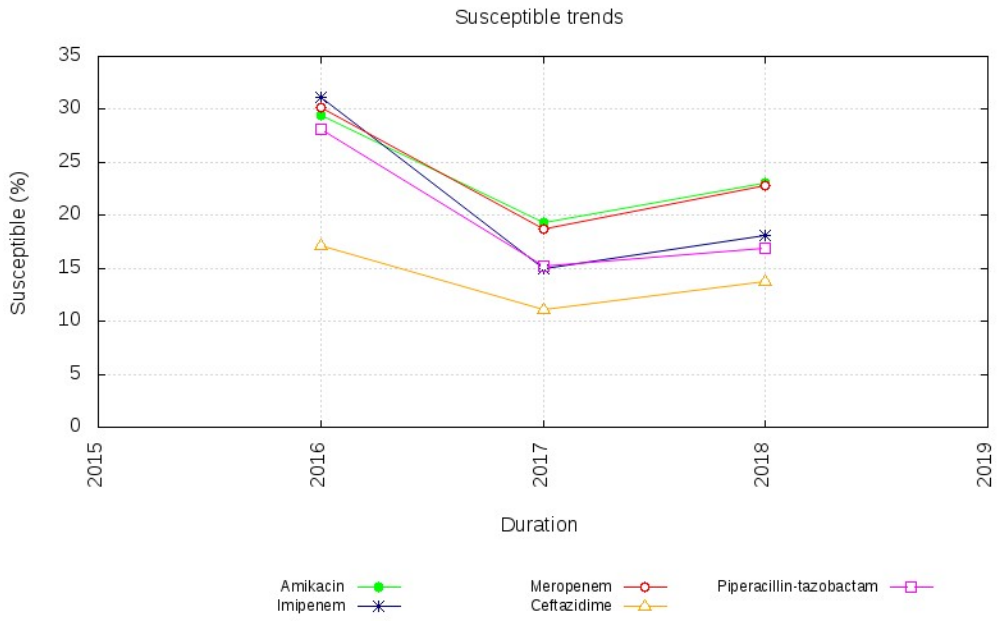


Figure 4.3: Yearly susceptible trend of *A. baumannii* isolated from all samples.

Pseudomonas aeruginosa: Antimicrobial susceptibility revealed lowest susceptible rates in isolates from ICU settings (50-60%), followed by Wards (60-70%) and OPD (80-90%) respectively. Notably, isolates from CSF and Urine were highly resistant compared to other specimens such as LRTI, Blood, SI and DI. Among the anti-pseudomonal agents, low susceptible rates for fluoroquinolones (~60%) were observed, followed by cephalosprorins (~65%), carbapenems (~69%), aminoglycosides (~70%) and colistin (91%). No significant differences in susceptibility were observed between different specimens except for CSF and urine (Table 4.5). Over the years 2017 – 2018, susceptibility to colistin and imipenem has decreased. No change in the trend was observed for amikacin and meropenem.

Table 4.4: Location-wise susceptible percentage of *Pseudomonas aeruginosa* isolated from all samples (except faeces) across OPD, Ward and ICU.

AMA	Total n=8725	OPD n=2769	Ward n=4575	ICU n=1381
	(S %)	(S %)	(S %)	(S %)
Amikacin	5887/8595 (68.5)	2127/2736 (77.7)	2946/4496 (65.5)	814/1363 (59.7)
Cefepime	5133/8135 (63.1)	1933/2572 (75.2)	2501/4267 (58.6)	699/1296 (53.9)
Ceftazidime	5537/8447 (65.5)	2055/2685 (76.5)	2710/4407 (61.5)	772/1355 (57)
Ciprofloxacin	4693/7877 (59.6)	1693/2526 (67)	2337/4082 (57.3)	663/1269 (52.2)
Colistin	847/937 (90.4)	346/385 (89.9)	351/389 (90.2)	150/163 (92)
Gentamicin	3949/6315 (62.5)	1471/2037 (72.2)	1924/3278 (58.7)	554/1000 (55.4)
Imipenem	5496/8222 (66.8)	1965/2564 (76.6)	2799/4323 (64.7)	732/1335 (54.8)
Levofloxacin	4684/8068 (58.1)	1651/2532 (65.2)	2387/4263 (56)	646/1273 (50.7)
Meropenem	5607/8141 (68.9)	1938/2532 (76.5)	2938/4289 (68.5)	731/1320 (55.4)
Piperacillin-tazobactam	5916/8362 (70.7)	2091/2644 (79.1)	3014/4398 (68.5)	811/1320 (61.4)
Tobramycin	3803/5593 (68)	1235/1530 (80.7)	2021/3168 (63.8)	547/895 (61.1)

Table 4.5: Sample-wise susceptible percentage of *Pseudomonas aeruginosa*.

AMA	Blood	LRT	Superficial Infection	Deep Infection	CSF	Urine
	n=747	n=2877	n=2571	n=533	n=47	n=903
Amikacin	458/737 (62.1)	2219/2860 (77.6)	1697/2544 (66.7)	363/525 (69.1)	18/42 (42.9)	450/884 (50.9)
Cefepime	440/690 (63.8)	1985/2754 (72.1)	1429/2386 (59.9)	315/492 (64)	15/47 (31.9)	357/824 (43.3)
Ceftazidime	512/737 (69.5)	2070/2829 (73.2)	1550/2483 (62.4)	362/529 (68.4)	16/47 (34)	370/821 (45.1)
Ciprofloxacin	397/704 (56.4)	1738/2567 (67.7)	1373/2308 (59.5)	299/498 (60)	14/45 (31.1)	351/856 (41)
Colistin	69/77 (89.6)	280/304 (92.1)	237/275 (86.2)	35/36 (97.2)	*3/3 (-)	122/132 (92.4)
Gentamicin	346/578 (59.9)	1277/1798 (71)	1233/1960 (62.9)	248/398 (62.3)	17/39 (43.6)	358/793 (45.1)
Imipenem	484/695 (69.6)	1831/2573 (71.2)	1715/2526 (67.9)	364/522 (69.7)	20/42 (47.6)	439/872 (50.3)
Levofloxacin	379/665 (57)	1904/2753 (69.2)	1319/2402 (54.9)	284/469 (60.6)	15/47 (31.9)	287/783 (36.7)
Meropenem	503/698 (72.1)	1870/2610 (71.6)	1683/2395 (70.3)	376/518 (72.6)	19/46 (41.3)	437/881 (49.6)
Piperacillin-tazobactam	517/722 (71.6)	2074/2780 (74.6)	1722/2450 (70.3)	379/517 (73.3)	18/47 (38.3)	475/864 (55)
Tobramycin	284/481 (59)	1631/2033 (80.2)	1119/1749 (64)	247/345 (71.6)	15/35 (42.9)	168/388 (43.3)

Table 4.6: Yearly susceptible trend of *Pseudomonas aeruginosa* isolated from all samples.

AMA	Year-2016	Year-2017	Year-2018
	Total n=1057	Total n=5687	Total n=8728
	(S%)	(S%)	(S%)
Amikacin	693/1030 (67.3)	3866/5609 (68.9)	5888/8598 (68.5)
Cefepime	585/981 (59.6)	3076/5003 (61.5)	5134/8138 (63.1)
Ceftazidime	624/1035 (60.3)	3604/5504 (65.5)	5539/8450 (65.6)
Ciprofloxacin	436/842 (51.8)	2932/5069 (57.8)	4694/7880 (59.6)
Colistin	711/723 (98.3)	1729/1740 (99.4)	849/939 (90.4)
Gentamicin	402/776 (51.8)	2528/4249 (59.5)	3950/6318 (62.5)
Imipenem	810/1017 (79.6)	4061/5514 (73.6)	5498/8225 (66.8)
Levofloxacin	536/958 (55.9)	3238/5351 (60.5)	4685/8071 (58)
Meropenem	651/970 (67.1)	3492/5083 (68.7)	5607/8144 (68.8)
Piperacillin-tazobactam	705/1036 (68.1)	3759/5450 (69)	5917/8363 (70.8)
Tobramycin	579/957 (60.5)	2955/4364 (67.7)	3803/5593 (68)

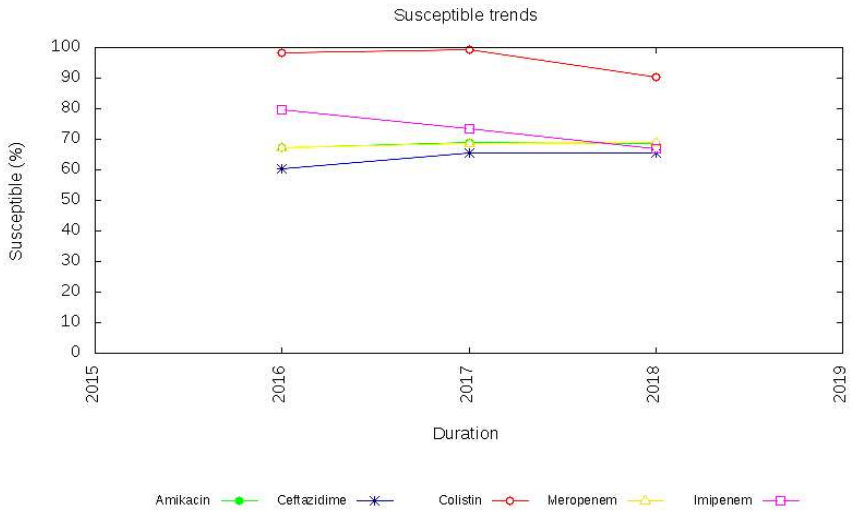


Figure 4.4: Yearly susceptible trend of *pseudomonas aeruginosa* isolated from all samples.

Burkholderia Cepacia: Table 4.7 shows the location-wise susceptibilities of *B. cepacia* across OPD, ward and ICU. Overall, ward and ICU had reduced susceptible rates in comparison to OPD. For ceftazidime, isolates from OPD showed susceptible rates of 86.8% whereas ward and ICU had <70%. Similarly, meropenem showed 92.5% susceptibility rate in OPD compared to ~80% in ward and ICU. Table 4.8 shows sample-wise susceptible rates for *B. cepacia*. Blood and LRT had almost equal susceptibilities for all antibiotics tested. Among which, ticarcillin-clavulanic acid showed <10% susceptible followed by ceftazidime 68.4%. Urine and superficial infections isolated lesser number of *B. cepacia*. For minocycline, susceptible rate in blood isolates were 75% compared to LRT (92.1%). Yearly susceptible trends of *B. cepacia* depicted in Table 4.9 and Figure 4.5 showed no major change between the years 2017 and 2018. The number of isolates from 2016 was lesser (n = 18). For minocycline, there has been a decrease in susceptibility rate of 78.5% in 2018 from 85.6% in 2017.

Table 4.7: Location-wise susceptible percentage of *Burkholderia cepacia* isolated from all samples across OPD, Ward and ICU.

AMA	*Burkholderia cepacia*			
	Total n=196	OPD n=44	Ward n=93	ICU n=59
	(S %)	(S %)	(S %)	(S %)
Ceftazidime	137/191 (71.7)	34/39 (87.2)	61/93 (65.6)	42/59 (71.2)
Chloramphenicol	*1/1	*0/0	*1/1	*0/0
Levofloxacin	34/66 (51.5)	17/29 (58.6)	10/24 (41.7)	*7/13
Meropenem	140/170 (82.4)	38/41 (92.7)	58/75 (77.3)	44/54 (81.5)
Minocycline	146/185 (78.9)	31/40 (77.5)	65/87 (74.7)	50/58 (86.2)
Ticarcillin-clavulanic acid	4/51 (7.8)	2/23 (8.7)	*2/18	*0/10
Trimethoprim-sulfamethoxazole	179/191 (93.7)	39/41 (95.1)	83/91 (91.2)	57/59 (96.6)

Table 4.8: Sample-wise susceptible percentage of *Burkholderia cepacia*.

AMA	All Specimens (except faeces)	Blood	LRT	Superficial Infection	Urine
	n=196	n=105	n=39	n=*13	n=*17
Ceftazidime	137/191 (71.7)	68/101 (67.3)	27/39 (69.2)	*10/12 (-)	*12/17 (-)
Chloramphenicol	*1/1 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)
Levofloxacin	34/66 (51.5)	20/35 (57.1)	*2/5 (-)	*0/5 (-)	*5/9 (-)
Meropenem	140/170 (82.4)	69/85 (81.2)	31/37 (83.8)	*9/11 (-)	*15/17 (-)
Minocycline	146/185 (78.9)	76/101 (75.2)	36/39 (92.3)	*10/12 (-)	*8/13 (-)
Ticarcillin-clavulanic acid	4/51 (7.8)	2/27 (7.4)	*0/4 (-)	*2/6 (-)	*0/3 (-)
Trimethoprim-sulfamethoxazole	179/191 (93.7)	99/104 (95.2)	37/39 (94.9)	*11/12 (-)	*14/16 (-)

Table 4.9: Yearly susceptible trend of *Burkholderia cepacia* isolated from all samples.

AMA	Year-2017	Year-2018
	Total n=112	Total n=196
	(S%)	(S%)
Ceftazidime	73/101 (72.3)	137/191 (71.7)
Chloramphenicol	*0/0	*1/1
Levofloxacin	*4/13	34/66 (51.5)
Meropenem	83/111 (74.8)	140/170 (82.4)
Minocycline	89/104 (85.6)	146/185 (78.9)
Ticarcillin-clavulanic acid	*0/9	4/51 (7.8)
Trimethoprim-sulfamethoxazole	84/109 (77.1)	179/191 (93.7)

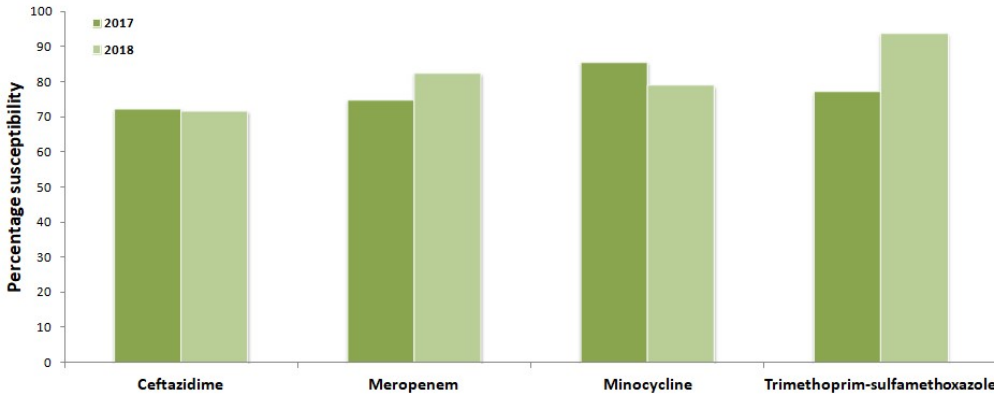


Figure 4.5: Yearly susceptible trend of *Burkholderia cepacia* isolated from all samples.

Stenotrophomonas maltophilia: Table 4.10 depicts location-wise susceptible trend of *S. maltophilia* across OPD, ward and ICU. No major change in susceptibility percentage were observed between the locations. In case of trimethoprim sulfamethoxazole, susceptibility was less in OPD patients (75.4%) in comparison to ward and ICU (87%). Table 4.11 depicts sample-wise susceptible trend of *S. maltophilia* which shows that among LRT samples ceftazidime has susceptible rate of (65.2%) followed by ticarcillin-clavulanic acid 76%. Trimethoprim-sulfamethoxazole and levofloxacin had high susceptible rate of 86.8% and 88% respectively. Among blood samples, susceptibility pattern is same for ceftazidime (67%) and trimethoprim-sulfamethoxazole, whereas minocycline showed susceptibility of 86.8%. Table 4.12 and Figure 4.6 shows year-wise susceptible trend of *S. maltophilia* from all samples. There was no major change observed between the years 2016 and 2018.

Table 4.10: Location-wise susceptible percentage of *Stenotrophomonas maltophilia* isolated from all samples across OPD, Ward and ICU.

AMA	*Stenotrophomonas maltophilia*			
	Total n=299	OPD n=70	Ward n=127	ICU n=102
	(S %)	(S %)	(S %)	(S %)
Ceftazidime	42/63 (66.7)	24/37 (64.9)	*8/12	*10/14
Chloramphenicol	*1/2	*0/0	*1/1	*0/1
Levofloxacin	216/246 (87.8)	47/56 (83.9)	93/104 (89.4)	76/86 (88.4)
Minocycline	261/288 (90.6)	60/67 (89.6)	107/123 (87)	94/98 (95.9)
Ticarcillin-clavulanic acid	45/60 (75)	27/37 (73)	*8/9	*10/14
Trimethoprim-sulfamethoxazole	249/297 (83.8)	52/69 (75.4)	110/126 (87.3)	87/102 (85.3)

Table 4.11: Sample-wise susceptible percentage of *Stenotrophomonas maltophilia*.

AMA	All Specimens (except faeces)	Blood	LRT	Superficial Infection	Urine
	n=299	n=111	n=115	n=21	n=*16
Ceftazidime	42/63 (66.7)	*12/18 (-)	15/23 (65.2)	*6/7 (-)	*6/7 (-)
Chloramphenicol	*1/2 (-)	*0/0 (-)	*0/0 (-)	*1/1 (-)	*0/0 (-)
Levofloxacin	216/246 (87.8)	93/98 (94.9)	82/93 (88.2)	*15/18 (-)	*6/10 (-)
Minocycline	261/288 (90.6)	94/107 (87.9)	112/115 (97.4)	17/20 (85)	*11/13 (-)
Ticarcillin-clavulanic acid	45/60 (75)	*12/15 (-)	19/25 (76)	*4/5 (-)	*6/7 (-)
Trimethoprim-sulfamethoxazole	249/297 (83.8)	95/110 (86.4)	99/115 (86.1)	17/21 (81)	*12/16 (-)

Table 4.12: Yearly susceptible trend of *Stenotrophomonas maltophilia* isolated from all samples.

AMA	Year-2017	Year-2018
	Total n=157	Total n=299
	(S%)	(S%)
Ceftazidime	15/27 (55.6)	42/63 (66.7)
Chloramphenicol	*0/0	*1/2
Levofloxacin	126/152 (82.9)	216/246 (87.8)
Minocycline	143/151 (94.7)	261/288 (90.6)
Ticarcillin-clavulanic acid	19/26 (73.1)	45/60 (75)
Trimethoprim-sulfamethoxazole	132/150 (88)	249/297 (83.8)

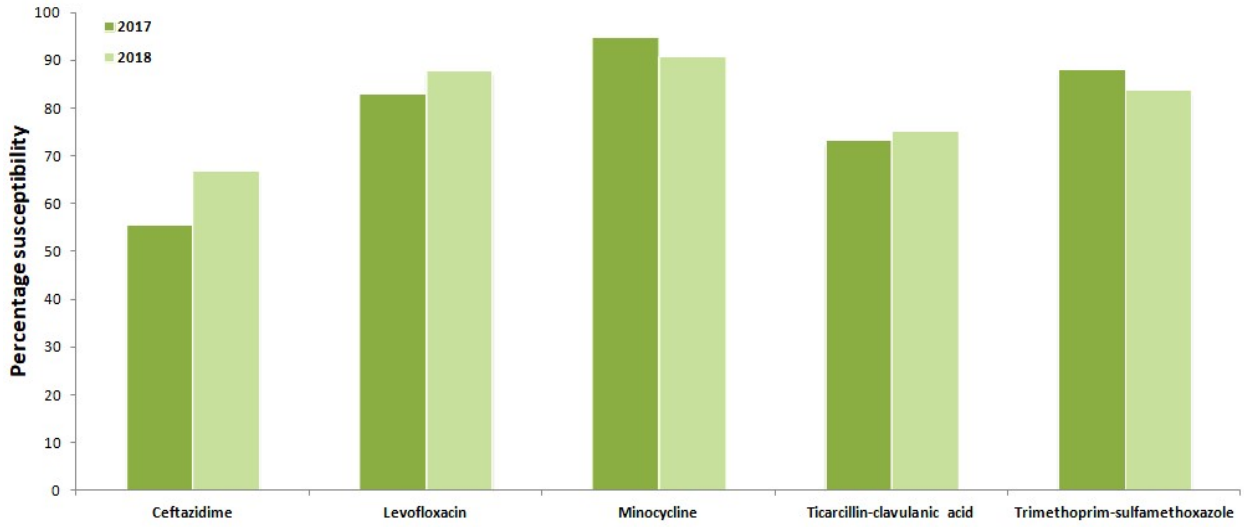


Figure 4.6: Yearly susceptible trend of *Stenotrophomonas maltophilia* isolated from all samples.

Molecular characterization of antimicrobial resistance determinants in *P.aeruginosa* and *A. baumannii*

P. aeruginosa

In addition to the existing 8 centers (CMC, AIIMS, PGIMER, JIPMER, Apollo, TATA Medical Centre, Sir Gangaram, MGIMS), seven more new sites have been included in the network during 2018 (PD-Hinduja, NIMS, SKIMS, KMC, IPGMER, AMC and AFMC). A total of 241 carbapenem resistant *P.aeruginosa* collected across 15 centers from several parts of India were characterized for molecular resistance mechanisms. Of the beta lactamases screened, bla_{VEB} was the most common ESBL followed by bla_{TEM} and few bla_{PER} genes were identified. While, among carbapenemase encoding genes, bla_{VIM} was the most common (1-56%), followed by bla_{NDM} (16-75%) and few bla_{IMP} and bla_{GES} were observed. bla_{IMP} and bla_{GES} are noted to be identified in the recent years, which needs to be monitored continuously. Additionally, co-producers of ESBLs plus carbapenemases (VEB+NDM) and two-carbapenemases (IMP+NDM, NDM+VIM) are increasingly been observed. Trend analysis revealed the increasing numbers of bla_{NDM} across all participating sites. No significant regional differences were observed in the molecular mechanisms studied, except $bla_{NDM,}$ which is increasingly being reported in the recent years.

Acinetobacter baumannii

Molecular characterization of antimicrobial resistance genes by PCR were performed for a total of 371 isolates from AIIMS, CMC, JIPMER, PGIMER, Apollo hospital, Sir Ganga Ram hospital, Tata Medical Center, Hindhuja hospital, MGIMS, Nizam Institute of

Medical sciences, Assam Medical College, Kasturba Medical College and KGMU. All the tested isolates were positive for intrinsic *bla*$_{\text{OXA-51}}$ like gene. Across all the centers, *bla*$_{\text{OXA-23}}$ like only is the predominant carbapenemase contributing to 30% of carbapenem resistance. Another class D acquired carbapenemase, *bla*$_{\text{OXA-58}}$ like was observed among isolates from PGIMER, Sir Ganga Ram hospital and Tata Medical Center. Across all the centers, co-producers of ESBLs with carbapenemases like *bla*$_{\text{OXA-23}}$ like with *bla*$_{\text{TEM}}$ like (7%) or *bla*$_{\text{PER}}$ like (22%) were found to be predominant. Combination of carbapenemases like *bla*$_{\text{OXA-23}}$ like with *bla*$_{\text{NDM}}$ like (20%) were also observed.

Chapter 5- Diarrheal pathogens

Summary of results

The distribution of faecal isolates in the year 2018 showed high rate of isolation (67%) in South India compared to other regions. The predominant species identified was *Aeromonas spp* (25%) followed by *Shigella spp* (14%) and *Salmonella spp* (8%). The location wise isolation pattern showed that *Aeromonas spp* was isolated in large numbers in OPD and ICU, which is followed by *Shigella spp*. *Salmonella spp* was isolated only from OPD and ward. Only less number of *Vibrio spp* was isolated.

Aeromonas spp

Aeromonas spp showed moderate resistance to all tested antibiotics and showed only 11% susceptibility to ciprofloxacin in 2018. There is no significant change was observed in the susceptibility trend from the last year. *Aeromonas spp* showed good susceptibility to tetracycline (85%) and, third generation cephalosporin (cefixime) (67%) which needs to be confirmed with more number of isolates. However, treatment failure may occur in severe infections while on treatment with third-generation cephalosporins or carbapenem monotherapy for *A. hydrophila* and *A. veronii*; and third-generation cephalosporin monotherapy for *A. caviae*. This is due to chromosome encoded inducible AmpC and MBL gene-carrying aeromonads. Definite therapy can be adjusted based on the species and its susceptibility profile.

Also carbapenems are increasingly used as empirical therapy for serious infections thus the clinical use of carbapenem monotherapy could result in treatment failure. In such case, the ideal choice could be fourth-generation cephalosporins. However, if the causative strain is a co-producer of ESBL and AmpC genes, the drug of choice will be limited. Further, fluoroquinolones, aminoglycosides, and trimethoprim-sulfamethoxazole could be considered as an alternative agents for treatment. Notably, usage of certain agents like ampicillin and first generation cephalosporin should be avoided, as all species of clinical aeromonads are resistant to ampicillin except for *A. trota* and sometimes *A. caviae* and *A. veronii* biovar sobria (formerly *Aeromonas sobria*) is uniformly resistant to first generation cephalosporins.

Shigella spp

S. sonnei and *S. flexneri* was the predominant serotype isolated. Decreased susceptibility was observed to first line antibiotics. The susceptibility to trimethoprim-sulfamethoxazole was observed as 23% and 0% in *S. flexneri* and *S. sonnei* respectively. Therefore this should not be recommended unless susceptibility is known or expected based on local surveillance. *S. flexneri* showed less susceptibility to ampicillin (23%) compared to *S. sonnei*.

Quinolones and third generation cephalosporins can be used as the first line therapy. However, emerging resistance was observed to cefixime in *S. flexneri*, which showed 83% susceptibility. This could be due to the increasing use of cefixime as an oral antibiotic. For resistant isolates, azithromycin can be used as a second-line oral therapy for both children and adults. Emerging resistance to these drugs are also observed. Hence continues surveillance on changing trend of antimicrobial susceptibility of this pathogen is essential particularly in *Shigella* endemic regions.

The resistance gene profile was consistent over the years and no change in pattern was observed in both *S. flexneri* and *S. sonnei*. The predominantly observed resistance genes in both *S. flexneri* and *S. sonnei* was *dhfr1a* (79%) and *sul*II (58%) that codes for trimethoprim and sulfamethoxazole. Among β-lactamases, bla_{OXA} (10%) and bla_{TEM} (42%) was predominantly identified in *S. flexneri*, while *S. sonnei* carried only$bla_{CTX\text{-}M\text{-}15}$ genes (12%). This mediates ampicillin resistance in both the species. This molecular observation correlates with the phenotypic results. For plasmid mediated quinolone resistance (PMQR), *qnr*B and *qnr*S was identified in both the species with the overall prevalence of 11% and 15% respectively.

Vibrio cholerae

The isolation of *V. cholerae* (5%) was comparatively lesser than other enteric pathogens identified. *V. cholerae* showed only 25% susceptibility to trimethoprim-sulfamethoxazole followed by ampicillin (71%). Therefore, this should be used only when the susceptibility is known. Only less number of isolates were tested for quinolones. Tetracycline/ doxycycline is generally used for cholera infections. However, increasing evidence of resistance to tetracycline and ciprofloxacin were reported in adults and children. Recently, azithromycin has shown to be clinically superior to tetracycline in treating cholera infections in children and can be considered as a first-line therapy. Similarly, erythromycin is clinically superior to ciprofloxacin and considered as a second-line therapy. However, emerging resistance needs to be monitored to control the further spread of antimicrobial resistance in *V. cholerae.*

The overall isolation rate of faecal pathogens among the culture positives was 0.5%, for the year 2018. The rate of isolation of pathogens from faeces samples was 45%. The positivity of faecal pathogens from other specimens includes 0.4% in sterile sites (SS), 0.1% in blood, superficial infection (SI) and deep infections, and 0.3% in others. The diarrheal pathogens such as *Aeromonas spp*, *Salmonella spp* and *Vibrio spp* were predominantly isolated from South India (67%), whereas *Shigella* was most commonly seen in East India (26%).

Detailed analysis of data

Figure 5.1 depicts the location wise isolation pattern which showed that *Aeromonas spp* was isolated in large numbers in OPD and ICU, which is followed by *Shigella spp*.

Salmonella spp was isolated only from OPD and ward. Only less number of *Vibrio spp* was isolated. The distribution of faecal isolates in the year 2018 showed high rate of isolation (67%) in South India compared to other regions. The predominant species identified was *Aeromonas spp* (21%) followed by *Shigella spp* (12%) and *Salmonella spp* (7%) (Figure 5.2).

Figure 3 depicts the isolation trend of *Aeromonas spp, Salmonella spp, Shigella spp and V. cholerae.* The isolation rate of *Aeromonas spp* is decreasing since 2016 from 37% to 22% in 2018. Whereas the isolation rate of *V. cholerae* and *Salmonella spp* increased by 5% since 2016. Overall isolation rates of fecal isolates in comparison to overall positivity shows that *Aeromonas spp* has highest among the other fecal pathogens (0.2%), whereas *Shigella spp* and *Salmonella spp* accounts for 0.1%.

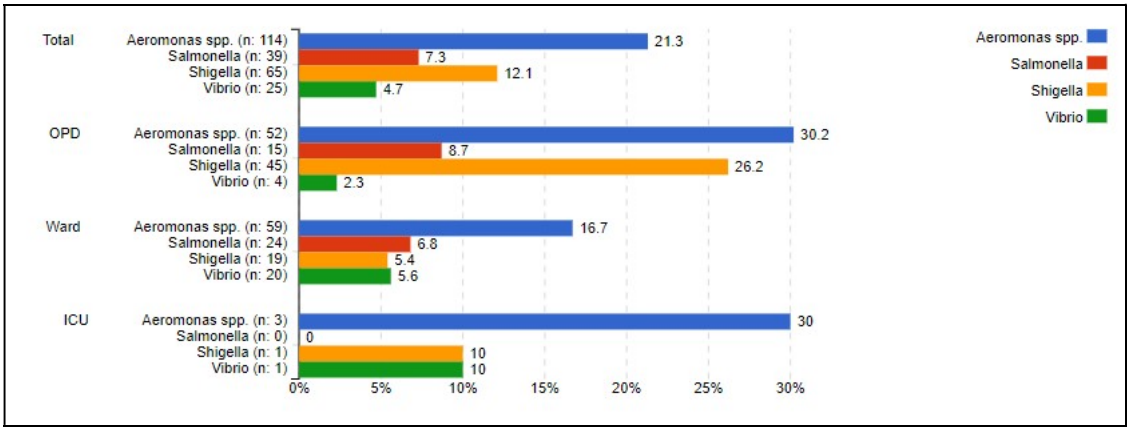


Figure 5.1 Location-wise Isolation pattern of Aeromonas species, Salmonella faecal, Shigella and Vibrio isolated from Faeces across OPD, Ward and ICU.

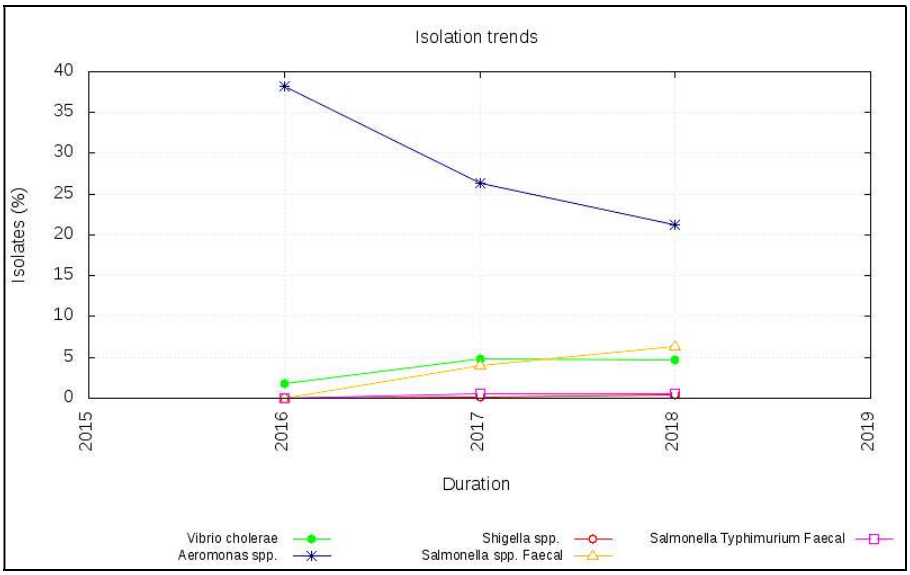


Figure 5.2 Yearly Isolation trends of *Aeromonas* species, Salmonella spp. faecal, *Salmonella typhimurium* faecal, Shigella spp. and Vibrio Cholerae isolated from Faeces.

Table 5.1: Isolation rates of Faecal isolates isolated in 2018.

Isolate	Total positive cultures 'n' = 583	
	n	%
Salmonella	49	8.4%
Salmonella enteritidis	7	1.2%
Salmonella heidelberg	0	-
Salmonella newport	0	-
Salmonella typhimurium faecal	7	1.2%
Salmonella spp faecal	35	6%
Shigella	80	13.7%
Shigella boydii	2	0.3%
Shigella dysenteriae	1	0.1%
Shigella flexneri	48	8.2%
Shigella sonnei	27	4.6%
Shigella spp	2	0.3%
Vibrio	28	4.8%
Vibrio cholerae	28	4.8%
Vibrio parahaemolyticus	0	-
Vibrio spp	0	-
Aeromonas spp	147	25.2%
Arizona spp	0	-
Campylobacter jejuni	0	-
Clostridium difficile	0	-
Escherichia coli Diarrhoeagenic	1	0.1%
Plesiomonas shigelloides	0	-
Yersinia enterocolitica	0	-

Aeromonas

Among *Aeromonas spp* isolated in 2018, susceptibility to ciprofloxacin was 10% followed by imipenem (53%), cefixime and meropenem (67%) respectively. Whereas, tetracycline susceptibility observed was 85% (Table 5.2). Overall, *Aeromonas spp* showed moderate resistance to all tested antibiotics except to ciprofloxacin in 2018 (Table 5.2, Table 5.3, Figure 5.3). There is no significant change was observed in the susceptibility trend from the last year. This needs to be confirmed with more number of isolates.

Table 5.2 Susceptible pattern of *Aeromonas spp* isolated in 2018

AMA	All Specimens
	Aeromonas spp. **n=147**
Cefixime	37/56 (66.1)
Ciprofloxacin	14/134 (10.4)
Imipenem	75/142 (52.8)
Meropenem	93/139 (66.9)
Norfloxacin	*9/12 (-)
Tetracycline	108/127 (85)

Table 5.3 Yearly susceptible trends of *Aeromonas spp*.

AMA	Year-2016	Year-2017	Year-2018
	Total n=28	Total n=158	Total n=147
	(S%)	(S%)	(S%)
Cefixime	*1/1	*8/11	37/56 (66.1)
Ciprofloxacin	*0/4	9/93 (9.7)	14/134 (10.4)
Imipenem	*0/0	32/58 (55.2)	75/142 (52.8)
Meropenem	*0/0	36/60 (60)	93/139 (66.9)
Norfloxacin	22/24 (91.7)	36/42 (85.7)	*9/12
Tetracycline	21/24 (87.5)	122/148 (82.4)	108/127 (85)

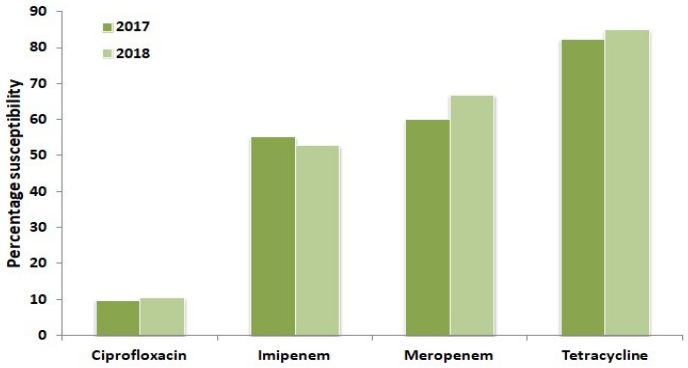


Figure 5.3 Yearly susceptible trends of *Aeromonas spp*

Shigella

S. sonnei and *S. flexneri* was the predominant serotype isolated. Decreased susceptibility was observed to first line antibiotics. The susceptibility to trimethoprim-sulfamethoxazole was observed as 23% and 0% in *S. flexneri* and *S. sonnei* respectively (Table 5.4). Therefore this should not be recommended unless susceptibility is known or expected based on local surveillance. *S. flexneri* showed less susceptibility to ampicillin (23%) compared to *S. sonnei*. Quinolones and third generation cephalosporins can be used as the first line therapy. However, emerging resistance was observed to cefixime in *S. flexneri*, which showed 83% susceptibility. This could be due to the increasing use of cefixime as an oral antibiotic.

Table 5.4 Susceptible pattern of *Shigella* species isolated in 2018

AMA	Faeces	
	Shigella flexneri **n=47**	***Shigella sonnei*** **n=26**
Ampicillin	12/47 (25.5)	18/24 (75)
Cefixime	38/46 (82.6)	25/26 (96.2)
Nalidixic acid	*0/15 (-)	*0/1 (-)
Norfloxacin	*1/16 (-)	*0/1 (-)
Trimethoprim-sulfamethoxazole	14/47 (29.8)	0/25 (0)

Shigella flexneri: Yearly susceptible trend of *S. flexneri* shows that there is a decrease in ampicillin susceptibility from 45% in 2017 to 23% in 2018. No major change in susceptibility of cefixime and trimethoprim-sulfamethoxazole was observed (Table 5.5: Figure 5.5).

Shigella sonnei: Trimethoprim-sulfamethoxazole showed poor susceptibility (<10%) followed by ampicillin (~70%). No major change in the susceptibility trend between 2017 and 2018 was observed (Table 5.6: Figure 5.6).

Table 5.5 Yearly susceptible trends of *Shigella flexneri*

AMA	Year-2017	Year-2018
	Total n=90	**Total n=48**
	(S%)	**(S%)**
Ampicillin	40/90 (44.4)	12/48 (25)
Cefixime	56/69 (81.2)	39/47 (83)
Nalidixic acid	0/25 (0)	*0/16
Norfloxacin	13/25 (52)	*2/17
Trimethoprim-sulfamethoxazole	7/72 (9.7)	14/48 (29.2)

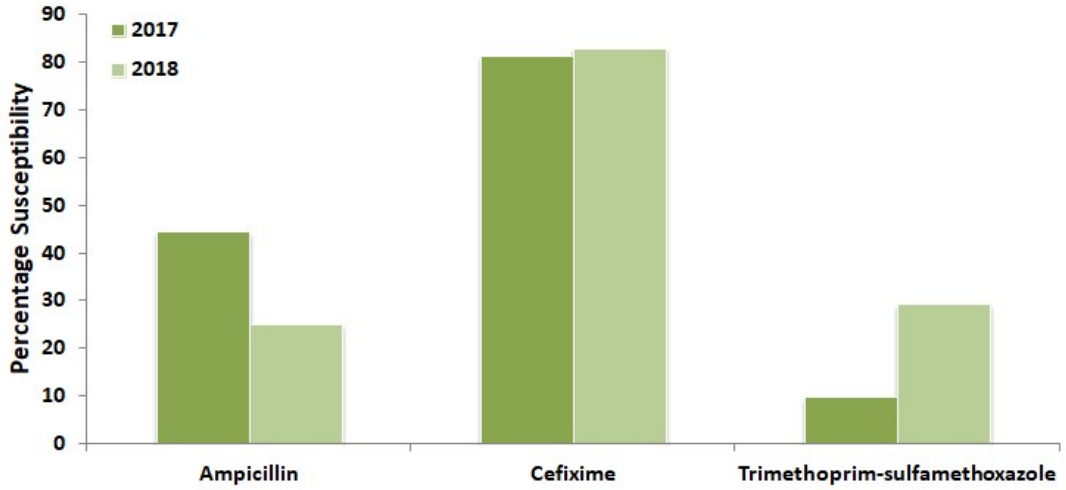


Figure 5.4 Yearly susceptible trends of *Shigella flexneri*

Table 5.6 Yearly susceptible trends of *Shigella sonnei*

AMA	Year-2017	Year-2018
	Total n=52	Total n=27
	(S%)	(S%)
Ampicillin	35/52 (67.3)	18/25 (72)
Cefixime	47/50 (94)	26/27 (96.3)
Nalidixic acid	*0/8	*0/1
Norfloxacin	*2/8	*0/1
Trimethoprim-sulfamethoxazole	4/52 (7.7)	0/26 (0)

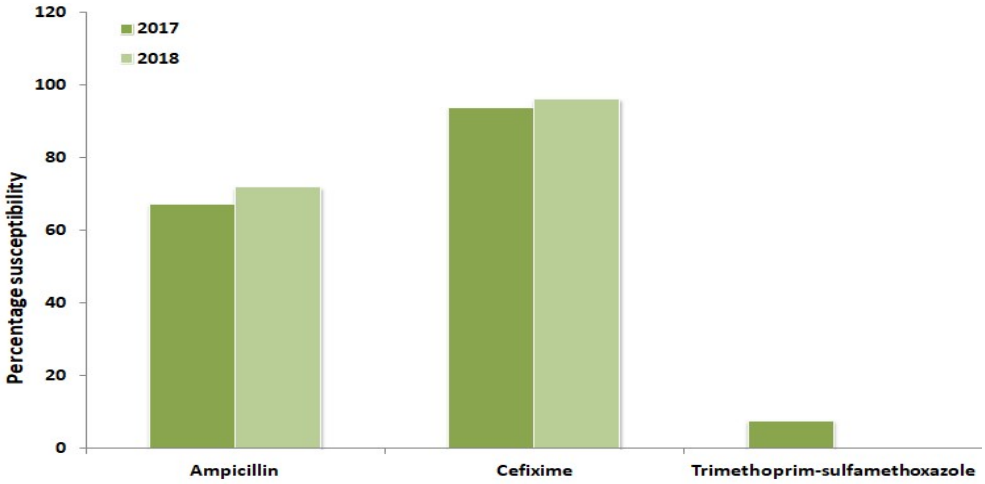


Figure 5.5 Yearly susceptible trends of *Shigella sonnei*

Vibrio cholerae

The isolation of *V. cholerae* (5%) was comparatively lesser than other enteric pathogens identified. *V. cholerae* showed only 25% susceptibility to trimethoprim-sulfamethoxazole followed by ampicillin (71%) (Table 5.7). Therefore, this should be used only when the susceptibility is known. Only less number of isolates were tested for quinolones. Yearly susceptible trend for *V. cholerae* shows that there is a decrease in susceptibility to ampicillin from 42% in 2017 to 25% in 2018. There is no change in susceptibility pattern for other antimicrobials (Table 5.8: Figure 5.7).

Table 5.7 Susceptible pattern of *Vibrio cholerae* isolated in 2018

AMA	Faeces
	Vibrio cholerae **n=25**
Ampicillin	17/24 (70.8)
Nalidixic acid	*0/4 (-)
Norfloxacin	*4/4 (-)
Tetracycline	*7/10 (-)
Trimethoprim-sulfamethoxazole	6/24 (25)

Table 5.8 Yearly susceptible trends of *Vibrio cholerae*

AMA	Year-2017	Year-2018
	Total n=29	Total n=28
	(S%)	(S%)
Ampicillin	22/29 (75.9)	17/27 (63)
Nalidixic acid	*2/9	*0/6
Norfloxacin	*13/19	*6/6
Tetracycline	24/26 (92.3)	*9/12
Trimethoprim-sulfamethoxazole	12/26 (46.2)	8/27 (29.6)

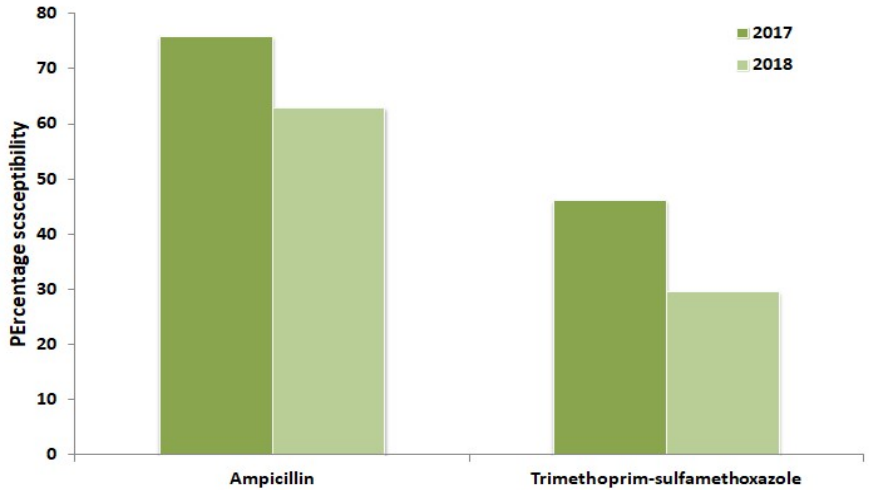


Figure 5.6 Yearly susceptible trends of *Vibrio Cholerae*

Molecular data of Diarrheagenic pathogens and its relevance

Shigella spp: Characterization of resistance mechanism

Totally, hundred and fourty two multi-drug resistant isolates of *Shigellaspp*collectedduring the year 2014 – 2017 at Christian Medical College, Vellore were characterized for their resistance mechanisms. This includes *S. flexneri* (*n* = 112), *S. sonnei* (*n* = 30). The presence of genes identified in the two predominant serogroup of *Shigella* showed the varying prevalence of antimicrobial resistance genes. Trimethoprim/sulfamethoxazole resistance genes such as *dhfr1a* and *sul*2 were commonly observed in both *S. flexneri* and *S. sonnei.* For beta-lactamses, bla_{OXA} (62.5%)

gene was predominantly seen followed by *bla*$_{TEM}$ (22%) and *bla*$_{CTX-M-15}$ (8%) in *S. flexneri*. While *bla*$_{OXA}$ gene was not identified in *S. sonnei*whereas*bla*$_{TEM}$and*bla*$_{CTX-M-15}$ gene was identified in 7% and 20% respectively. AmpC genes were identified in 11% and 3% of the *S. flexneri* and *S. sonnei* isolates. For plasmid mediated quinolone resistance, *qnr*Svariant was predominantly seen in the study isolates than *qnr*B. Among *S. flexneri* isolates, *qnr*S and *qnr*B genes were identified in 15% and 1% respectively. Only *qnr*S gene was identified in single isolate of*S. sonnei.*

Molecular characterization of AMR mechanism in *S. flexneri* and *S. sonnei* (2014 – 2017)

Sixty *Shigellaspp* were studied to determine the prevalence of resistance genes against various classes of antibiotics through whole genome sequencing. Among *Shigella spp*, ampicillin resistance was usually encoded by OXA-type β-lactamase genes. In the present study, *bla*$_{OXA}$ genes were identified in 30% of the isolates. While *bla*$_{TEM}$, another most common β-lactamase gene associated with ampicillin resistancewas identified in 22% of the isolates. Gene conferring resistance to third generation cephalosporins such as *bla*$_{CTX-M-15}$ was found in 10% of the isolates and plasmid mediated AmpC β-lactamases genes were identified only in few isolates. For plasmid mediated quinolone resistance, *qnr*S gene was widely distributed among our *Shigella* isolates. Further, resistance genes for Trimethoprim/sulfamethoxazole, tetracycline, aminoglycosides and chloramphenicol were commonly seen in most of our study isolates.

Table 5.9 Molecular identification of antimicrobial resistance mechanism in *S flexneri*

S. flexneri (n = 112)	*dhfr1a*	*Sul II*	*blaOXA*	*blaTEM*	*blaCTX-M-15*	AmpC	*qnr* A, B,S
2014 (n = 22)	22	15	12	4	2	2	qnrS - 6
2015 (n =35)	28	27	18	11	1	7	*qnr*S - 5
2016 (n =24)	24	17	18	1	1	1	*qnr*S - 2 *qnr*B – 1
2017 (n =31)	26	3	22	9	5	2	*qnr*S - 4
Total	**100**	**62**	**70**	**25**	**9**	**12**	***qnr*B – 1** ***qnr*S - 17**

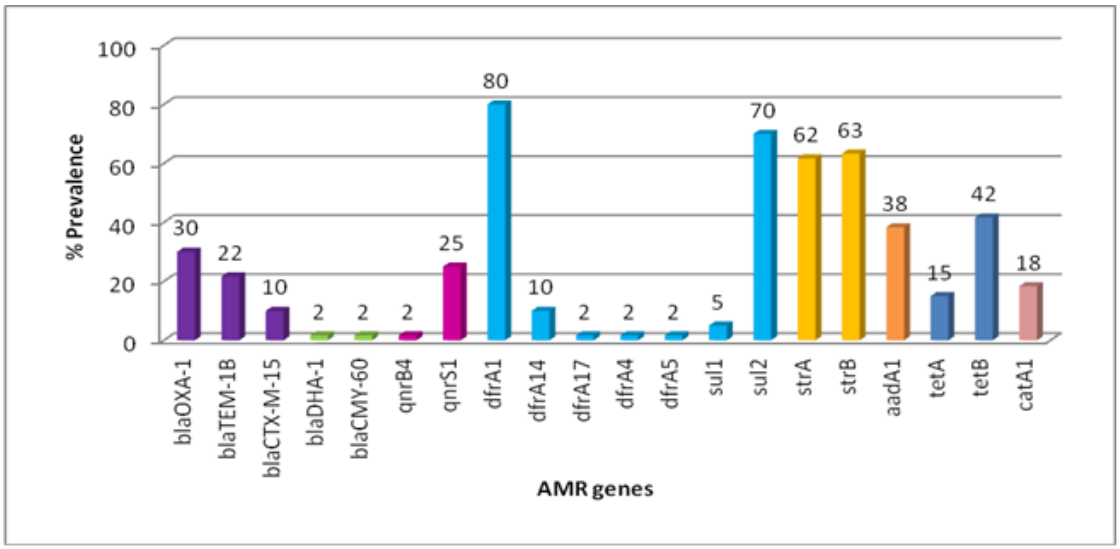


Figure 5.7 Distribution of AMR genes among *Shigella* spp as observed by whole genome sequencing

Table 5.10 Molecular identification of antimicrobial resistance mechanism in *S sonnei*

S. sonnei (n = 30)	*dhfr1a*	*Sul II*	*blaOXA*	*blaTEM*	*blaCTX-M-15*	*AmpC*	*qnr* A, B,S
2014 (n = 6)	6	5	-	-	1	-	*qnr*S - 1
2015(n =9)	9	5	-	1	1	-	-
2016(n =2)	2	2	-	-	-	-	-
2017(n =13)	12	4	-	1	4	1	-
Total	**29**	**16**	**-**	**2**	**6**	**1**	***qnr*S - 1**

Non-Typhoidal *Salmonella*

Twenty six ceftriaxone-resistant non typhoidal salmonella (CR-NTS) strains from stool specimen were characterized for their mechanism of resistance. The MIC range of ceftriaxone for these isolates were from 32 - 1024 µg/ml. This includes (STM – 23 and Salmonella group C – 3)

Molecular screening of β-lactamases shown that, all the CR-NTS isolates harboured either *bla*$_{\text{CTX-M-1 like}}$ or *bla*$_{\text{CMY}}$ gene. Among these, 54 % (n=14) and 46 % (n=12) of the isolates harboured*bla*$_{\text{CTX-M-1 like}}$ and *bla*$_{\text{CMY}}$gene respectively. Notably, 46 % (n=12) of the *bla*$_{\text{CTX-M-1 like}}$ positives also co-harboured*bla*$_{\text{TEM}}$ gene (Dual ESBLs). While, 4 % (n=1) of the *bla*$_{\text{CMY}}$positives co-harboured*bla*$_{\text{TEM}}$ gene (Amp+ESBL). MIC's associated with the β-lactamases found to vary significantly. High level resistance of MIC being 1024 µg/mL was noticed for CR-NTS harbouring *bla*$_{\text{CTX-M-1}}$. Conversely, *bla*$_{\text{CMY}}$ positive isolates showed MIC ranging from 32 to 256 µg/mL, which is comparatively 4 fold lesser than *bla*$_{\text{CTX-M-1}}$ producers. This characteristically explains high level resistance to ceftriaxone mediated by ESBLs (*bla*$_{\text{CTX-M-1}}$) than AmpC (*bla*$_{\text{CMY}}$) β-lactamases.

Aeromonas spp

Thirty *Aeromonas spp* obtained from the faeces sample of patients were characterized for the presence of plasmid mediated colistin resistance genes. Isolates were screened for *mcr*-1, *mcr*-2, *mcr*-3 and *mcr*-4 by PCR. Colistin susceptibility testing was performed by broth microdilution method. Of the 30 *Aeromonas* isolates screened for *mcr* genes, one *Aeromonas hydrophila* was positive for *mcr*-3. The PCR products positive for *mcr*-3 were sequenced using Sanger sequencing method followed by BLAST analysis. Further, next-generation sequencing (NGS) was performed for the isolate to study the genetic environment of *mcr*-3. Conjugation experiments were performed to confirm the transferability of *mcr*-3.

Sanger sequencing confirmed the *mcr*-3 sequence with 100% identity to the reported reference in NCBI. However, phenotypically the isolate was susceptible to colistin with MIC 0.5 µg/ml. Similarresults were previously reported for *mcr*-1 from *E. coli*. NGS revealed the presence of IS elements ISAs18 belonging to IS4 family on the upstream and ISKpn3 belonging to IS1595 family on the downstream of *mcr*-3. In addition, the presence of *bla*OXA-12 and *bla*CEPH-A3 responsible for carbapenem resistance were identified. Notably, this is the first observation of *mcr*-3 gene in India.

Table 5.11 Antimicrobial susceptibility and PCR results for mcr positive Aeromonas isolate

	Disk diffusion	***MIC(microbroth dilution)***		***mcr gene PCR***		
Sample ID	**Resistant profile**	***Imi***	***Mero***	***Col***	***mcr1 & 2***	***mcr3***	***mcr4***
FC951	AMP-TET-IMI-MEM	*1 (S)*	*16 R*	*0.5 (S)*	-	+	-

Vibrio cholera

The whole genome sequencing of *V. cholerae* O139 isolates revealed that all isolates were of same sequence type (ST69) which belongs to seventh pandemic clone, with same virulence gene profile and, antimicrobial resistance gene profile except for two isolates. Among resistance genes, *cat*B9 gene responsible for chloramphenicol resistance was found common in all isolates. *str*A and *str*B (streptomycin resistance), *flo*R (florfenicol/chloramphenicol resistance), and *sul*II (sulphonamide resistance) genes were identified in all except two isolates.

Table 5.12 Whole genome sequencing of *V cholerae* isolates

V. cholerae O139(*n* = 10)	***strA***	***strB***	***floR***	***catB9***	***sulII***
Total	8	8	8	10	8

Chapter 6- Staphylococci and Enterococci

Summary of results

Staphylococcus aureus- The overall prevalence of MRSA in the initial 2 years of the project (2014, 2015) was 37.3% with rates ranging from 21% in AIIMS, New Delhi, 48% in PGI, Chandigarh, 35% in JIPMER and 45% in CMC, Vellore. This variation may be indicative of the differences in the antibiotic prescription practices and usage in the different regions. There has been a gradually declining trend in the MRSA rates over the later 3 years in JIPMER (28% in 2015, 23.5% in 2017 and 21% in 2018). However, the national figures for MRSA rates was slightly higher, 32.9% in 2017 and 38.6% in 2018. There were significant differences observed between the various zones of India, the highest in the North (52.8%), followed by West (48.1%) and East (42.5%). Central (38.5%) and Southern zones (23.8%) demonstrated much lower MRSA rates. The resistance rates of MRSA to non beta lactam antibiotics was significantly higher when compared to MSSA. This was particularly observed for ciprofloxacin, clindamycin and mupirocin.

Most laboratories depend on cefoxitin disc diffusion to identify MRSA. It has been observed that this test tends to misidentify a significant number of isolates. This feature was noticed with both our isolates as well as those received as part of EQAS from regional centres. Some of the centres identified MRSA based on VITEK results. Here a discrepancy was found between cefoxitin and oxacillin results. As per the data shared by ICMR, MRSA rate based on cefoxitin DD results is 38.6% whereas, the rate was 46.2% based on oxacillin MIC results. This discrepancy could be due to the much lower number of isolates being tested by oxacillin MIC. Moreover the same isolates may not have been tested by both the methods.

The MRSA phenotype was conferred by *mecA* gene as determined by PCR of randomly selected isolates from all centres. However in less than 1% of MRSA, *mec*A PCR was negative. PCR for *mec*C gene was also negative in these isolates. Recently plasmid mediated *mec*B gene has been reported in *S.aureus* which may complicate detection methods even further (Becker K, 2018). A few randomly selected MSSA isolates were found to carry the *mec*A gene demonstrating the occurrence of dormant MRSA.

Among the non beta lactam antibiotics, macrolide resistance was conferred either through *ermA* or *ermC* gene, with *ermC* gene being more common. *erm*A was detected almost exclusively in south Indian isolates. A few isolates from JIPMER were found to be *ermB* positive in 2017. Resistance to the high level mupirocin (200 µg) was conferred by *mupA* gene but resistance to this antibiotic was fortunately low throughout the study period, never going above 3-4%.

None of the centres reported full blown resistance to vancomycin. However, VISA and hVISA were both encountered, albeit in small numbers. An MIC creep to vancomycin was observed between 2014-2016. However, due to unknown reasons this trend showed a reversal in 2017 and 2018, with MIC_{50} being lower than the previous years. This lower vancomycin MIC values in 2018 compared to earlier years was observed for all the other 3 nodal centres. A similar trend was also observed for linezolid, daptomycin and tigecycline with the 2018 MIC_{50} and MIC_{90}.

Coagulase negative staphylococci (CoNS)- A variety of CoNS species were isolated from various centres, with the predominant species being *S.haemolyticus* and *S.epidermidis*, followed by *S.hominis* and *S.lugdunensis* The first 2 species showed a much higher degree of antimicrobial resistance. No resistance was observed to vancomycin. However, linezolid resistance was observed in 15 isolates of *S.haemolyticus* from JIPMER, 6 from PGI (all but one of them mediated by *cfr* gene). As most of the CoNS were isolated from blood, their significance remains doubtful.

Enterococci- As expected *E.faecalis* was the commonest species followed by *E.faecium*. Lowest susceptibility was observed against ciprofloxacin (10.3%), followed by HLG (43.3%) and ampicillin (51.6%). Susceptibility to nitrofurantoin was relatively high at 77.6%. Surprisingly fosfomycin resistance was encountered in 12.5% of the isolates even though this antibiotic is not used commonly. All the susceptibility rates were higher among *E.faecalis* when compared to *E.faecium*.

Overall, VRE rates have also shown declining trend, starting at 7% in 2015, going down to 4% in 2018. Vancomycin resistance was 5 times more common in *E.faecium* than in *E.faecalis*. All VRE from our centre as well as other regional centres was mediated solely by *van*A gene. No other *van* genes were detected. A peculiar and unexpected finding in a few *Enterococcus* isolates was teicoplanin resistance in vancomycin sensitive isolates. Linezolid resistance was observed in 2.8% of the isolates and was seen in both vancomycin sensitive as well as vancomycin resistant isolates.

Detailed analysis of results (For January to December 2018)

Pathogen group (Staphylococci and Enterococci)

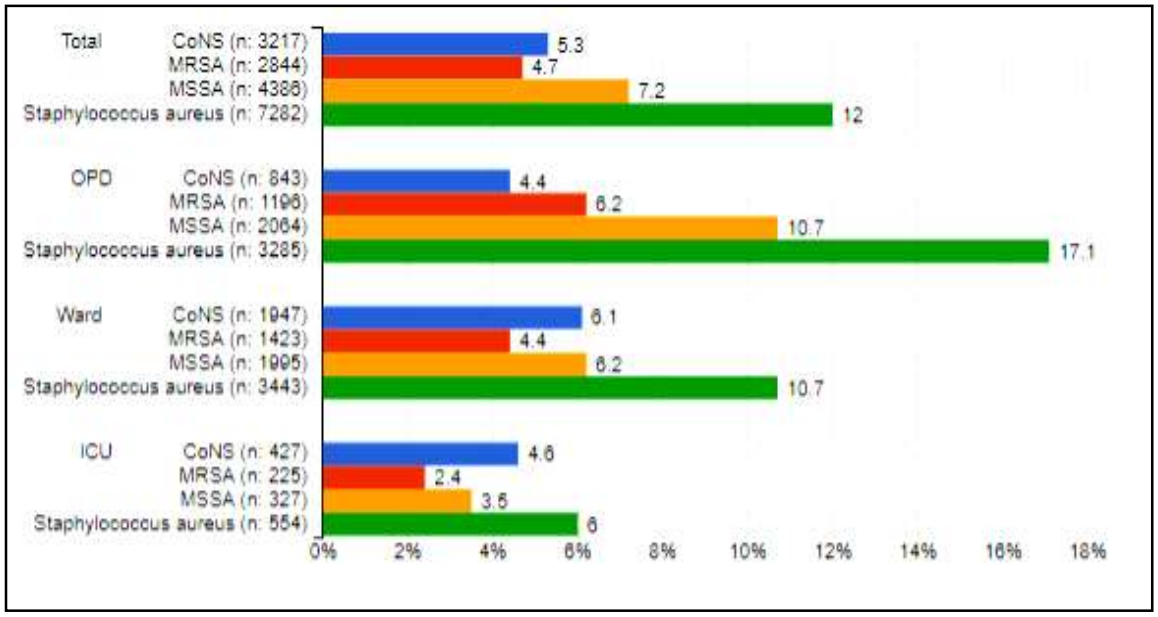


Figure 6.1 Location-wise Isolation pattern of Staph aureus, CoNS, MRSA, MSSA isolated from All Samples across OPD, Ward and ICU

The proportion of MRSA was 36.4% among OPD isolates, 41.3% among ward isolates and 40.6% among ICU isolates. Most isolates of *S.aureus* and CoNS were obtained from wards (3443 and 1947 respectively) with a minority from the ICUs (554 and 427 respectively). OPD isolates of *S.aureus* nearly equalled those from the ward (3285), which is expected as this organism is a common community as well as a nosocomial pathogen.

Table 6.1 Percentage Susceptibility of *Staphylococcus aureus*, CoNS, MRSA, MSSA isolated from all samples

AMA	All Specimens			
	Sau n=7939	MSSA n=4712	MRSA n=3168	CoNS n=3778
Cefoxitin	4467/7274 (61.4%)	4464/4464 (100%)	3/2810 (0.1%)	952/3415 (27.9%)
Ciprofloxacin	1399/7438 (18.8%)	1084/4422 (24.5%)	310/2964 (10.5%)	1068/2814 (38%)
Clindamycin	5853/7768 (75.3%)	3954/4609 (85.8%)	1868/3102 (60.2%)	2008/3717 (54%)
Erythromycin	3289/7418 (44.3%)	2529/4429 (57.1%)	748/2961 (25.3%)	705/3227 (21.8%)
Linezolid	7484/7577 (98.8%)	4446/4470 (99.5%)	2988/3056 (97.8%)	3578/3672 (97.4%)
Mupirocin High Level	3633/3719 (97.7%)	2402/2429 (98.9%)	1227/1286 (95.4%)	*0/0
Oritavancin	*0/1 (-)	*0/0	*0/0	*0/0
Oxacillin	915/1701 (53.8%)	897/897 (100%)	18/804 (2.2%)	*11/12 (-)
Penicillin	215/3461 (6.2%)	189/1719 (11%)	24/1726 (1.4%)	172/1797 (9.6%)
Tedizolid	*1/1 (-)	*0/0	*1/1 (-)	*0/0
Teicoplanin	5921/6068 (97.6%)	3273/3310 (98.9%)	2596/2701 (96.1%)	2700/2860 (94.4%)
Telavancin	*0/0	*0/0	*0/0	*0/0
Tetracycline	5707/6445 (88.5%)	3487/3787 (92.1%)	2172/2605 (83.4%)	2059/2589 (79.5%)
Tigecycline	1056/1062 (99.4%)	620/620 (100%)	436/442 (98.6%)	298/304 (98%)
Trimethoprim-sulfamethoxazole	4276/6880 (62.2%)	2721/4082 (66.7%)	1525/2742 (55.6%)	1460/3222 (45.3%)
Vancomycin	4158/4158 (100%)	2778/2778 (100%)	1363/1363 (100%)	1497/1497 (100%)

Note: The teicoplanin results are based on disc diffusion testing which is no longer recommended by CLSI. This could explain the non-susceptibility seen in some isolates of *S.aureus*.

As seen from Table 6.1, a total of 7939 isolates of *S.aureus* and 3778 isolates of CoNS were reported from different centres across India. Of the total *S.aureus* isolates, MRSA accounted for 38.6%. Susceptibility to penicillin across the different species was very low ranging from 2-12%. Cefoxitin resistance, the surrogate marker for MRSA, was observed twice as commonly among CoNS as *S.aureus* (71.5% vs 37.6%). On the other hand, oxacillin resistance was found to detect a larger percentage of MRSA when compared to cefoxitin although this discrepancy could be because of the smaller number of isolates tested against oxacillin than against cefoxitin. Moreover the same isolates may not have been tested by both the methods. Susceptibility to erythromycin, clindamycin, ciprofloxacin, co-trimoxazole and high level mupirocin was more evident in MSSA when compared to MRSA. Fortunately, the anti MRSA antibiotics such as vancomycin, linezolid, teicoplanin, daptomycin and tigecycline continued to show excellent in vitro activity. A few of the isolates of S.aureus demonstrated resistance to teicoplanin. However the methodology employed was disc diffusion which is likely to lead to errors. CLSI no longer recommends DD for teicoplanin testing.

Table 6.2 Location-wise susceptibility of *Staphylococcus aureus*, MRSA, MSSA isolated from all samples (except urine and faeces)

AMA	*Staphylococcus aureus*				*MSSA*				*MRSA*				*CoNS*			
	Total n=7750	OPD n=3411	Ward n=3745	ICU n=594	Total n=4609	OPD n=2137	Ward n=2131	ICU n=341	Total n=3083	OPD n=1247	Ward n=1586	ICU n=250	Total n=3709	OPD n=888	Ward n=2307	ICU n=514
	(S %)	(S %)	(S %)	(S %)	(S %)	(S %)	(S %)	(S %)	(S %)	(S %)	(S %)	(S %)	(S %)	(S %)	(S %)	(S %)
Cefoxitin	4364/7086 (61.6)	2021/3082 (65.6)	2020/3458 (58.4)	323/546 (59.2)	4361/4361 (100)	2019/2019 (100)	2020/2020 (100)	322/322 (100)	3/2725 (0.1)	2/1063 (0.2)	0/1438 (0)	1/224 (0.4)	930/3350 (27.8)	282/806 (35)	558/2084 (26.8)	90/460 (19.6)
Ciprofloxacin	1348/7253 (18.6)	530/3257 (16.3)	694/3461 (20.1)	124/535 (23.2)	1050/4321 (24.3)	439/2045 (21.5)	520/1973 (26.4)	91/303 (30)	293/2881 (10.2)	89/1190 (7.5)	172/1462 (11.8)	32/229 (14)	1040/2746 (37.9)	337/746 (45.2)	602/1644 (36.6)	101/356 (28.4)
Clindamycin	5726/7588 (75.5)	2627/3349 (78.4)	2687/3677 (73.1)	412/562 (73.3)	3871/4513 (85.8)	1804/2097 (86)	1786/2099 (85.1)	281/317 (88.6)	1824/3019 (60.4)	810/1226 (66.1)	886/1551 (57.1)	128/242 (52.9)	1973/3658 (53.9)	536/871 (61.5)	1210/2277 (53.1)	227/510 (44.5)
Erythromycin	3226/7256 (44.5)	1515/3214 (47.1)	1473/3491 (42.2)	238/551 (43.2)	2479/4342 (57.1)	1177/2042 (57.6)	1112/1987 (56)	190/313 (60.7)	735/2887 (25.5)	332/1163 (28.5)	356/1489 (23.9)	47/235 (20)	687/3169 (21.7)	203/771 (26.3)	410/1973 (20.8)	74/425 (17.4)
Linezolid	7313/7402 (98.8)	3256/3265 (99.7)	3496/3572 (97.9)	561/565 (99.3)	4355/4379 (99.5)	2038/2043 (99.8)	1998/2016 (99.1)	319/320 (99.7)	2909/2973 (97.8)	1196/1200 (99.7)	1473/1530 (96.3)	240/243 (98.8)	3513/3605 (97.4)	849/864 (98.3)	2171/2240 (96.9)	493/501 (98.4)
Mupirocin High Level	3564/3646 (97.8)	1594/1617 (98.6)	1717/1770 (97)	253/259 (97.7)	2367/2392 (99)	1087/1100 (98.8)	1114/1126 (98.9)	166/166 (100)	1193/1250 (95.4)	506/516 (98.1)	601/642 (93.6)	86/92 (93.5)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)
Oritavancin	*0/1 (-)	*0/1 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)
Oxacillin	887/1663 (53.3)	512/945 (54.2)	306/583 (52.5)	69/135 (51.1)	871/871 (100)	507/507 (100)	296/296 (100)	68/68 (100)	16/792 (2)	5/438 (1.1)	10/287 (3.5)	1/67 (1.5)	*11/12 (-)	*7/8 (-)	*4/4 (-)	*0/0 (-)
Penicillin	202/3285 (6.1)	98/1487 (6.6)	84/1546 (5.4)	20/252 (7.9)	176/1623 (10.8)	89/796 (11.2)	70/709 (9.9)	17/118 (14.4)	24/1647 (1.5)	8/688 (1.2)	14/828 (1.7)	2/131 (1.5)	171/1731 (9.9)	66/496 (13.3)	91/999 (9.1)	14/236 (5.9)
Tedizolid	*1/1 (-)	*1/1 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*1/1 (-)	*1/1 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)
Teicoplanin	5763/5904 (97.6)	2692/2731 (98.6)	2639/2728 (96.7)	432/445 (97.1)	3184/3219 (98.9)	1561/1580 (98.8)	1396/1411 (98.9)	227/228 (99.6)	2528/2629 (96.2)	1107/1124 (98.5)	1219/1291 (94.4)	202/214 (94.4)	2639/2797 (94.4)	647/676 (95.7)	1641/1753 (93.6)	351/368 (95.4)
Telavancin	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)
Tetracycline	5577/6276 (88.9)	2568/2817 (91.2)	2575/2974 (86.6)	434/485 (89.5)	3407/3698 (92.1)	1624/1746 (93)	1520/1679 (90.5)	263/273 (96.3)	2122/2526 (84)	922/1047 (88.1)	1031/1269 (81.2)	169/210 (80.5)	2015/2522 (79.9)	603/742 (81.3)	1143/1450 (78.8)	269/330 (81.5)
Tigecycline	1031/1037 (99.4)	622/623 (99.8)	321/324 (99.1)	88/90 (97.8)	603/603 (100)	377/377 (100)	179/179 (100)	47/47 (100)	428/434 (98.6)	245/246 (99.6)	142/145 (97.9)	41/43 (95.3)	292/298 (98)	150/151 (99.3)	99/103 (96.1)	43/44 (97.7)
Trimethoprim-sulfamethoxazole	4165/6701 (62.2)	1808/2946 (61.4)	2007/3219 (62.3)	350/536 (65.3)	2649/3985 (66.5)	1189/1837 (64.7)	1241/1836 (67.6)	219/312 (70.2)	1487/2661 (55.9)	605/1082 (55.9)	753/1358 (55.4)	129/221 (58.4)	1421/3161 (45)	404/839 (48.2)	809/1863 (43.4)	208/459 (45.3)
Vancomycin	4112/4112 (100)	1953/1953 (100)	1826/1826 (100)	333/333 (100)	2749/2749 (100)	1335/1335 (100)	1199/1199 (100)	215/215 (100)	1346/1346 (100)	613/613 (100)	616/616 (100)	117/117 (100)	1478/1478 (100)	429/429 (100)	817/817 (100)	232/232 (100)

Table 6.2 shows the susceptibility pattern of *S.aureus* across different hospital locations. The susceptibility to most antibiotics was similar among ward and ICU isolates and together these were lower than susceptibility rates observed among OPD isolates except for co-trimoxazole where the OPD isolates showed a slightly higher rate of non-susceptibility probably reflecting the more common use of this antibiotic in the community than in hospital settings.

Table 6.3 Susceptibility pattern of *Staphylococcus aureus* isolated from all samples except faeces and urine across different regions of India

Antibiotic	National (n=7750)		North (n=2669)		Central (n=97)		East (n=317)		West (n=1509)		South (n=3158)	
	n(%)	%Range	n(%)	%Range	n(%)	%Range	n(%)	%Range	n(%)	%Range	n(%)	%Range
Tigecycline	1031/1037 (99.4)	96.9-100	242/247 (98)	98.3	31/32 (96.9)	96.9	112/112 (100)	100	575/575 (100)	100	71/71 (100)	100
Linezolid	7313/7402 (98.8)	89.9-100	2612/2619 (99.7)	97.9-100	95/96 (99)	99	306/316 (96.8)	94.2-100	1435/1497 (95.9)	89.9-100	2865/2874 (99.7)	98.2-100
Mupirocin High Level	3564/3646 (97.8)	87.7-99.8	929/938 (99)	88.9-99.8	69/74 (93.2)	93.2	129/142 (90.8)	91.1	157/172 (91.3)	87.7-93.9	2280/2320 (98.3)	98.3
Teicoplanin	5763/5904 (97.6)	61.1-100	2576/2617 (98.4)	61.1-100	86/88 (97.7)	97.7	273/293 (93.2)	85.7-100	1403/1478 (94.9)	89.6-100	1425/1428 (99.8)	99.2-100
Vancomycin	4112/4112 (100)	100-100	835 /835 (100)	100-100	31/31 (100)	100-100	113/113 (100)	100-100	672/672 (100)	100-100	2461/2461 (100)	100-100
Tetracycline	5577/6276 (88.9)	69.8-99.3	1666/1833 (90.9)	76.3-99.3	81/93 (87.1)	87.1	282/314 (89.8)	88-91.9	1189/1476 (80.6)	69.8-87.7	2359/2560 (92.1)	91.8-97.2
Clindamycin	5726/7588 (75.5)	40-98.6	1778/2642 (67.3)	46.8-81.9	75/96 (78.1)	78.1	233/312 (74.7)	65.2-95.4	1167/1499 (77.9)	40-84.9	2473/3039 (81.4)	74.3-98.6
Trimethoprim-sulfamethoxazole	4165/6701 (62.2)	38.4-91.7	1020/1806 (56.5)	38.4-73.2	44/83 (53)	53	220/311 (70.7)	62.7-75.6	941/1470 (64)	60-74.8	1940/3031 (64)	60-91.7
Cefoxitin	4364/7086 (61.6)	30-79.1	972/2061 (47.2)	30.2-60.1	59/96 (61.5)	61.5	180/313 (57.5)	39.6-67	779/1502 (51.9)	30-63.4	2374/3114 (76.2)	54.5-79.1
Oxacillin	887/1663 (53.3)	38.8-73.6	323/803 (40.2)	38.8-43.6	18/27 (66.7)	66.7	77/112 (68.8)	68.5	405/630 (64.3)	64.3	64/91 (70.3)	73.6
Erythromycin	3226/7256 (44.5)	20-63.8	978/2586 (37.8)	22.2-40.3	39/91 (42.9)	42.9	94/314 (29.9)	26.4-36.9	495/1374 (36)	20-48.4	1620/2891 (56)	35.4-63.8
Ciprofloxacin	1348/7253 (18.6)	4.5-58.8	233/2624 (8.9)	4.5-16.5	9/95 (9.5)	9.5	102/313 (32.6)	13.4-58.8	243/1476 (16.5)	7.9-31.8	761/2745 (27.7)	16.7-29.4
Penicillin	202/3285 (6.1)	0-12	53/1201 (4.4)	3.4-10.2	2/87 (2.3)	2.3	20/189 (10.6)	9.4-11.1	100/1462 (6.8)	0-12	27/346 (7.8)	7.7

Table 6.3 demonstrates the susceptibility of *S.aureus* isolates region wise. There were significant differences in MRSA rates observed between the various zones of India, the highest in the North (52.8%), followed by West (48.1%), East (42.5%) and Central (38.5%) zones. Southern zones (23.8%) demonstrated much lower MRSA rates. This difference was observed for most of the other antibiotics as well. The range of susceptibility to antibiotics was very large, for example the range for cefoxitin was 30-79% while that for clindamycin was 40-98.6%. These unexpected differences could be a reflection of the methodologies employed or the pattern of antibiotic usage in the different regions.

Table 6.4 Year wise susceptibility trends of *Staphylococcus aureus* from all samples

AMA	Year-2016	Year-2017	Year-2018
	Total n=960	Total n=5708	Total n=7939
	(S%)	(S%)	(S%)
Cefoxitin	686/958 (71.6)	3805/5668 (67.1)	4467/7274 (61.4)
Ciprofloxacin	191/838 (22.8)	1224/5260 (23.3)	1399/7438 (18.8)
Clindamycin	729/921 (79.2)	4235/5475 (77.4)	5853/7768 (75.3)
Erythromycin	492/955 (51.5)	2755/5570 (49.5)	3289/7418 (44.3)
Linezolid	860/863 (99.7)	5424/5445 (99.6)	7484/7577 (98.8)
Mupirocin High Level	573/584 (98.1)	2971/3012 (98.6)	3633/3719 (97.7)
Oritavancin	*0/0	*0/0	*0/1
Oxacillin	*0/0	314/438 (71.7)	915/1701 (53.8)
Penicillin	60/737 (8.1)	267/3519 (7.6)	215/3461 (6.2)
Tedizolid	*0/0	*0/0	*1/1
Teicoplanin	877/880 (99.7)	5233/5257 (99.5)	5921/6068 (97.6)
Telavancin	*0/0	*0/0	*0/0
Tetracycline	669/738 (90.7)	3492/3860 (90.5)	5707/6445 (88.5)
Tigecycline	*0/0	433/435 (99.5)	1056/1062 (99.4)
Trimethoprim-sulfamethoxazole	513/852 (60.2)	3064/4306 (71.2)	4276/6880 (62.2)
Vancomycin	565/565 (100)	2602/2602 (100)	4158/4158 (100)

Table 6.4 and Figure 2 compare the susceptibility rates of *S.aureus* across 3 years of study i.e. 2016-18. Almost all antibiotics showed a decreasing trend in susceptibility rates. MRSA rates steadily increased from 28.4% in 2016 to 38.6% in 2018 while susceptibility to ciprofloxacin, erythromycin and clindamycin showed a declining trend. On the contrary, susceptibility to high level mupirocin remained almost constant. Resistance to tigecycline was not seen in 2016 and it appeared in a small number of isolates in 2017 and 2018.

Figure 6.2 Year wise susceptibility trends of *Staphylococcus aureus* from all samples

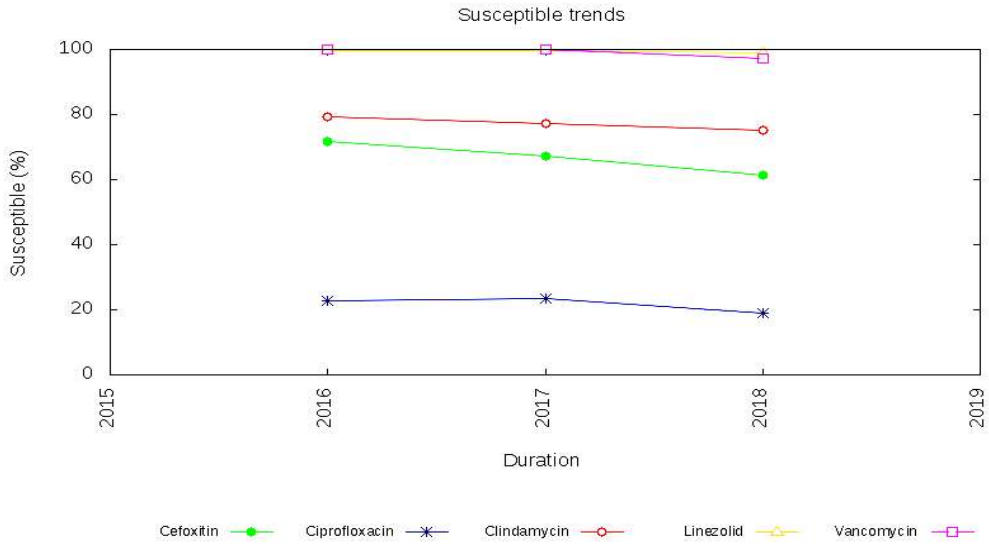


Table 6.5 Susceptibility pattern of MRSA isolated from all samples except faeces and urine across different regions of India

Antibiotic	National (n=3083)		North (n=1433)		Central (n=39)		East (n=134)		West (n=723)		South (n=754)	
	n(%)	Range(%)	n(%)	Range(%)	n(%)	Range(%)	n(%)	Range(%)	n(%)	Range(%)	n(%)	Range(%)
Tigecycline	428/434 (98.6)	96.9-100	134/139 (96.4)	96.9	15/16 (-)	-	37/37 (100)	100	212/212 (100)	100	30/30 (100)	100
Linezolid	2909/2973 (97.8)	88.2-100	1390/1396 (99.6)	96.7-100	39/39 (100)	100	125/133 (94)	90.3-100	671/717 (93.6)	88.2-100	684/688 (99.4)	97.1-100
Teicoplanin	2528/2629 (96.2)	81.8-100	1371/1399 (98)	96.9-100	33/35 (94.3)	94.3	102/119 (85.7)	81.8-100	652/705 (92.5)	87.2-99.6	370/371 (99.7)	99.6-100
Mupirocin High Level	1193/1250 (95.4)	82-99.8	580/587 (98.8)	89.7-99.8	30/31 (96.8)	96.8	46/56 (82.1)	82	77/91 (84.6)	82.7-87.2	460/485 (94.8)	94.8
Vancomycin	1346 /1346 (100)	100-100	487/487 (100)	100-100	16/16 (100)	100	37/37 (100)	100	256/256 (100)	100	550/550 (100)	100-100
Tetracycline	2122/2526 (84)	70.4-100	988/1097 (90.1)	71.4-99.4	28/36 (77.8)	77.8	116/132 (87.9)	80-94.6	544/704 (77.3)	70.4-86.4	446/557 (80.1)	78-100
Clindamycin	1824/3019 (60.4)	35.4-100	807/1414 (57.1)	35.4-74.5	26/39 (66.7)	66.7	75/132 (56.8)	40-91.4	474/719 (65.9)	63.6-71.2	442/715 (61.8)	56.7-100
Trimethoprim-sulfamethoxazole	1487/2661 (55.9)	32.8-92.9	598/1080 (55.4)	32.8-70.6	13/32 (40.6)	40.6	77/128 (60.2)	56.7-67.6	404/698 (57.9)	52.8-61.2	395/723 (54.6)	45.1-92.9
Erythromycin	735/2887 (25.5)	14-46.2	382/1396 (27.4)	18.8-30.5	9/34 (26.5)	26.5	20/132 (15.2)	14-19.4	161/666 (24.2)	14-30.6	163/659 (24.7)	14.6-46.2
Ciprofloxacin	293/2881 (10.2)	0.8-46.7	96/1407 (6.8)	2.5-12.8	4/39 (10.3)	10.3	30/130 (23.1)	8.3-46.7	79/701 (11.3)	0.8-19.4	84/604 (13.9)	7.1-14.8
Oxacillin	16/792 (2)	0-32.1	0/480 (0)	0-0	6/15 (-)	-	1/36 (2.8)	0	0/225 (0)	0	9/36 (25)	32.1
Penicillin	24/1647 (1.5)	0-6.9	12/736 (1.6)	0-6.9	0/35 (0)	0	0/83 (0)	0-0	11/694 (1.6)	0-6.2	1/99 (1)	0

Table 6.5 depicts the region wise differences in susceptibility rates of MRSA to various antibiotics. As with *S.aureus*, MRSA isolates too showed significant differences among the various zones of the country. While ciprofloxacin susceptibility was least in the north (6.8%) and highest in the East (23.1%), clindamycin susceptibility was least in the East (56.8%) and highest in the central zone (66.7%). High level mupirocin showed notable difference in susceptibility rates with both east and west zones showing much lower rates compared to other regions. South zone showed least susceptibility rate to mupirocin (94.8%). Erythromycin susceptibility, on the other hand was almost similar regardless of the region.

Table 6.6 Year wise susceptibility trends of MRSA from all samples

AMA	Year-2016	Year-2017	Year-2018
	Total n=272	Total n=1870	Total n=3168
	(S%)	(S%)	(S%)
Cefoxitin	0/272 (0)	4/1867 (0.2)	3/2810 (0.1)
Ciprofloxacin	23/228 (10.1)	165/1718 (9.6)	310/2964 (10.5)
Clindamycin	167/259 (64.5)	1067/1802 (59.2)	1868/3102 (60.2)
Erythromycin	72/270 (26.7)	494/1813 (27.2)	748/2961 (25.3)
Linezolid	225/228 (98.7)	1779/1794 (99.2)	2988/3056 (97.8)
Mupirocin High Level	139/144 (96.5)	852/873 (97.6)	1227/1286 (95.4)
Oritavancin	*0/0	*0/0	*0/0
Oxacillin	*0/0	8/132 (6.1)	18/804 (2.2)
Penicillin	1/180 (0.6)	12/1111 (1.1)	24/1726 (1.4)
Tedizolid	*0/0	*0/0	*1/1
Teicoplanin	240/242 (99.2)	1719/1735 (99.1)	2596/2701 (96.1)
Telavancin	*0/0	*0/0	*0/0
Tetracycline	141/181 (77.9)	983/1193 (82.4)	2172/2605 (83.4)
Tigecycline	*0/0	133/133 (100)	436/442 (98.6)
Trimethoprim-sulfamethoxazole	99/223 (44.4)	851/1332 (63.9)	1525/2742 (55.6)
Vancomycin	137/137 (100)	667/667 (100)	1363/1363 (100)

Table 6.6 and figure 3 depict trends in antimicrobial resistance in MRSA isolates across the 3 years (2016-18). Unlike *S.aureus* which clearly demonstrated downward trends in susceptibility, no such trend could be observed for MRSA. Susceptibility rates across the years were similar to most antibiotics like ciprofloxacin, clindamycin, mupirocin etc. The only antibiotic which showed slightly higher rates of resistance in 2018 compared to 2016 was linezolid (2.2% vs 1.3%).

Figure 6.3 Year wise susceptibility trends of MRSA from All Samples

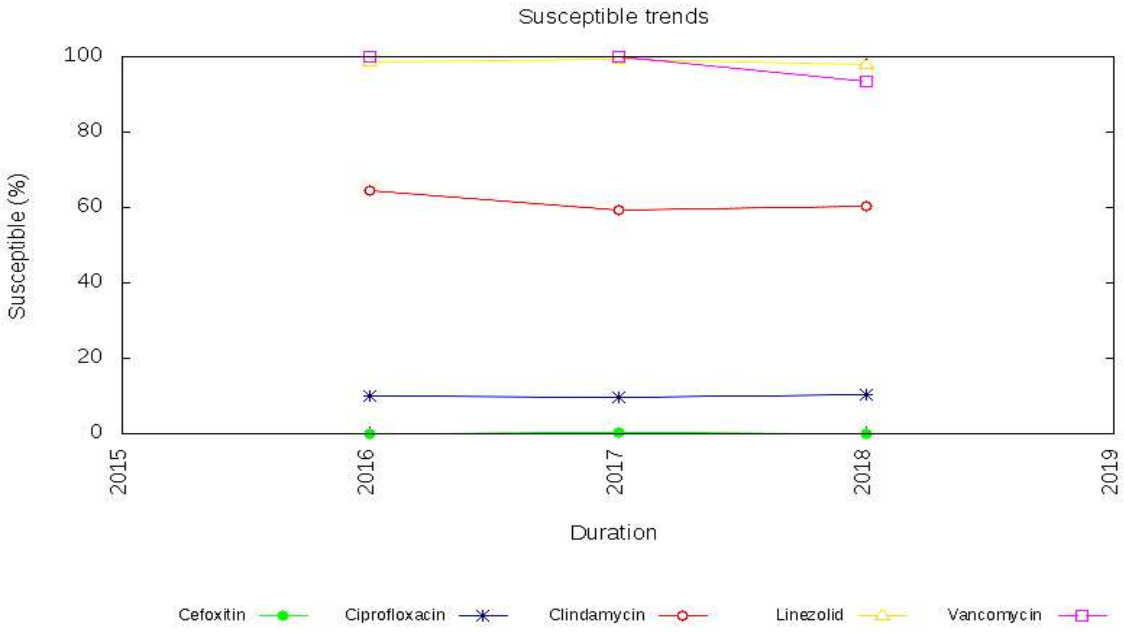


Table 6.7 Susceptibility pattern of MSSA isolated from All samples except faeces and urine across different regions of India

Antibiotic	National (n=4609)		North (n=1189)		Central (n=58)		East (n=183)		West (n=779)		South (n=2400)	
	n(%)	Range(%)	n(%)	Range(%)	n(%)	Range(%)	n(%)	Range(%)	n(%)	Range(%)	n(%)	Range(%)
Oxacillin	871/871 (100)	100-100	323/323 (100)	100-100	12/12 (-)	-	76/76 (100)	100	405/405 (100)	100	55/55 (100)	100
Cefoxitin	4361/4361 (100)	100-100	971/971 (100)	100-100	57/57 (100)	100	180/180 (100)	100-100	779/779 (100)	100-100	2374/2374 (100)	100-100
Tigecycline	603/603 (100)	100-100	108/108 (100)	100	16/16 (-)	-	75/75 (100)	100	363/363 (100)	100	41/41 (100)	100
Linezolid	4355/4379 (99.5)	93.1-100	1179/1180 (99.9)	99.9-100	56/57 (98.2)	98.2	181/183 (98.9)	97.6-100	759/774 (98.1)	93.1-100	2180/2185 (99.8)	98.8-100
Mupirocin High Level	2367/2392 (99)	90.7-100	349/351 (99.4)	99.7	39/43 (90.7)	90.7	83/86 (96.5)	96.5	76/77 (98.7)	98.2-100	1820/1835 (99.2)	99.2
Vancomycin	2749 /2749 (100)	100-100	331/331 (100)	100-100	15/15 (100)	100	76/76 (100)	100	416/416 (100)	100	1911/1911 (100)	100-100
Teicoplanin	3184/3219 (98.9)	93.8-100	1161/1171 (99.1)	99.4-100	53/53 (100)	100	171/174 (98.3)	98.8-100	747/767 (97.4)	93.8-98.7	1052/1054 (99.8)	98.8-100
Tetracycline	3407/3698 (92.1)	69-100	636/691 (92)	82.4-99.1	53/57 (93)	93	166/182 (91.2)	86.8-100	639/765 (83.5)	69-96.9	1913/2003 (95.5)	95.2-100
Clindamycin	3871/4513 (85.8)	63.9-97.7	947/1183 (80.1)	63.9-94.4	49/57 (86)	86	158/180 (87.8)	80-97.3	689/773 (89.1)	78.4-94.2	2028/2320 (87.4)	83-97.7
Trimethoprim-sulfamethoxazole	2649/3985 (66.5)	37.3-90.9	401/681 (58.9)	37.3-77.7	31/51 (60.8)	60.8	143/183 (78.1)	71.4-84.7	533/766 (69.6)	63.6-90.4	1541/2304 (66.9)	63.9-90.9
Erythromycin	2479/4342 (57.1)	32.5-74.4	588/1174 (50.1)	48.4-57.4	30/57 (52.6)	52.6	74/182 (40.7)	37.6-45.3	332/701 (47.4)	32.5-58.3	1455/2228 (65.3)	46.9-74.4
Ciprofloxacin	1050/4321 (24.3)	6.7-76.2	134/1176 (11.4)	6.7-22.6	5/56 (8.9)	8.9	72/183 (39.3)	15.8-76.2	162/768 (21.1)	12-42.8	677/2138 (31.7)	19.9-33.3
Penicillin	176/1623 (10.8)	3.2-25	41/460 (8.9)	7.9-25	2/52 (3.8)	3.8	20/106 (18.9)	17.6-23.8	88/761 (11.6)	3.2-17	25/244 (10.2)	10.3

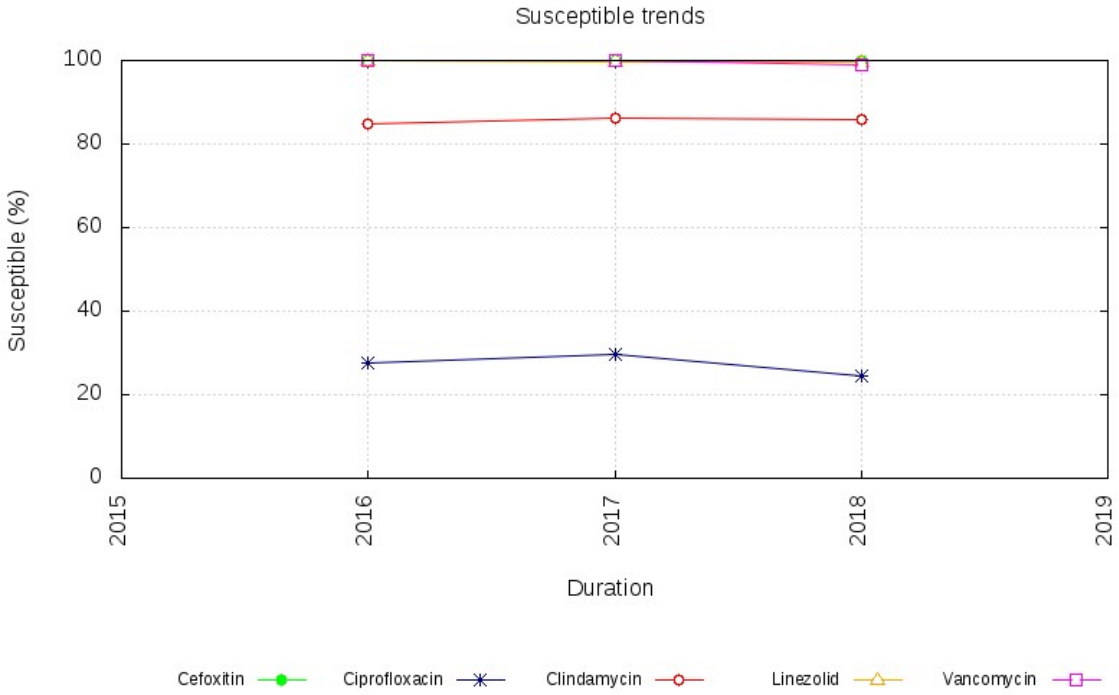
As seen in Table 6.7, there were 4361 MSSA isolates reported from across the country. Ciprofloxacin susceptibility was low even among MSSA, though marginally more than MRSA. Susceptibility to clindamycin and erythromycin was significantly higher in MSSA compared to MRSA (85.8 and 57.1 % vs 60.4 and 25.5%).

Table 6.8 Year wise susceptibility trends of MSSA from all samples

AMA	Year-2016	Year-2017	Year-2018
	Total n=686	Total n=3819	Total n=4712
	(S%)	(S%)	(S%)
Cefoxitin	686/686 (100)	3801/3801 (100)	4464/4464 (100)
Ciprofloxacin	168/609 (27.6)	1051/3524 (29.8)	1084/4422 (24.5)
Clindamycin	561/661 (84.9)	3162/3666 (86.3)	3954/4609 (85.8)
Erythromycin	419/684 (61.3)	2251/3739 (60.2)	2529/4429 (57.1)
Linezolid	634/634 (100)	3630/3636 (99.8)	4446/4470 (99.5)
Mupirocin High Level	434/440 (98.6)	2119/2139 (99.1)	2402/2429 (98.9)
Oritavancin	*0/0	*0/0	*0/0
Oxacillin	*0/0	306/306 (100)	897/897 (100)
Penicillin	59/557 (10.6)	248/2393 (10.4)	189/1719 (11)
Tedizolid	*0/0	*0/0	*0/0
Teicoplanin	636/636 (100)	3509/3517 (99.8)	3273/3310 (98.9)
Telavancin	*0/0	*0/0	*0/0
Tetracycline	528/557 (94.8)	2508/2665 (94.1)	3487/3787 (92.1)
Tigecycline	*0/0	300/302 (99.3)	620/620 (100)
Trimethoprim-sulfamethoxazole	414/629 (65.8)	2202/2959 (74.4)	2721/4082 (66.7)
Vancomycin	428/428 (100)	1935/1935 (100)	2778/2778 (100)

Table 6.8 and figure 4 depict trends in antimicrobial susceptibility among MSSA isolates across the 3 years of study (2016-18). Although *S.aureus*, overall, showed increasing trends of resistance to most antibiotics over the years, no such prominent trend could be observed with MSSA isolates. There was only a marginal decrease in the susceptibility rates to ciprofloxacin

Figure 6.4 Year wise susceptibility trends of MSSA from All Samples



CoNS:

Table 6.9 Susceptibility percentages of CoNS isolated from all specimens

AMA	All Specimens					
	Staphylococcus epidermidis **n=845**	***Staphylococcus haemolyticus*** **n=827**	***Staphylococcus hominis*** **n=440**	***Staphylococcus lugdunensis*** **n=58**	***Staphylococcus saprophyticus*** **n=20**	***Staphylococcus spp.*** **n=1588**
Cefoxitin	251/749 (33.5)	91/720 (12.6)	102/318 (32.1)	33/56 (58.9)	*13/17 (-)	462/1555 (29.7)
Ciprofloxacin	377/841 (44.8)	146/824 (17.7)	201/439 (45.8)	35/58 (60.3)	*18/19 (-)	291/633 (46)
Clindamycin	464/835 (55.6)	311/821 (37.9)	257/434 (59.2)	42/57 (73.7)	*9/15 (-)	925/1555 (59.5)
Erythromycin	206/814 (25.3)	97/803 (12.1)	89/420 (21.2)	26/56 (46.4)	*8/15 (-)	279/1119 (24.9)
Linezolid	817/833 (98.1)	789/807 (97.8)	412/414 (99.5)	51/55 (92.7)	20/20 (100)	1489/1543 (96.5)
Penicillin	43/458 (9.4)	19/312 (6.1)	34/140 (24.3)	14/47 (29.8)	*2/10 (-)	60/830 (7.2)
Teicoplanin	734/766 (95.8)	655/682 (96)	361/401 (90)	46/54 (85.2)	*15/15 (-)	889/942 (94.4)
Tetracycline	536/657 (81.6)	593/693 (85.6)	229/308 (74.4)	47/57 (82.5)	*19/19 (-)	635/855 (74.3)
Tigecycline	125/128 (97.7)	73/76 (96.1)	62/62 (100)	*0/0 (-)	*3/3 (-)	35/35 (100)
Trimethoprim-sulfamethoxazole	282/648 (43.5)	235/692 (34)	144/301 (47.8)	39/58 (67.2)	17/20 (85)	743/1503 (49.4)
Vancomycin	334/334 (100)	466/466 (100)	203/203 (100)	21/21 (100)	*14/14 (100)	459/459 (100)

Table 6.9 represents the susceptibility data of CoNS species isolated across India from all specimens. The common species were *S.haemolyticus, S.epidermidis, S.hominis, S.lugdunensis* and *S.saprophyticus*. Cefoxitin resistance was highest in *S.haemolyticus* (87.4%) followed by *S.hominis* (67.9%) and *S.epidermidis* (66.5%). With the exception of tetracycline, *S.haemolyticus* exhibited much lower rates of susceptibility to all other antibiotics when compared to the other species. Linezolid resistance was observed in a small number of isolates belonging to all the identified species except *S.saprophyticus*.

Table 6.10 Susceptibility pattern of CoNS isolated from all samples except faeces and urine across different regions of India

Antibiotic	National (n=3710)		North (n=1398)		Central (n=73)		East (n=67)		West (n=996)		South (n=1176)	
	n(%)	%Range	n(%)	%Range	n(%)	%Range	n(%)	%Range	n(%)	%Range	n(%)	%Range
Tigecycline	292/298 (98)	90-100	5/6 (-)	-	18/20 (90)	90	43/43 (100)	100	222/225 (98.7)	98.6	4/4 (-)	-
Linezolid	3514/3606 (97.4)	82.6-100	1336/1346 (99.3)	95.1-100	62/67 (92.5)	92.5	66/66 (100)	100	901/961 (93.8)	82.6-100	1149/1166 (98.5)	98-99.1
Vancomycin	1479/1479 (100)	100-100	242 /242 (100)	100-100	21/21 (100)	100	47/47 (100)	100	593/593 (100)	100-100	576/576 (100)	100
Teicoplanin	2640/2798 (94.4)	86.9-100	1302/1380 (94.3)	90.4-99.7	55/61 (90.2)	90.2	63/66 (95.5)	93.5	898/969 (92.7)	86.9-95.8	322/322 (100)	100
Tetracycline	2016/2523 (79.9)	61.9-97.6	779/900 (86.6)	63.3-97.6	57/69 (82.6)	82.6	49/66 (74.2)	66.7	638/906 (70.4)	61.9-74.7	493/582 (84.7)	85.2
Clindamycin	1973/3659 (53.9)	36.4-70.7	563/1389 (40.5)	36.4-48.8	37/71 (52.1)	52.1	43/61 (70.5)	70.7	560/979 (57.2)	52.9-66	770/1159 (66.4)	63.4-69.2
Trimethoprim-sulfamethoxazole	1421/3161 (45)	34-71.1	332/889 (37.3)	34-71.1	36/62 (58.1)	58.1	27/65 (41.5)	37.8	519/979 (53)	46.9-59.1	507/1166 (43.5)	38.6-48.4
Ciprofloxacin	1041/2747 (37.9)	12.2-45.4	471/1384 (34)	12.2-40.6	33/73 (45.2)	45.2	30/66 (45.5)	37.8	241/635 (38)	33.2-44.4	266/589 (45.2)	45.4
Cefoxitin	930/3351 (27.8)	16.4-47.2	296/1116 (26.5)	24.1-31.8	17/62 (27.4)	27.4	10/37 (27)	0	250/967 (25.9)	16.4-47.2	357/1169 (30.5)	28.8-32.5
Erythromycin	687/3170 (21.7)	10.9-27.4	253/1367 (18.5)	12.2-23.3	12/72 (16.7)	16.7	10/67 (14.9)	10.9	219/939 (23.3)	20.9-26.7	193/725 (26.6)	22-27.4
Penicillin	171/1731 (9.9)	3.1-16.5	81/643 (12.6)	12.6-15	6/63 (9.5)	9.5	3/19 (-)	-	77/982 (7.8)	3.1-16.5	4/24 (16.7)	0

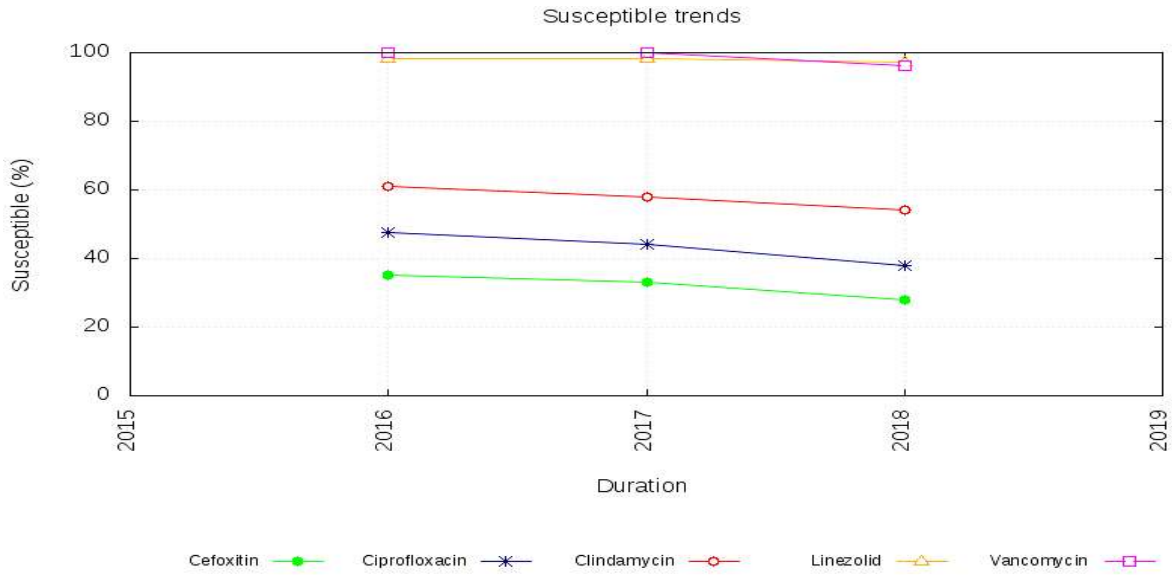
As per table 6.10, where region wise susceptibility rates of CoNS is displayed, it can be observed that there is no substantial differences in these rates for most antibiotics except for linezolid where a disproportionately higher percentage resistance is observed in central and western zones compared to the other regions.

Table 6.11 Year wise susceptibility trends of CoNS from All Samples

AMA	Year-2016	Year-2017	Year-2018
	Total n=490	Total n=2830	Total n=3782
	(S%)	(S%)	(S%)
Cefoxitin	173/490 (35.3)	930/2810 (33.1)	952/3419 (27.8)
Ciprofloxacin	159/335 (47.5)	986/2236 (44.1)	1069/2817 (37.9)
Clindamycin	297/488 (60.9)	1613/2782 (58)	2011/3721 (54)
Erythromycin	148/488 (30.3)	742/2679 (27.7)	705/3231 (21.8)
Linezolid	375/381 (98.4)	2638/2680 (98.4)	3582/3676 (97.4)
Oxacillin	*0/0	*3/3	*11/12
Penicillin	58/224 (25.9)	223/1227 (18.2)	172/1800 (9.6)
Teicoplanin	335/336 (99.7)	2212/2236 (98.9)	2703/2864 (94.4)
Tetracycline	176/226 (77.9)	1177/1358 (86.7)	2062/2593 (79.5)
Tigecycline	*0/1	165/167 (98.8)	300/306 (98)
Trimethoprim-sulfamethoxazole	199/379 (52.5)	923/1940 (47.6)	1461/3225 (45.3)
Vancomycin	86/86 (100)	718/718 (100)	1500/1500 (100)

Table 6.11 and figure 5 depict the trends in susceptibility rates of CoNS from 2016-2018. It can be clearly observed that there is a decrease in susceptibility rates to almost all the antibiotics from 2016 to 2018 most notably with cefoxitin and linezolid.

Figure 6.5 Year wise susceptibility trends of CoNS from All Samples



Enterococci

Table 6.12 Susceptibility pattern of Enterococci from all samples except urine

AMA	All Specimens (except urine)		Blood		Superficial Infection		Deep Infection		CSF	
	E.faecalis n=1178	*E.faecium* n=887	*E.faecalis* n=247	*E.faecium* n=460	*E.faecalis* n=489	*E.faecium* n=213	*E.faecalis* n=236	*E.faecium* n=62	*E.faecalis* n=*10	*E.faecium* n=*18
Ampicillin	748/1071 (69.8)	149/775 (19.2)	141/212 (66.5)	88/411 (21.4)	319/452 (70.6)	35/185 (18.9)	165/213 (77.5)	9/46 (19.6)	*5/9 (-)	*1/17 (-)
Gentamicin HL	558/1101 (50.7)	194/701 (27.7)	91/194 (46.9)	74/294 (25.2)	254/478 (53.1)	58/206 (28.2)	118/231 (51.1)	27/61 (44.3)	*4/9 (-)	*0/18 (-)
Linezolid	1085/1106 (98.1)	820/846 (96.9)	221/228 (96.9)	429/441 (97.3)	465/470 (98.9)	197/208 (94.7)	222/223 (99.6)	54/54 (100)	*9/9 (-)	*18/18 (-)
Oritavancin	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)
Tedizolid	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)
Teicoplanin	1097/1158 (94.7)	673/879 (76.6)	219/244 (89.8)	335/452 (74.1)	460/480 (95.8)	162/213 (76.1)	231/234 (98.7)	52/62 (83.9)	*8/8 (-)	*12/18 (-)
Telavancin	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)
Vancomycin	1113/1170 (95.1)	669/880 (76)	229/245 (93.5)	340/454 (74.9)	462/485 (95.3)	156/213 (73.2)	232/236 (98.3)	50/61 (82)	*9/9 (-)	*11/18 (-)

Table 6.12 depicts the susceptibility rates of enterococci from different specimens. *E. faecalis* was the predominant species accounting for 58.4% of the total followed by *E.faecium*. While *E.faecalis* was the major species from superficial and deep infections, *E.faecium* dominated in blood and CSF samples. Vancomycin resistance was 11.5% overall. However, it was 5 times higher in *E.faecium* compared to *E.faecalis* (22% vs 4% respectively). This difference was observed for all the other antibiotics as well.

Table 6.13 Susceptibility pattern of Enterococci from Urine

AMA	Urine	
	E.faecalis **n=750**	***E.faecium*** **n=485**
Ampicillin	522/667 (78.3)	61/358 (17)
Ciprofloxacin	83/630 (13.2)	25/425 (5.9)
Fosfomycin	468/535 (87.5)	*0/0 (-)
Gentamicin HL	385/712 (54.1)	148/453 (32.7)
Linezolid	669/679 (98.5)	439/466 (94.2)
Nitrofurantoin	691/744 (92.9)	256/476 (53.8)
Oritavancin	*0/0 (-)	*0/0 (-)
Tedizolid	*0/0 (-)	*0/0 (-)
Teicoplanin	710/728 (97.5)	392/479 (81.8)
Telavancin	*0/0 (-)	*0/0 (-)
Vancomycin	725/744 (97.4)	391/481 (81.3)

Table 6.13 depicts the susceptibility rates of enterococci from urine samples. A similar pattern as the rest of the specimens was noted for urine isolates. Ciprofloxacin appeared to be equally ineffective against both the species while nitrofurantoin susceptibility was high in. *E faecalis*. Surprisingly fosfomycin resistance was observed in 12.5% of *E.faecalis* isolates.

Table 6.14 Susceptibility pattern of Enterococci from all samples (except faeces) across OPD, Ward and ICU

AMA	*E.faecalis*				*E.faecium*			
	Total n=1926 (S%)	OPD n=552 (S%)	Ward n=1143 (S%)	ICU n=231 (S%)	Total n=1367 (S%)	OPD n=234 (S%)	Ward n=844 (S%)	ICU n=289 (S%)
Ampicillin	1270/1737 (73.1)	426/498 (85.5)	721/1033 (69.8)	123/206 (59.7)	210/1128 (18.6)	54/195 (27.7)	127/693 (18.3)	29/240 (12.1)
Ciprofloxacin	84/631 (13.3)	38/225 (16.9)	38/353 (10.8)	8/53 (15.1)	25/425 (5.9)	6/56 (10.7)	16/310 (5.2)	3/59 (5.1)
Fosfomycin	469/536 (87.5)	169/176 (96)	264/312 (84.6)	36/48 (75)	*0/0 (-)	*0/0 (-)	*0/0 (-)	*0/0 (-)
Gentamicin HL	943/1812 (52)	316/517 (61.1)	526/1080 (48.7)	101/215 (47)	341/1149 (29.7)	63/202 (31.2)	220/704 (31.3)	58/243 (23.9)
Linezolid	1753/1784 (98.3)	468/475 (98.5)	1066/1088 (98)	219/221 (99.1)	1254/1307 (95.9)	217/227 (95.6)	774/804 (96.3)	263/276 (95.3)
Nitrofurantoin	691/744 (92.9)	285/294 (96.9)	352/388 (90.7)	54/62 (87.1)	256/476 (53.8)	42/70 (60)	179/336 (53.3)	35/70 (50)
Teicoplanin	1805/1884 (95.8)	523/532 (98.3)	1074/1121 (95.8)	208/231 (90)	1060/1353 (78.3)	175/232 (75.4)	663/836 (79.3)	222/285 (77.9)
Vancomycin	1836/1912 (96)	537/547 (98.2)	1091/1135 (96.1)	208/230 (90.4)	1055/1356 (77.8)	174/230 (75.7)	666/837 (79.6)	215/289 (74.4)

Table 6.14 shows the susceptibility in enterococci across different locations in the hospitals. As expected most antibiotics showed lower rates of susceptibility among ICU isolates when compared to ward or OPD isolates. This difference was marked in *E.faecalis* (except for ciprofloxacin) while it was not particularly noticeable among *E.faecium* isolates.

Table 6.15 Year wise susceptibility trends of *Enterococcus faecalis* from all samples

AMA	Year-2016	Year-2017	Year-2018
	Total n=126	Total n=1034	Total n=1928
	(S%)	(S%)	(S%)
Ampicillin	82/123 (66.7)	633/987 (64.1)	1270/1738 (73.1)
Ciprofloxacin	3/40 (7.5)	41/358 (11.5)	84/631 (13.3)
Fosfomycin	*0/0	209/222 (94.1)	469/536 (87.5)
Gentamicin HL	73/119 (61.3)	512/993 (51.6)	943/1813 (52)
Linezolid	123/126 (97.6)	998/1011 (98.7)	1754/1785 (98.3)
Nitrofurantoin	38/40 (95)	352/375 (93.9)	691/744 (92.9)
Oritavancin	*0/0	*0/0	*0/0
Tedizolid	*0/0	*0/0	*0/0
Teicoplanin	124/126 (98.4)	992/1030 (96.3)	1807/1886 (95.8)
Telavancin	*0/0	*0/0	*0/0
Vancomycin	123/125 (98.4)	978/1016 (96.3)	1838/1914 (96)

Table 6.15 and figure 6 depict the year wise susceptibility rates of *E.faecalis*. Although and decreasing trend of susceptibility was observed, the fall was more noticeable between 2016 and 2017. The susceptibility rates did not show much difference between 2017 and 2018.

Figure 6.6 Year wise susceptibility trends of *Enterococcus faecalis* from all samples

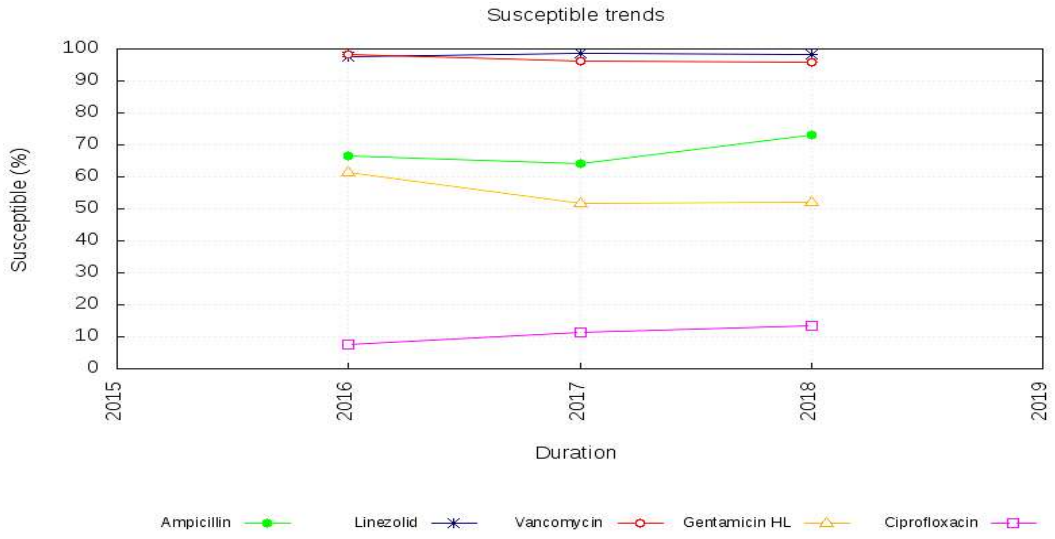
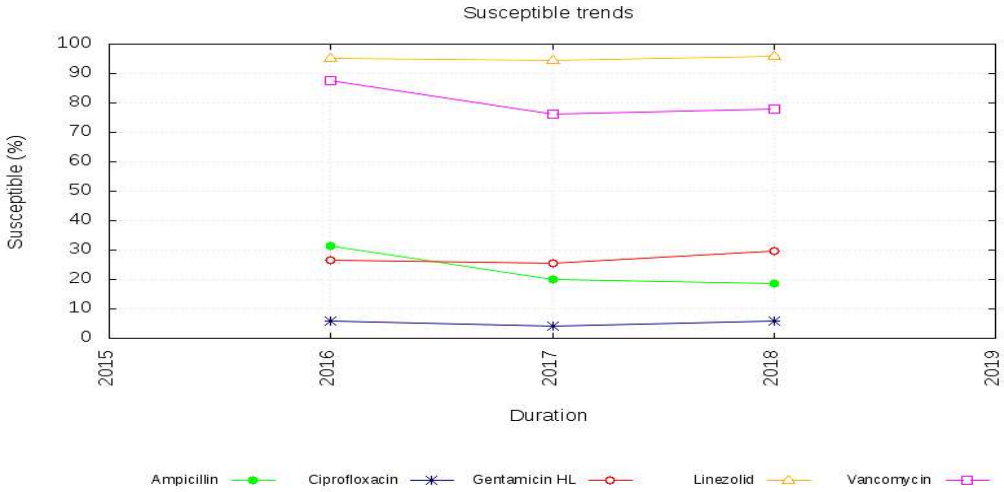


Table 6.16 Year wise susceptibility trends of *Enterococcus faecium* from all samples

AMA	Year-2016	Year-2017	Year-2018
	Total n=180	Total n=937	Total n=1372
	(S%)	(S%)	(S%)
Ampicillin	56/178 (31.5)	172/860 (20)	210/1133 (18.5)
Ciprofloxacin	2/34 (5.9)	10/230 (4.3)	25/425 (5.9)
Fosfomycin	*0/0	*0/0	*0/0
Gentamicin HL	27/102 (26.5)	208/812 (25.6)	342/1154 (29.6)
Linezolid	170/179 (95)	860/910 (94.5)	1259/1312 (96)
Nitrofurantoin	16/33 (48.5)	181/251 (72.1)	256/476 (53.8)
Oritavancin	*0/0	*0/0	*0/0
Tedizolid	*0/0	*0/0	*0/0
Teicoplanin	158/179 (88.3)	740/926 (79.9)	1065/1358 (78.4)
Telavancin	*0/0	*0/0	*0/0
Vancomycin	156/178 (87.6)	697/914 (76.3)	1060/1361 (77.9)

Table 6.16 and figure 7 depict the trends in antibiotic susceptibility rates in *E.faecium* from 2016-18. While ciprofloxacin and high level gentamicin susceptibility rates remained steady, rates of ampicillin and vancomycin susceptibility were lower in the later years.

Figure 6.7 Year wise susceptibility trends of *Enterococci faecium* from all samples



Molecular epidemiology of MRSA (hVISA) isolates was studied using PFGE and MLST

PFGE results-Five different pulsotypes were observed among the 36 isolates tested. There were 16 isolates with identical PFGE patterns. However, these isolates were not from an outbreak and neither were they related in time and space, being from different wards and different time periods. A few isolates were closely or possibly related while 2 were completely different when compared to the 16 isolates (type A).

MLST results -ST22 was the most predominant clone (23.3%) followed by ST239, ST772 and ST672. The occurrence of ST772, ST22 and ST239 in India has already been reported in global epidemiologic trials. Subsequently D'Souza et al in 2010 described the emergence of ST772 and ST22 replacing ST239 in Indian hospitals. ST772, which is a highly successful CA-MRSA clone, has now been also reported in England, Hong Kong, Germany, Abu Dhabi and Ireland. The second most frequent ST is ST217, which was not encountered in our group of isolates. Finally, a large diversity of other STs were characterized, some of them being common to MRSA and hVISA (ST22, ST239, ST772 and ST672). In an earlier study from our centre (PhD work of Nivethitha Nagasundaram (unpublished data), MLST of 38 MRSA isolates was performed, in which ST772 was the commonest ST observed, followed by ST368. These two STs persisted through all three years of study (2012 to 2014). ST772 was present even in 2016 isolates, while ST368 was not found. Instead, ST22 emerged as the commonest sequence type in 2016.

Chapter 7 Fungal pathogens

Summary of results

A total of 1191 isolates were recorded during the study period, of those nearly 60% (n=713) of the strains were isolated from blood. *Candida albicans* (n=376, 31.5%) and *Candida tropicalis* (n=362, 30.3%) were the two major yeast species isolated. The emergence of *C. auris* (n=25, 2.1%) infection reported from 5 centres (PGIMER, Chandigarh; Apollo hospital, Chennai; Hinduja hospital, Mumbai; Ganga Ram hospital, New Delhi; JIPMER, Puduchery) is a major concern, as the isolates were resistant to fluconazole and increased MIC had been observed to amphotericin B and echinocandin. The molecular mechanism of resistance in *Candida tropicalis* (azole resistance) and *Candida auris* (echinocandin resistance) were evaluated. In *C. tropicalis*, over-expression of efflux pumps, mutation in ergosterol pathway genes and transcription factor were found to be responsible. In the study of *C. auris* resistance to echinocandin, a novel transversion mutation at 635 position of FKS gene was found. Two nosocomial outbreaks due to *C. krusei* and *C. utilis* in the paediatric wards and ICUs were observed during study period. The molecular epidemiology of outbreaks is being studied.

Candida tropicalis is the most common agent causing candidemia in the Indian hospitals. As fluconazole is the commonly used to treat *Candida* infections, the emerging fluconazole drug resistant strains of *C. tropicalis* would pose a challenge while managing such patients. The present data would also help in development of country-specific management guideline. Similarly, the emergence of *Candida auris* is a major concern and these isolates are found to be resistant to fluconazole and increased MIC to amphotericin B and echinocandin. The present data would be important for tertiary care centres to control the impending outbreaks.

Detailed analysis of results

Though *C. tropicalis* tops the list of *Candida* species isolated, during last one year the rate has come down with the rise of *C. parapsilosis* isolates (figure 7.1). The majority of *Candida* species isolated are from wards, followed by ICUs (figure 7.2, table 7.1). In ICUs, *C. glabrata* (33%), *C. utilis* (28%) and *C. tropicalis* (25%) are predominant *Candida* species. In wards, *C. albicans* (74%), *C. utilis* (70%) and *C. tropicalis* (69%) formed the majority. Susceptible pattern of *Candida* species in all samples: About 95% of *C. tropicalis* isolates were susceptible to fluconazole, followed by *C. albicans* (92%) and *C. parapsilosis* (82%). Majority of the isolates in *Candida* species showed high susceptibility to voriconazole: *C. albicans* (93.1%), *C. glabrata* (97.1%) and *C. tropicalis* (98.4%). About 95% of *C. albicans and C. tropicalis* isolates tested were susceptible to echinocandins (table 7.2 & 7.3). However, *C. auris* was least susceptible to fluconazole (100%), voriconazole (41%) and echinocandins (78-83%) (table 7.2 & 7.3).

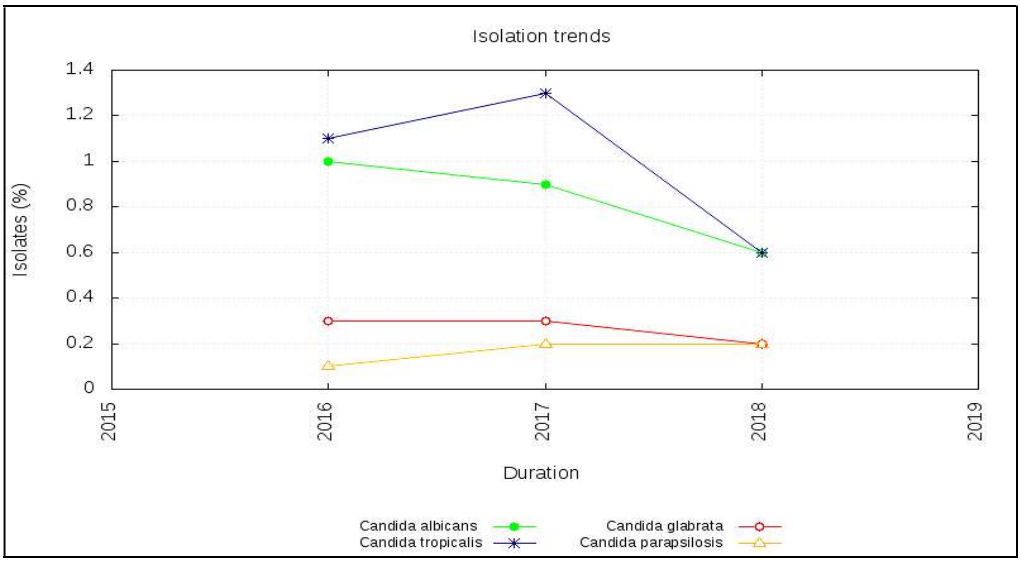


Figure 7.1 Yearly Trends for isolation of *Candida* species isolated from All Samples.

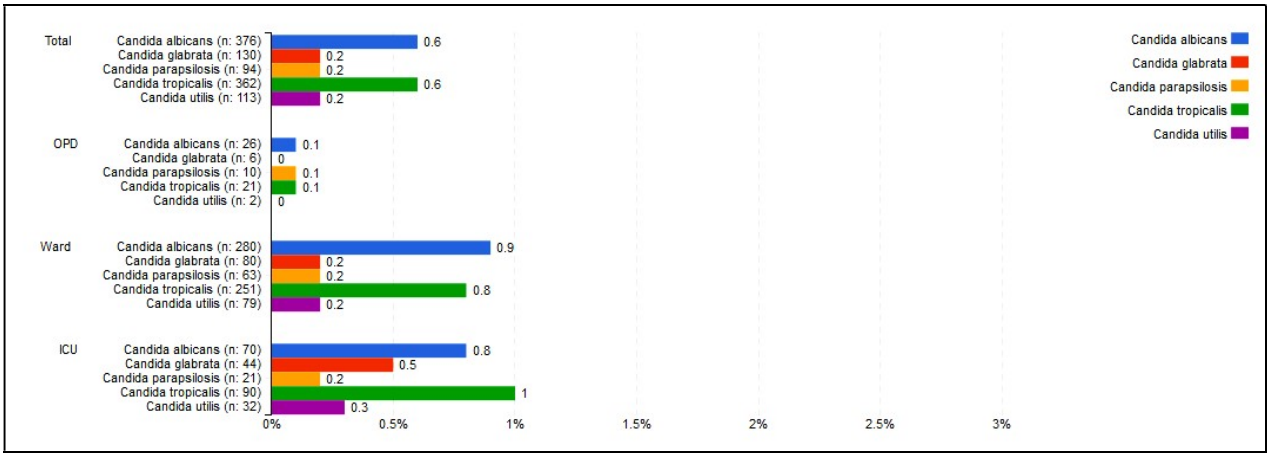


Figure 7.2 Location-wise Isolation pattern of *Candida* species isolated from All Samples across OPD, Ward and ICU.

Table 7.1 Isolation pattern of *Candida* species isolated from All Samples across OPD, Ward and ICU.

Organism	All Departments			
	All Specimen			
	Total	OPD	Ward	ICU
Candida albicans	376/60497 (0.6)	26/19210 (0.1)	280/32046 (0.9)	70/9241 (0.8)
Candida auris	25/60497 (0)	2/19210 (0)	20/32046 (0.1)	3/9241 (0)
Candida glabrata	130/60497 (0.2)	6/19210 (0)	80/32046 (0.2)	44/9241 (0.5)
Candida krusei	28/60497 (0)	5/19210 (0)	19/32046 (0.1)	4/9241 (0)
Candida parapsilosis	94/60497 (0.2)	10/19210 (0.1)	63/32046 (0.2)	21/9241 (0.2)
Candida tropicalis	362/60497 (0.6)	21/19210 (0.1)	251/32046 (0.8)	90/9241 (1)
Candida utilis	113/60497 (0.2)	2/19210 (0)	79/32046 (0.2)	32/9241 (0.3)

Table 7.2 Susceptible pattern of *Candida* species isolated from All samples

AMA	All Specimens						
	Candida albicans **n=395**	***Candida auris*** **n=25**	***Candida glabrata*** **n=143**	***Candida krusei*** **n=35**	***Candida parapsilosis*** **n=102**	***Candida tropicalis*** **n=384**	***Candida utilis*** **n=151**
Anidulafungin	124/125 (99.2)	*5/8 (-)	45/53 (84.9)	22/22 (100)	41/41 (100)	210/217 (96.8)	147/150 (98)
Caspofungin	157/166 (94.6)	*14/18 (-)	–	15/26 (57.7)	58/58 (100)	234/247 (94.7)	151/151 (100)
Fluconazole	365/395 (92.4)	0/25 (0)	100/142 (70.4)	8/35 (22.9)	84/102 (82.4)	364/384 (94.8)	149/151 (98.7)
Micafungin	96/96 (100)	*15/18 (-)	*13/15 (-)	*7/9 (-)	28/29 (96.6)	80/81 (98.8)	*13/13 (-)
Voriconazole	363/390 (93.1)	*7/17 (-)	136/140 (97.1)	34/35 (97.1)	95/98 (96.9)	359/365 (98.4)	151/151 (100)

Table 7.3 Susceptible pattern of *Candida* species isolated from Blood

AMA	Blood						
	Candida albicans **n=149**	***Candida auris*** **n=20**	***Candida glabrata*** **n=83**	***Candida krusei*** **n=22**	***Candida parapsilosis*** **n=94**	***Candida tropicalis*** **n=261**	***Candida utilis*** **n=150**
Anidulafungin	90/91 (98.9)	*4/7 (-)	27/32 (84.4)	*19/19 (-)	40/40 (100)	177/183 (96.7)	147/150 (98)
Caspofungin	97/102 (95.1)	*10/14 (-)	–	12/20 (60)	54/54 (100)	188/198 (94.9)	150/150 (100)
Fluconazole	147/149 (98.7)	0/20 (0)	51/82 (62.2)	5/22 (22.7)	77/94 (81.9)	249/261 (95.4)	148/150 (98.7)
Micafungin	53/53 (100)	*11/14 (-)	*8/9 (-)	*5/7 (-)	25/26 (96.2)	56/56 (100)	*12/12 (-)
Voriconazole	145/146 (99.3)	*7/14 (-)	77/80 (96.3)	22/22 (100)	87/90 (96.7)	242/246 (98.4)	150/150 (100)

Table 7.4 Susceptible pattern of *Candida* species isolated from Urine

AMA	Urine		
	Candida albicans **n=57**	***Candida glabrata*** **n=*12**	***Candida tropicalis*** **n=68**
Anidulafungin	*1/1 (-)	*0/1 (-)	*0/0 (-)
Caspofungin	*17/17 (-)	*2/3 (-)	*12/12 (-)
Fluconazole	53/57 (93)	*7/12 (-)	67/68 (98.5)
Micafungin	*16/16 (-)	*2/2 (-)	*12/12 (-)
Voriconazole	53/55 (96.4)	*12/12 (-)	68/68 (100)

Table 7.5 Susceptible pattern of *Candida* species isolated from Genital samples

AMA	Genital		
	Candida albicans **n=140**	***Candida glabrata*** **n=22**	***Candida tropicalis*** **n=*17**
Anidulafungin	*0/0 (-)	*0/0 (-)	*0/0 (-)
Caspofungin	*0/0 (-)	*0/0 (-)	*0/0 (-)
Fluconazole	117/140 (83.6)	20/22 (90.9)	*14/17 (-)
Micafungin	*0/0 (-)	*0/0 (-)	*0/0 (-)
Voriconazole	117/140 (83.6)	22/22 (100)	*15/17 (-)

Susceptibility pattern of *Candida* species in urine showed that 93% of the *C. albicans* were susceptible to fluconazole (table 7.4). Whereas, in the genital specimens only 83% of the *C. albicans* strains were susceptible to both fluconazole and voriconazole (table 7.5).

***Aspergillus* species:** No drug resistance was observed in *A. flavus* and *A. fumigates* (table 7.6).

Table 7.6 Susceptible pattern of Aspergillus species isolated from All Samples

AMA	All Specimens	
	Aspergillus flavus **n=*17**	***Aspergillus fumigatus*** **n=*16**
Amphotericin B	*17/17 (-)	*16/16 (-)
Caspofungin	*17/17 (-)	*16/16 (-)
Itraconazole	*17/17 (-)	*16/16 (-)
Posaconazole	*17/17 (-)	*16/16 (-)
Voriconazole	*17/17 (-)	*16/16 (-)

Molecular data and its relevance

Among *C. tropicalis* isolates multiple mechanisms were found to be implicated in resistant phenotypes such as over expression of the efflux-pump genes, mutations in ergosterol pathway genes and transcription factors. Out of isolates analysed, 38% of isolates showed amino acid substitution (Y132F and S154F) in lanosterol-14-α-demethylase (*ERG11*) gene due to A395T and C461T mutation. Amino acid substitutions were present at the active drug binding site indicating interference in binding. Other isolates showed an azole-resistant phenotype in absence of any amino acid substitution in the *ERG11* gene. Further study on these isolates is being planned to find any novel in-sights into the mechanism of drug resistance.

Similarly, in *Candida auris*, a novel transversion mutation (phenylalanine to tyrosine substitution) at 635th position of FKS gene (ß-1-3-glucan synthase) is found to be responsible for echinocandin resistance in one isolate. As previously reported in literature we observed mutation in FKS gene at 639th position (serine to phenylalanine) in two isolates during the study period.

Understanding the molecular mechanism of resistance would help to find out the reasons of high resistance of *C. tropicalis* and rapid development of resistance to multiple drugs in *C. auris.*

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