Cause or effect? Does hospital antibiotic use influence changes in bacterial resistance?

Esther Robinson[2], Ed Moran[1], Chris Green[1], Matt Keeling[3], Ben Collyer[3]

Heartlands Hospital, Birmingham[1]. Birmingham Public Health Laboratory, Public Health England[2]. Zeeman Institute, University of Warwick[3].

INTRODUCTION

- Antibiotic resistance is increasing. It is a major patient safety issue, and a public health priority.
- Resistant strains are associated with increases in length of hospital stay, cost of care, morbidity and mortality.
- Studies in primary care – facilitated by many years of electronic prescribing systems – have clearly demonstrated an association between antibiotic use and the development of resistance at the patient level. Contrariwise, restricting use may be associated with a decline in resistance.
- There is a dearth of such patient-level studies conducted within healthcare institutions. yet hospitals are the biggest consumers of the very broad-spectrum agents used for the treatment of resistant organisms. Inappropriate use of such drugs is associated with the development of highly resistant, near-untreatable, bacterial strains.
- It is vital that we improve our understanding of this phenomenon within hospitals at the patient-level if we are implement evidence-based measures to help guide empirical antibiotic selection, preserve antibiotic effectiveness and slow the emergence of resistance.
- Heart of England NHS FT was among the first secondary care users of electronic prescribing in the UK. It has been used throughout the organisation for 8 years.
- We examined antibiotic use and Gram-negative bacterial resistant in all samples from people admitted to our institution over an 8 year period. We looked at temporal changes in the use of antibiotics and identified risk factors associated with the emergence of resistant organisms.

METHODS

- We extracted and anonymised basic demographics, previous admissions dates, and electronic prescribing data for all patients from whom *E. coli, K. pnemumoniae*, or *Ps. aeruginosa* were isolated over a 7 year period.
- This represented 27,350 patient admissions of which 10,440 had associated electronic prescribing data.
- Antibiotic usage was expressed as “defined daily dose”, calculated as described by World Health Organisation methodology.
- Antibiotic sensitivity data was separated into that from samples taken within 48 hours of a recorded admission date and that after 48 hours.
- The Granger-causality test was used to test for relationships between prescribing trends and change in bacterial antibiotic resistance.
- Logistic regression was used to identify factors from demographic, coding and prescribing data that were associated with isolation of organisms resistant to either co-amoxiclav or piperacillin-tazbactam.

RESULTS

Changes in antibiotic use

- Use of co-amoxiclav was high and fairly consistent over the period studied. Piperacillin-tazobactam use was lower but increased by 39% between 2009 and 2016.
- Use of gentamicin decreased, ceftriaxone and ciprofloxacin use was low but increased. Carbapenem use was variable.

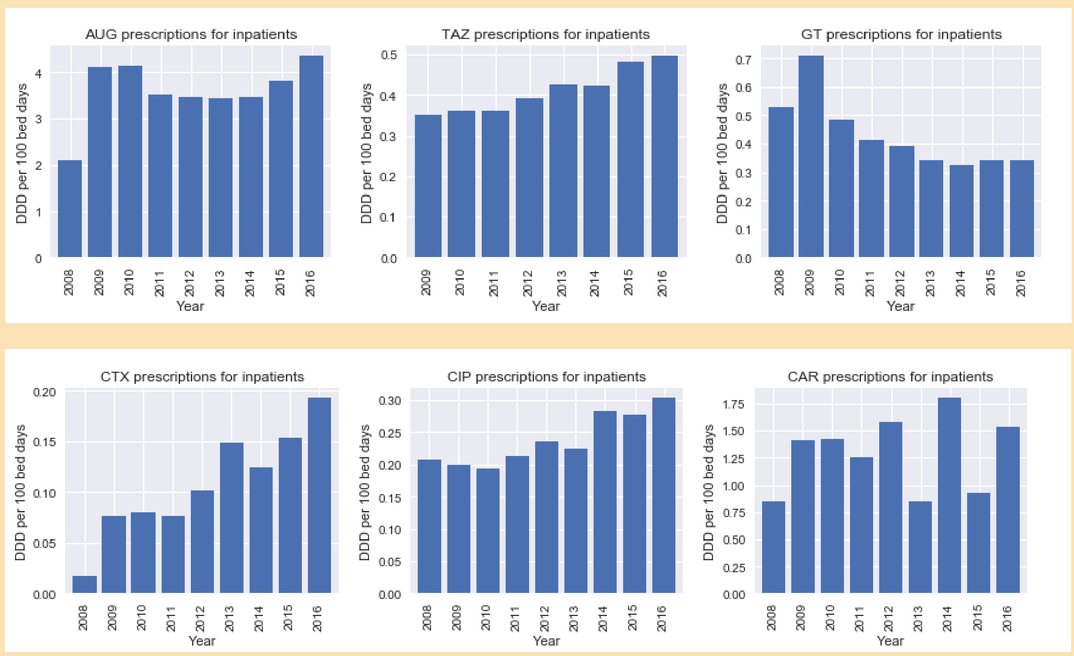

Figure 1. Defined daily dose of specific antibiotics by year

Changes in bacterial resistance

- *E. coli* resistance to co-amoxiclav remained stable over the period studies. Isolates from samples taken over 48 hours after admission were more likely to be resistant, most strikingly to co-amoxiclav but also piperacillin-tazobactam. Gentamicin and ceftriaxone resistance was low for both pre- and post-48 hour specimens (fig 2).

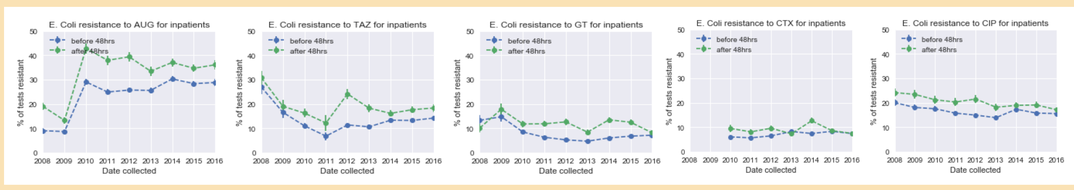

Figure 2. E coli resistance to antibiotic agents, pre and post 48h from admission

- Resistance rates were more variable for *K. pneumoniae* and *Ps. aeruginosa*. Post-48h specimens tended to be more resistant and *Ps. aeruginosa* resistance to piptaz rose significantly over the study period reflecting the hospitals role as the regional cystic fibrosis centre (fig 3).

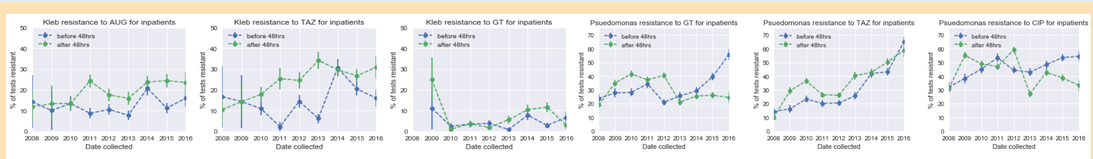

Figure 3. *K. pneumoniae* and *Ps. aeruginosa* resistance pre and post 48h from admission

Is increasing piperacillin/tazobactam use in response to increasing resistance to co-amoxiclav?

- The Granger-causality test was used to test for a relationship between prescribing and resistance.
- There was no detectable relationship between prescribing and resistance to co-amoxiclav and piperacillin-tazobactam for *E coli* or *K. pneumoniae.*

What factors are associated with isolation of a co-amoxiclav or piperacillin-tazobactam resistant isolate?

- Logistic regression was used to identify factors associated with isolation of a resistant organism (table 1).

Factor	E coli (co-amox)	K pneumo (co-amox)	E coli (pip-taz)	K pneumo (pip-taz)	Pseudo (pip-taz)
Prior co-amox R	2.6 (2.25-3)	2.52 (1.42-4.45)	1.27 (1.1-1.47)	2.46 (1.42-4.24)	
Prior co-amox S	0.74 (0.69-0.79)	0.91 (0.74-1.13) p=0.42	0.86 (0.78-0.94)	1.24 (0.996-1.55)	
Prior pip-taz R		0.94 (0.63-1.41) p=0.78	2.33 (1.93-2.82)	2.78 (1.78-4.35)	1.07 (1.05-1.09)
Prior pip-taz S		0.711 (0.57-0.881)	0.87 (0.79-0.96)	0.8 (0.65-0.998)	0.99 (0.97-1.00)
Indian ethnicity	2.0 (1.32-3.05)	1.78 (0.67-4.75) p=0.244	1.49 (0.88-2.53) p=0.137		
Pakistani ethnicity	1.63 (1.21-2.18)	0.61 (0.29-1.30) p=0.20	1.26 (0.86-1.85) p=0.232		0.34 (0.2-0.59)
Age	1.54 (1.13-2.1)	2.15 (0.68-6.8) p=0.191	2.74 (1.74-4.31)		
Comorbidity “septicaemia”	1.54 (1.33-1.79)		1.54 (1.27-1.86)		
Comorbidity “acute cerebrovascular disease”		5.7 (2.12-15.47)		3.68 (1.36-9.99)	
Comorbidity “biliary tract disease”					3.87 (1.9-7.88)
Previous received co-amox	1.05 (1.03-1.07)	1.06 (0.97-1.15) p=0.146	1.03 (1.00-1.06)		
Previous received pip-taz		1.06 (0.887-1.27) p=0.513	1.04 (0.99-1.08) p=0.108		1.12 (1.08-1.17)
Admitted via surgical assessment unit	2.99 (1.7-5.26)				
Admitted to “general surgery”		3.4 (1.51-7.75)			
Admitted to “general medicine”					2.0 (1.42-2.83)
Admitted to general respiratory ward		15.9 (2.5-100.7)			
Admitted from home			0.53 (0.32-0.87)	0.32 (0.13-0.75)	

Table 1: Factors associated with resistance to the named antibiotic expressed as odd ratios (95% CI). p values<0.02 unless otherwise stated.

- Prior resistance to the agent used was strongly associated with resistance later. Prior sensitivity was associated with repeat sensitivity for *E. coli*.
- Indian or Pakistani ethnicity was associated with *E. coli* resistance to co-amoxiclav and *Pseudomonal* sensitivity to piperacillin-tazobactam. Associations were not significant with other organisms or antibiotics.
- Certain admission routes and co-morbidities – mostly those likely to lead to a long inpatient stay – were associated with resistance. This probably reflects a patient cohort likely to receive significant antibiotic exposure.

Is antibiotic use on a specific ward associated with greater risk of the later emergence of resistance?

- Analysis of ward level resistance data detected no specific area of the hospital with greater levels of resistance.

DISCUSSION

- Co-amoxiclav use remained steady over the 7 years observed. Piperacillin-tazobactam use increased by 39% between 2010 and 2016. This was not explained by any increase in resistance to co-amoxiclav over this time and causality testing detected no significant relationship between changes in antibiotic use and subsequent development of resistance, or vice versa.
- It seems likely that the increase piperacillin-tazobactam is due to the prescribing behaviour of medical staff rather than clinical need.
- Co-amoxiclav resistance is particularly high among inpatients with *E. coli* and *K. pneumoniae* infections.
- Age, prior resistance and ethnicity were the factors most consistently associated with resistance.

CONCLUSIONS

- Whilst popularly accepted that use of broad-spectrum antibiotics in hospitals drives resistance, this is not apparent over the 7 year period studied at either an institutional or ward level. This is in contrast to the risk of emergence within individuals and it may be that at a population level community prescribing is more important.
- The increase in the use of broad spectrum agents is not justified by changes in resistance – with the exception of *Ps. aeruginosa* resistance to piperacillin-tazobactam in the cystic fibrosis unit. Interventions need to be aimed at prescriber behaviour.
- Gentamicin remains an effective piperacillin-tazobactam or carbapenem sparing antibiotic in combination with another agent.

ACKNOWLEDGEMENTS

- Ben Collyer is an INTEGRATE AMR Early Career Research Fellow, and would like to acknowledge support and funding from EPSRC’s ‘Bridging the Gaps’ initiative.
- NHS data was shared only after anonymisation and under a Privacy Impact Assessment.
- Ethical approval was given by the Health Research Authority.