

## SUPPLEMENTARY MATERIAL

### *Escherichia coli* infection resistant to expanded-spectrum cephalosporins in low-prevalence countries

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## Supplementary Material

- A. Additional definitions
- B. Details of healthcare exposure by Friedman classification
- C. Comparison of multivariate models using alternative definitions
- D. Comparison of multivariate models using alternative patient groups
- E. Comparison of healthcare associated and non-healthcare associated ESC-R-EC
- F. Analysis of correlates of ESC resistance enzyme class
- G. References for Supplementary material

### A. Additional Definitions

**Chronic renal failure** was a baseline creatinine clearance  $<50\text{ml/min/m}^2$ ; **Chronic heart failure**(1), **chronic lung disease**(2) were based on published functional definitions; **Chronic liver disease** included a history of cirrhosis or hepatic decompensation; **Active malignancy** was any malignancy, except isolated skin malignancy;; **Indigenous** patients were members of the Australian Aboriginal, Maori or Torres Strait islander community. **Meat consumption** (red meat, poultry, pork and processed meat) was any consumption in the month preceding infection.

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#### **B. Healthcare exposure analysis using the Friedman classification**

Details of healthcare exposure using the Friedman classification with and without the inclusion of day-procedures as healthcare exposure.

Time since exposure <sup>1</sup>	Frequency in ESC-R Cases (%) n=91	Frequency in ESC-S Controls (%) n=91	Odds Ratio	(95% CI)	p value
<b>Including day surgical and medical procedures<sup>2</sup></b>					
No healthcare exposure	26 (29)	42 (46)	Reference		
Healthcare <1 month ago	16 (18)	7 (8)	3.692	(1.34-10.18)	0.012
2-6 months ago	40(44)	30 (33)	2.154	(1.09-4.25)	0.027
7-12 months ago	9 (10)	12 (13)	1.212	(0.45-3.27)	0.705
<b>Excluding day surgical and medical procedures<sup>3</sup></b>					
No healthcare exposure	55 (60)	34 (37)	Reference		
Healthcare <1 month ago	11 (12)	5 (5)	3.559	(1.14-11.14)	0.029
2-6 months ago	37(41)	20 (22)	2.993	(1.50-5.98)	0.002
7-12 months ago	9 (10)	11 (12)	1.323	(0.50-3.52)	0.575

<sup>1</sup>Durations are calculated from the date-of-discharge to date of first presentation of the current infection.

<sup>2</sup>With day-procedures: AUC = 0.62, Sensitivity = 62% Specificity = 59%.

<sup>3</sup>Without day-procedures: AUC = 0.64, Sensitivity=53% Specificity = 73%.

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#### C. Comparison of the final multivariate model and models using alternative definitions.

Parameters changed in the alternative models are underlined. Where the significance (of the odds ratios) has moved across the pre-defined (p=0.05) threshold when compared with the final model, this is shaded in grey.

Final Model	Final Model Odds Ratio (95% CI) p value	Alternative 1 Healthcare Including day procedures	Alternative 1 Odds Ratio (95% CI) p value	Alternative 2 Any healthcare exposure in the previous year	Alternative 2 Odds Ratio (95% CI) p value	Alternative 3 Birth in high-risk regions	Alternative 3 Odds Ratio (95% CI) p value	Alternative 4 Travel to Indian subcontinent	Alternative 4 Odds Ratio (95% CI) p value	Alternative 5 Exposure TMP/SMX without combining ESC	Alternative 5 Odds Ratio (95% CI) p value
Healthcare exposure in the previous 6 months (excluding day procedures)	3.16 (1.54-6.46) 0.002	<u>Healthcare exposure in the previous 6 months</u>	2.22 (1.11-4.43) 0.023	<u>Any healthcare exposure in the previous year</u>	1.90 (0.90-3.99) 0.092	As per final model	2.68 (1.33-5.41) 0.006	As per final model	2.58 (1.30-5.10) 0.006	As per final model	3.24 (1.59-6.60) 0.001
UTIs in previous year (per UTI)	1.43 (1.16-1.82) 0.003	As per final model	1.44 (1.14-1.83) 0.002	As per final model	1.44 (1.14-1.83) 0.002	As per final model	1.38 (1.09-1.75) 0.008	As per final model	1.39 (1.10-1.75) 0.005	As per final model	1.43 (1.13-1.81) 0.003
Birth on the Indian subcontinent	11.13 (2.17-56.96) 0.004	As per final model	10.63 (2.08-54.26) 0.004	As per final model	9.67 (1.91-48.95) 0.006	<u>Birth in high-risk regions</u>	2.05 (0.6-5.52) 0.0157	As per final model	8.48 (1.43-50.41) 0.019	As per final model	10.60 (2.08-54.09) 0.005
Travel to high-risk regions	3.09 (1.29-7.38) 0.011	As per final model	2.60 (1.10-6.13) 0.029	As per final model	2.65 (1.12-6.28) 0.027	As per final model	2.76 (1.13-6.74) 0.026	<u>Travel to the Indian subcontinent</u>	2.99 (0.23-39.38) 0.23	As per final model	2.88 (1.21-6.85) 0.016
Trimethoprim +/- Sulfamethoxazole &/or ESC	3.67 (1.30-10.35) 0.014	As per final model	3.75 (1.33-10.54) 0.012	As per final model	3.57 (1.27-10.08) 0.016	As per final model	3.48 (1.24-9.79) 0.018	As per final model	3.10 (1.12-8.60) 0.003	<u>Trimethoprim +/- Sulfamethoxazole</u>	2.66 (0.91-7.75) 0.073
Male sex	2.17 (0.97-4.84) 0.060	As per final model	2.20 (0.99-4.87) 0.052	As per final model	2.34 (1.07-5.13) 0.034	As per final model	2.30 (1.05-5.06) 0.037	As per final model	2.52 (1.14-5.54) 0.022	As per final model	2.31 (1.04-5.12) 0.039
Characteristics: ROC AUC GOF=Goodness of fit	0.772 GOF=0.289		0.766 GOF = 0.36		0.762 GOF = 0.15		0.752 GOF=0.12		0.7614 GOF=0.35		0.763 GOF=0.28

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#### D. Comparison of multivariate model using alternative patient groups

The group used in the alternative model is contained in the first row. Where the significance (of the odds ratios) has moved across the pre-defined ( $p=0.05$ ) threshold when compared with the final model, this is shaded in grey.

Final Model	Final Model Odds Ratio (95% CI) p value	Alternative 1 Exclusion of asymptomatic patients Case n=73 Control n=68  Odds Ratio (95% CI) p value	Alternative3 Inclusion of only CTX-M <i>E. coli</i> cases Case n=74 Control n=91  Odds Ratio (95% CI) p value	Alternative3 Inclusion of only ST131 <i>E. coli</i> cases Case n=40 Control n=91  Odds Ratio (95% CI) p value
Healthcare exposure in the previous 6 months (excluding day procedures)	3.16 (1.54-6.46) 0.002	3.66 (1.61-8.32) 0.002	6.62 (2.81-15.61) <0.001	7.67 (2.66-4.15) <0.001
UTIs in previous year (per UTI)	1.43 (1.16-1.82) 0.003	1.47 (1.10-1.95) 0.008	1.30 (0.99-1.72) 0.062	1.39 (1.01-1.92) 0.044
Birth on the Indian subcontinent	11.13 (2.17-56.96) 0.004	9.19 (2.02-57.42) 0.004	18.1 (3.21-102.04) 0.001	34.11 (5.25-221.49) <0.001
Travel to high-risk regions	3.09 (1.29-7.38) 0.011	2.60 (1.01-6.65) 0.047	5.72 (2.10-15.54) 0.001	4.10 (1.10-15.29) 0.036
Trimethoprim +/- Sulfamethoxazole &/or ESC	3.67 (1.30-10.35) 0.014	3.02 (0.94-9.73) 0.064	3.91 (1.29-12.21) 0.016	3.52 (0.91-13.70) 0.069
Male sex	2.17 (0.97-4.84) 0.060	2.56 (1.06-6.16) 0.036	2.09 (0.88-4.98) 0.095	2.17 (0.77-6.15) 0.143
Characteristics: ROC AUC GOF=Goodness of fit	0.772 GOF=0.289	0.780 GOF = 0.247	0.818 GOF = 0.138	0.830 GOF = 0.018

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**E. Differences in risks between healthcare associated (HA) and non-healthcare associated (non-HA) ESC-R-EC groups after stratification by healthcare contact in the previous six months excluding day-procedures.**

Potential Risk	Healthcare associated cohort (n=73)			Non-healthcare associated cohort (n=109)		
	Count of cases with characteristic n=48 (%)	Count of controls with characteristic n=25 (%)	p value for comparison case vs. controls	Count of cases with characteristic n=43 (%)	Count of controls with characteristic n=66 (%)	p value for comparison case vs. controls
Birth on the Indian subcontinent	2 (4)	0 (0)	0.543	9 (21)	2 (3)	0.006
Travel to high-risk regions	4 (8)	3 (12)	0.685	20 (47)	11 (17)	0.001
Trimethoprim +/- Sulfamethoxazole &/or ESC use	15 (31)	2 (8)	0.039	5 (12)	4(6)	0.313
Male sex	16 (33)	7 (28)	0.642	14 (33)	9(14)	0.018
UTIs in previous year (Count, 25-75%)	1, 0-3	1, 0-1	0.347	0, 0-3	0, 0-1	0.146

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**F. Analysis of correlates of ESC resistance enzyme class**

Comparing characteristics of patients harbouring CTX-M group enzymes to those harbouring ‘Non-CTX-M’ group enzymes.

Variable	Frequency in CTX-M group (%) n=74	Frequency in non-CTX-M group (%) n=15	p value CTX-M vs. Non-CTX-M
<b><i>Variables included in the multivariate model</i></b>			
Male Sex	26 (35)	4(27)	0.527
Charlson score $\geq 1$	38 (51)	6(40)	0.423
Immune suppression	17 (23)	1(7)	0.288
Anatomical or structural abnormality	18(24)	4(26)	1.0
UTIs in past 12 months (Median & (25-75 <sup>th</sup> centile))	0 (0-2)	2(0-4)	0.054
SXT use	14 (19)	2(13)	1.0
ESC use	5 (7)	2(13)	0.336
High risk travel	23(31)	1(7)	0.061
Birth on Indian Subcontinent	11 (15)	0(0)	0.199
Healthcare Exposure (6 months)	45(61)	3(20)	0.005
<b><i>Other variables</i></b>			
Age (Median & (25-75 <sup>th</sup> centile))	60 (41-71)	70(58-78)	0.061
Any overseas travel	27 (36)	1(7)	0.031
Any antimicrobial use	54 (73)	14(93)	0.108
Renal transplant	8 (11)	0 (0)	0.342
Fluoroquinolone use	6(8)	1(7)	1.0
$\beta$ -lactam + $\beta$ -lactamase inhibitor use	9 (12)	5(33)	0.055
Carbapenem use	3(4)	0(0)	1.0
Aminoglycosides use	5(7)	0(0)	0.584
Macrolide use	4(5)	1(7)	1.0
Narrow spectrum cephalosporin use	13(18)	2(13)	1.0
Narrow spectrum penicillins use	8(9)	0(0)	0.342