Social Science Research on Antimicrobial Resistance

Medical Impact of Antimicrobial Resistance

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Impact of antimicrobial resistance

- Infection is more difficult to treat in individual patients and outcomes are worse
- Antibiotics used to prevent infection are ineffective, i.e. post surgery
- Infection control activities need to be increased to prevent further spread
- Costs are increased (length of stay, lab costs, drug costs etc)

What is antibiotic resistance?

(1) phenotypic change in susceptibility compared to the normal bacterial population

or

(2) presence of a genotypic change which adversely impacts on susceptibility

or

(3) level of susceptibility likely to result in a higher than expected level of therapeutic failure

(1) and (2) are defined by “epidemiological cut offs (ECOFFS), and (3) is defined by “clinical breakpoint”

How can the impact of “resistance” be measured?

- mortality
- morbidity
  - fever days
  - resolution of WBC
  - length of stay
  - ICU admission/days
  - reconsultation
  - second courses of antibiotics
- pathogen persistence/increased resistance
- financial cost

Methodologies used:-

- prospective cohort or case control studies
- retrospective cohort or case control studies
- no randomised controlled clinical trials (moral and ethics)

Impact of appropriate antibiotics for sepsis

Impact of empiric appropriate antibiotics for sepsis

Paul et al, 2010. AAC 54; 4851-63

- 70 studies, 21,338 patients
- 26 studies in ICU, 42 studies BSI, 15 studies pneumonia

- End point in all cause mortality

- Number to treat to avoid one fatal outcome: 10 (95% CI 8-15)
- Impact of inappropriate therapy: Pooled OR 2.11 (95% CI 1.8 – 2.4) on mortality

Impact of empiric appropriate antibiotics for sepsis

– **Settings, sources and pathogens**

		Adjusted OR	
		OR	**Studies (*n*)**
Clinical setting	ICU	2.4 (1.5 – 3.8)	18
	Non ICU	1.8 (1.5 – 2.1)	30
Bacteraemia	All	1.9 (1.5 – 2.4)	31
	Some	2.4 (1.7 – 3.4)	17
Pathogen	MRSA	1.7 (0.5 – 6.0)	2
	P. aeruginosa	2.0 (1.1 – 3.6)	4
	Acinetobacter	7.6 (2.5 – 22.9)	2
Source	Pneumonia	2.2 (1.3 – 3.5)	10
	Other	2.0 (1.6 – 2.5)	38

Impact of empiric appropriate antibiotics for sepsis
- Severity and co-morbidities

		Adjusted OR	
		OR	**Studies (*n*)**
Definition of appropriate	In vitro only	2.3 (1.7 – 3.1)	24
	Pharmacokinetic	1.7 (1.3 – 2.3)	15
Adjust for sepsis severity	Yes	2.2 (1.8 – 2.7)	43
	No	1.5 (1.0 – 2.1)	5
Adjust for co-morbidity	Yes	1.6 (1.4 – 1.8)	32
	No	3.3 (2.1 – 5.0)	16
Adjust for neutropaenia	Yes	1.6 (1.3 – 1.9)	19
	No	2.4 (1.8 – 3.2)	29

Resistance in Gram-positive bacteria causing blood stream infection

Year	S.aureus			Enterococcus
	OXA R MecA^{+}(%)	Erythromycin R(%)	Ciprofloxacin R(%)	Vancomycin %R
2001	43.3	41.2	37.3	7.7
2003	40.3	39.6	44.5	10.2
2005	35.7	31.1	33.2	16.5
2007	36.3	33.5	31.9	13.4
2009	22.8	24.5	22.7	14.4
2010	19.4	21.4	20.7	15.6
2011	13.0	22.4	20.2	13.0
2012	11.3	16.2	15.6	8.5
2013	10.3	14.8	15.7	16.4

- Decline in MRSA
- Increase in vancomycin resistant Enterococci

www.bsacsurv.org

Resistance in Gram-negative bacteria causing blood stream infection

Year	E.coli			
	CTX-R (%)	CTX-M producer %	Ciprofloxacin resistant %	Imipenem resistant %
2001	-	0	8.2	0
2003	2.0	1.6	10.5	0
2005	7.7	6.1	16.6	0
2007	11.3	7.7	24.2	0
2009	6.8	5.4	13.6	0
2010	6.4	5.8	16.0	0
2011	9.0	-	20.9	0
2012	11.0	-	22.9	0
2013	11.5	-	20.2	0

- Rise and fall and rise of E.coli CTX-M producers
- No detectable carbapenem resistance – first isolates in 2011

www.bsacsurv.org

Antibiotic resistance and bacteraemia

Specific pathogens: MRSA

Paul et al 2010
Retrospective cohort study of 510 episodes of MRSA BSI in Israel.
Mortality was 49.1% (168/152) in inappropriate therapy 33.3% (56/168) for appropriate therapy

Fang et al 2006
Retrospective cohort study of 162 BSI – Taiwan
Analysis of appropriate therapy before 48h and >48h on
30 day mortality showed no impact of early empirical therapy

Antibiotic resistance and bacteraemia

Carbapenemase producing Enterobacteriaceae

Ben-David et al 2012

K.pneumoniae blood stream infection with CPE, ESBL and sensitive K.pneumoniae. Independent risk factors for death were PITT score, Charlson score and carbapenem resistance.

Diakos et al, 2009

Prospective observational study of VIM 1 producing Kleb pneumoniae BSI. Carbapenem resistance – MIC >4mg/L, age, severity of underlying disease, were independent predictors of 14 day mortality, VIM production no impact.

Antibiotic resistance in UTI

- RCT of ciprofloxacin vs co-trimoxazole in UTI co-t R associated with lower eradication and more failures (McCarthy et al, 1999)

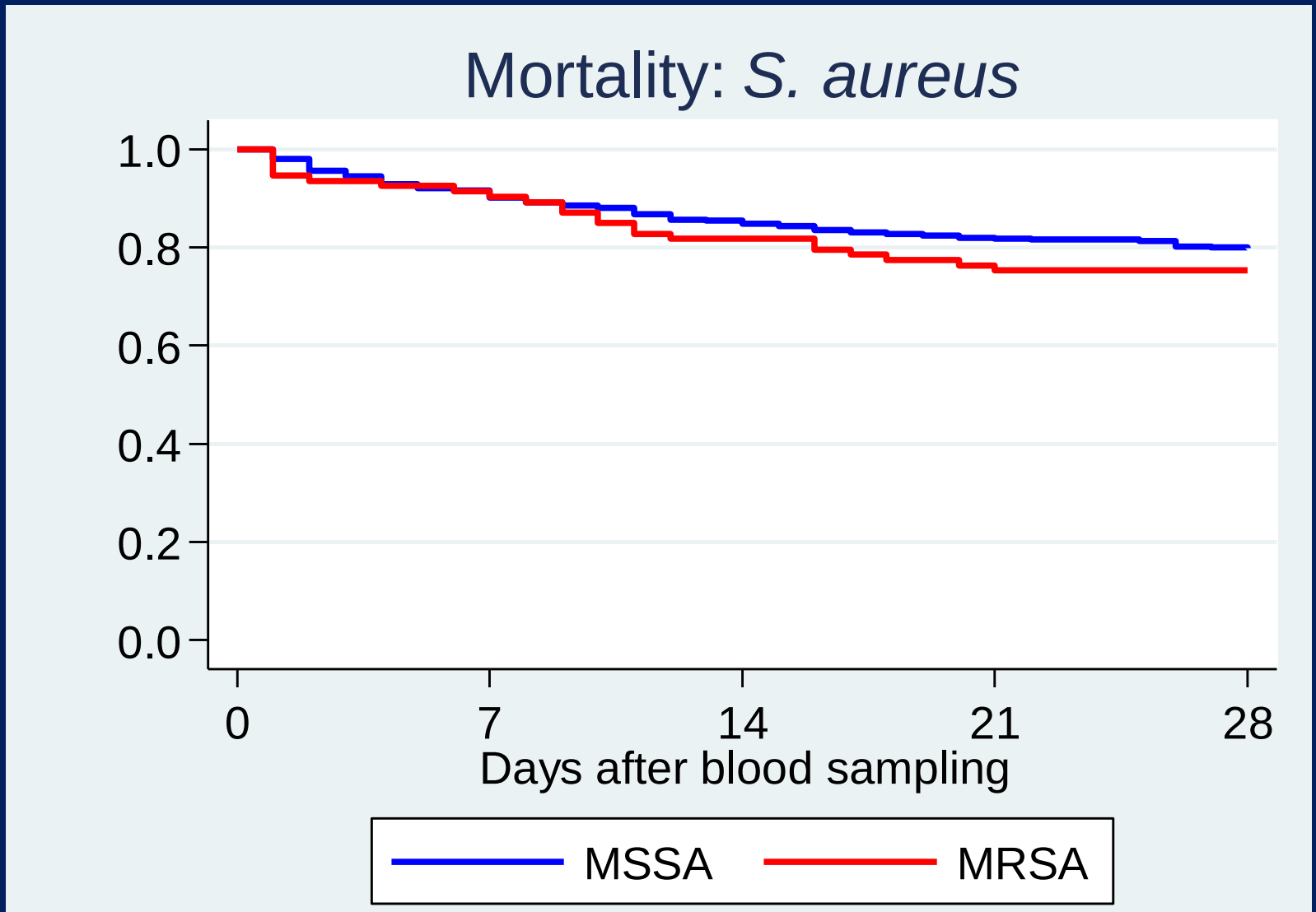
- RCT of ciprofloxacin vs co-trimoxazole in acute pyelenephritis – high rates of microbiology and clinical failure with Co-t R strains (Talan et al, 2000)

- impact of co-t R in uncomplicated UTI clinical and microbiological outcomes significantly worse if Co-t R *E.coli* (Raz et al, 2002)

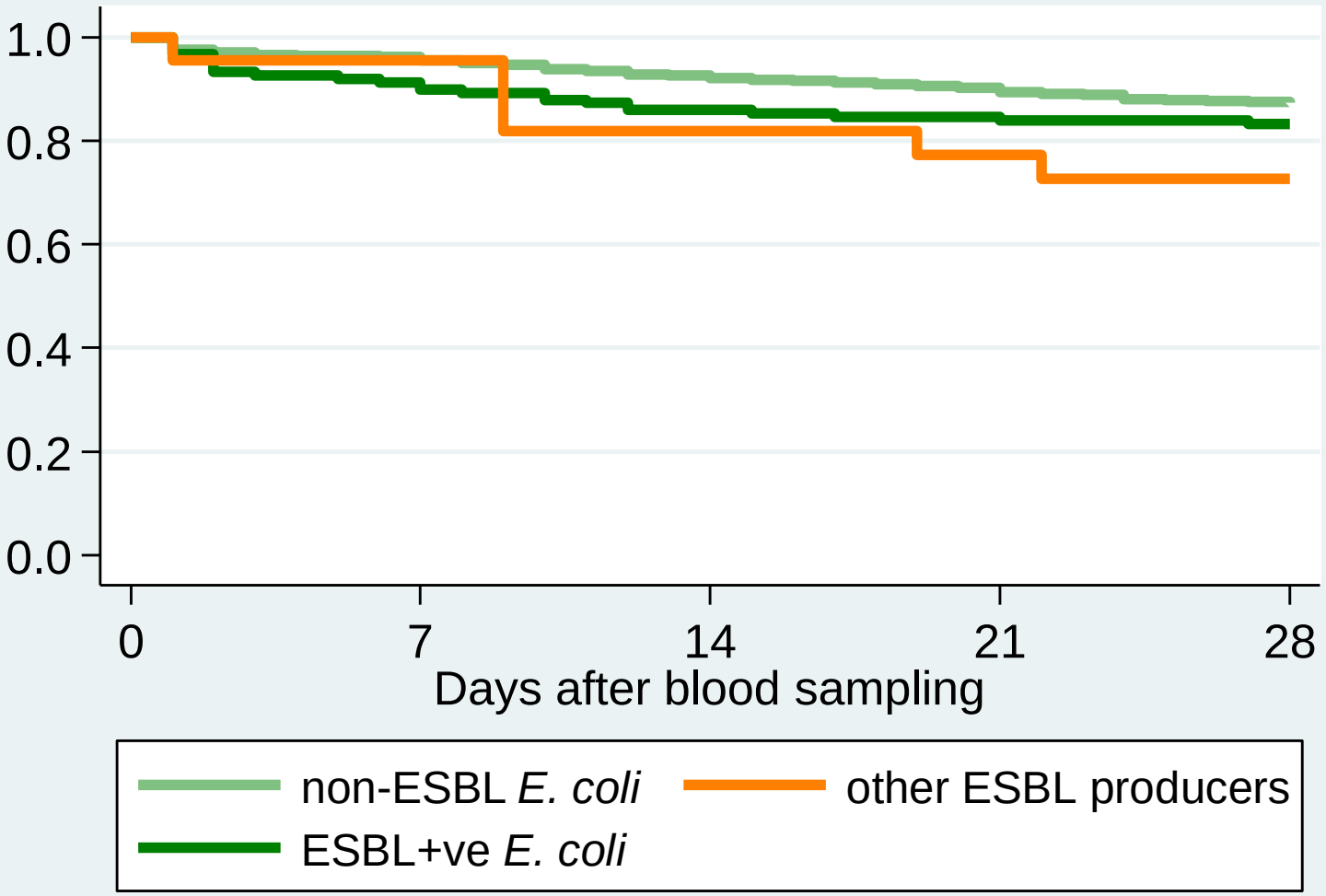
- tmp R associated with longer time to symptom resolution, more reconsultations, higher bacteriological failures (McNulty, 2006)

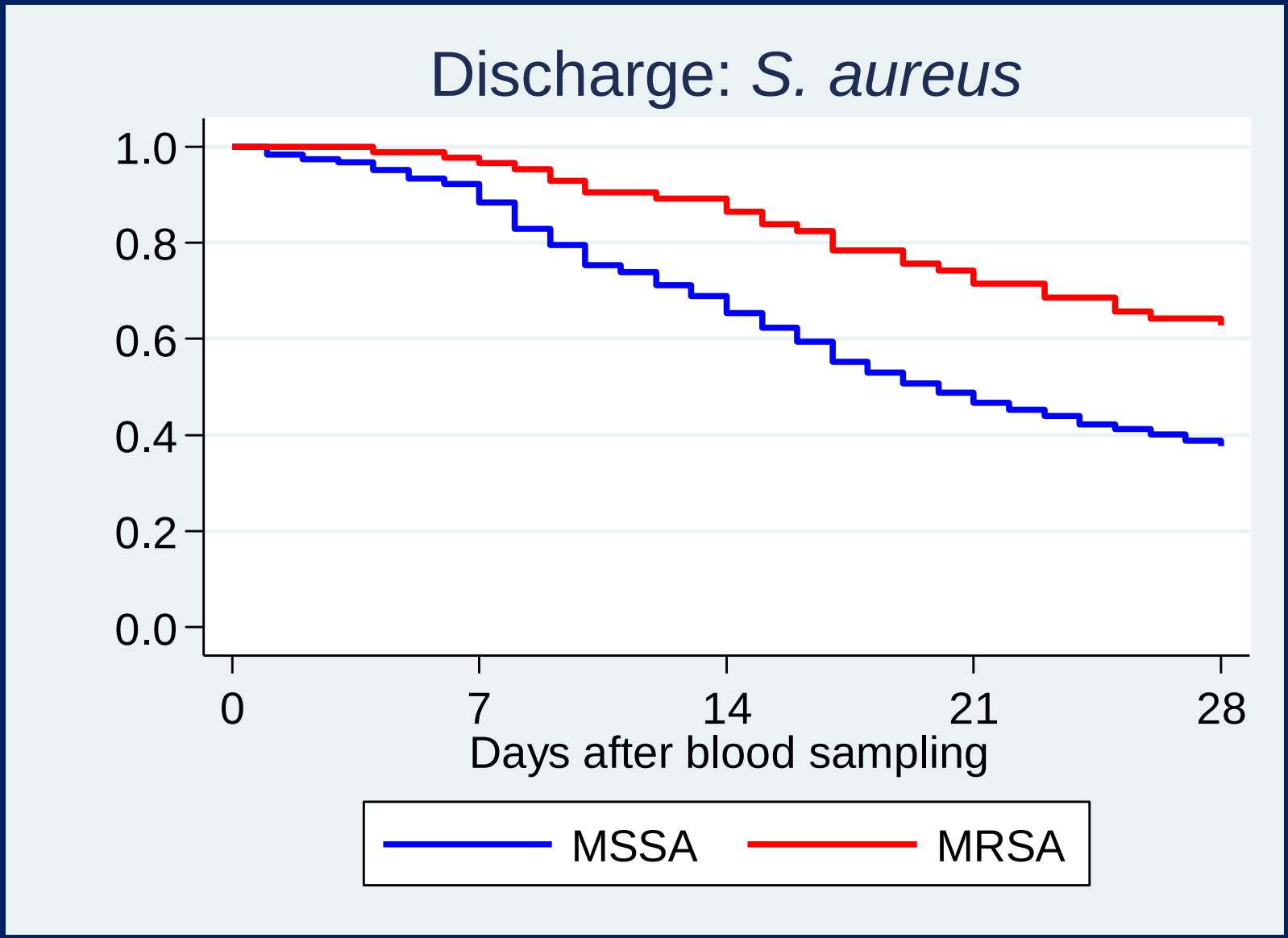
Data from the NHS in England

- Observational study of 1700 patients with blood stream infection
  - > mortality MSSA vs MRSA
  - > mortality ESBL producers vs non-ESBL producers
  - > time to discharge MSSA vs MRSA
  - > time to discharge ESBL producers vs non-ESBL producers
  - > days to appropriate therapy – S.aureus BSI

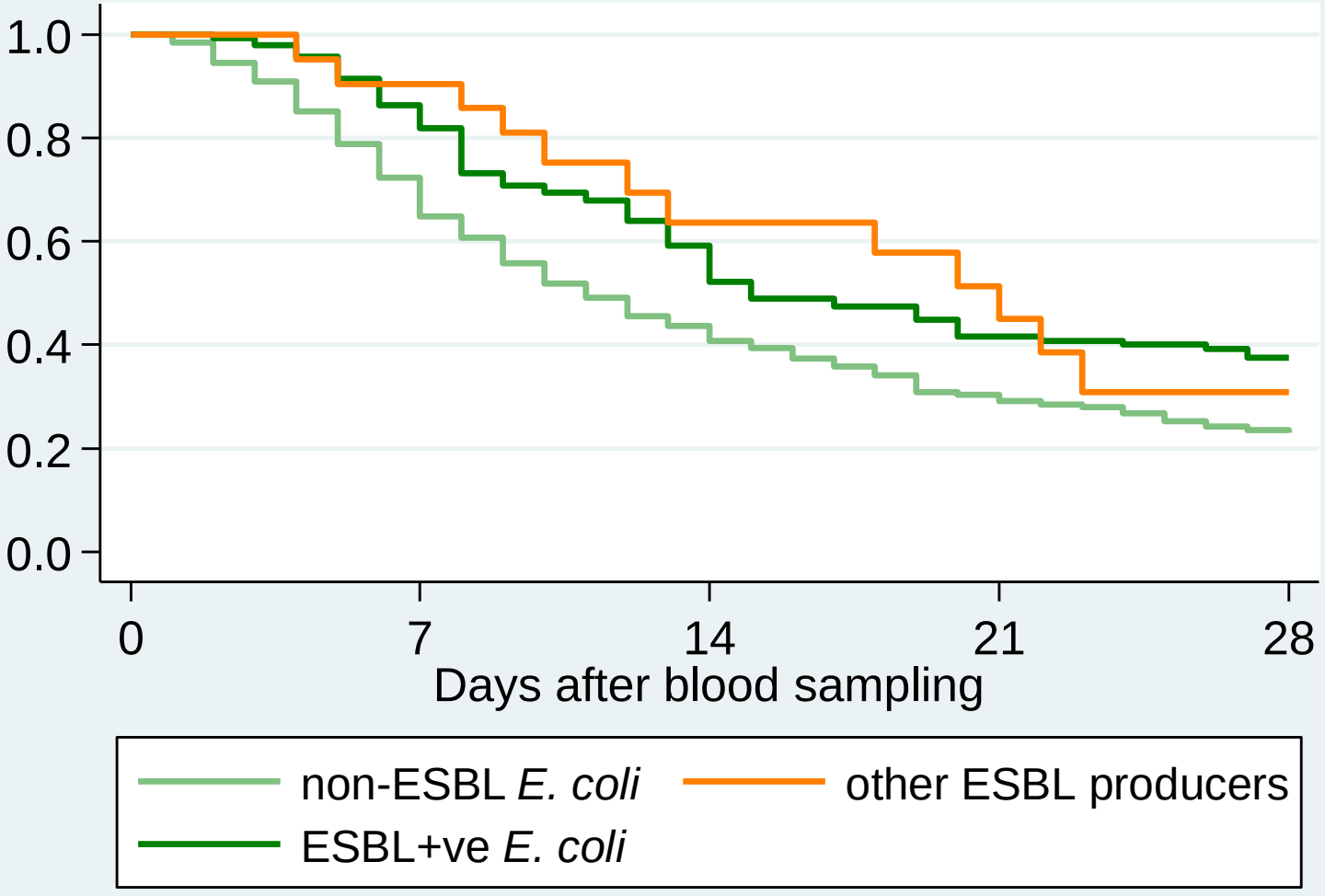

Mortality: S. aureus
1.0
0.8
0.6
0.4
0.2
0.0
0
7
14
21
28
Days after blood sampling
MSSA
MRSA

Mortality: Enterobacteriaceae

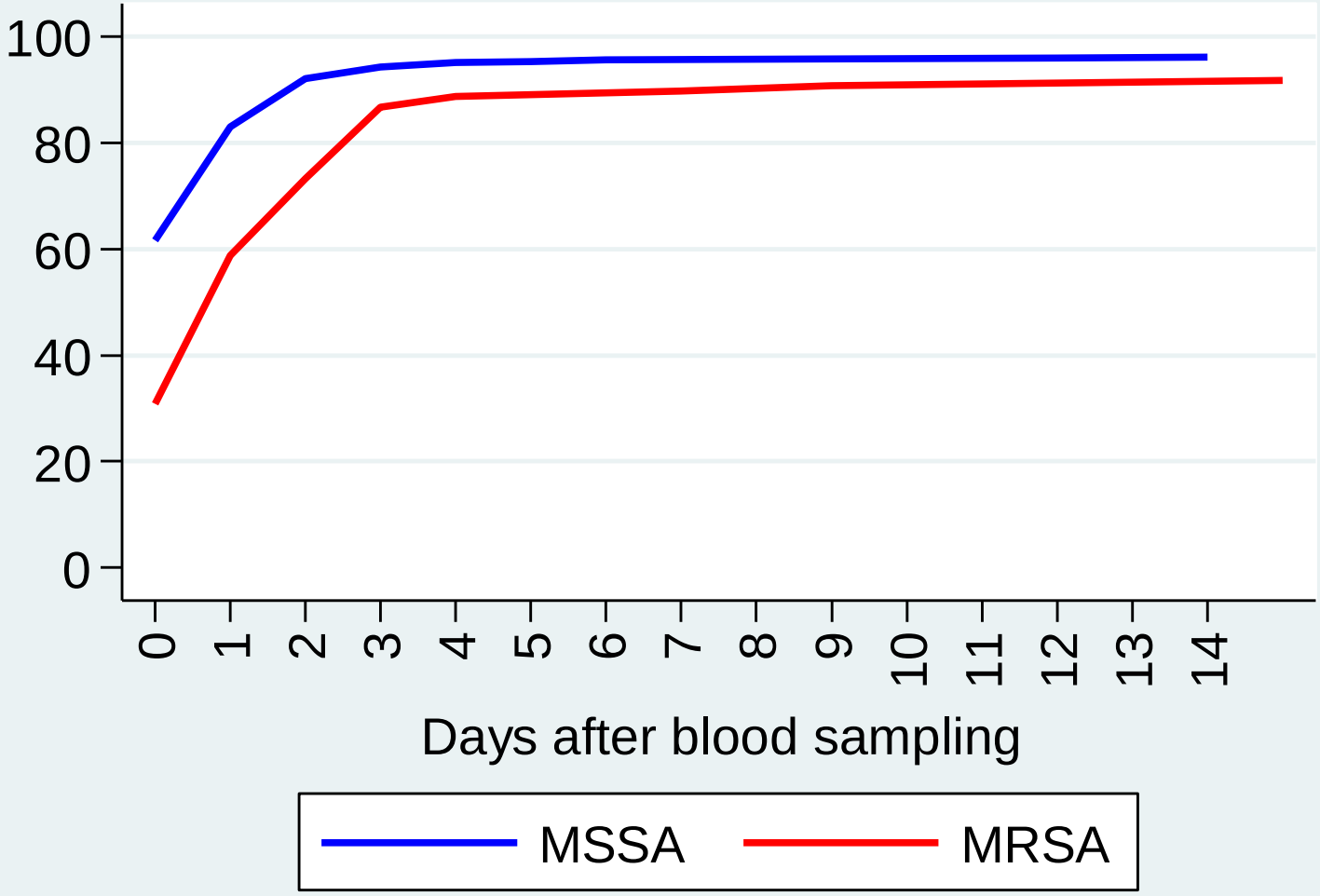



Discharge: S. aureus
1.0
0.8
0.6
0.4
0.2
0.0
0
7
14
21
28
Days after blood sampling
MSSA
MRSA

Discharge: Enterobacteriaceae



Days to appropriate drug: *S. aureus*



Conclusions

- Antimicrobial resistance impacts on clinical outcomes
- Antimicrobial resistance adds cost to healthcare
- Multiple interventions are required (UK Five Year Resistance Strategy 2013-18)

Infection Control; antibiotic stewardship; education, training and public engagement; new treatments and diagnostics; better surveillance, prioritisation of research; international collaboration