

Study Protocol

Title

Effect of General Practice characteristics and antibiotic prescribing on *E. coli* antibiotic non-susceptibility in the West Midlands region of England – a four year ecological study.

Collaborators

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Background

Antimicrobial resistance (AMR) has been linked with inappropriate use of antibiotics although the published evidence for its role in selection of resistance is mixed [1]. In the United Kingdom (UK), 74% of antibiotic prescribing occurs in community settings [2], and therefore a number of initiatives have been implemented that focus on antibiotic stewardship in primary care with the aim of promoting appropriate use of antibiotics and reducing the total amount prescribed. Urinary Tract Infections (UTI) are one of the most common clinical presentations in both primary care and hospital patients and urine samples are the most common specimens sent for microbiological examination from the community [3].

Escherichia coli (*E.coli*) is the most common uropathogen identified in both sexes and in all age groups from both community and hospital settings [4].

Trends in AMR among UTI patients and its relationship with antibiotic prescribing in community settings was examined in Wales in 2007 and showed that decreased antibiotic prescribing leads to reduced local antimicrobial resistance [5].

In England, the increasing coverage and availability of timely AMR and antibiotic prescribing data has provided an opportunity to investigate the epidemiology of AMR among UTI patients in community settings, and the relationship with antibiotic prescribing. We intend to use data from the West Midlands for non-susceptibility of *E.coli* isolated from urine to a range of antibiotics and antibiotic prescribing data from primary care settings for 2010 to 2013.

Aims and objectives

To examine the relationship between antimicrobial non-susceptibility among *E.coli* urine isolates and antibiotics prescribing in community settings in the West Midlands.

- Describe the epidemiology of *E.coli* non-susceptibility in urine isolates identified in community settings, 2010 to 2013.
- Describe antibiotic prescribing in the West Midlands and quantify variation in prescribing between General Practices
- Examine and compare the rate of *E.coli* resistance to specific antibiotics and antibiotic prescribing within the same General Practice.
- Use multilevel modelling to assess the association between *E.coli* antibiotic non-susceptibility and antibiotic prescribing in the West Midlands in order to identify key predictors of resistance.

Methods

Population and setting

The study will be based in the West Midland region of England. The West Midlands has 15 diagnostic microbiology laboratories and approximately 950 GP practices serving a population of 5.6 million.

Antibiotic non-susceptibility is defined as a susceptibility test result of either 'intermediate' or 'resistant' ('I' or 'R').

Study design

Retrospective ecological study

Data Sources

1. Antibiotic prescribing data from individual West Midland GP practices for 2010 to 2013 provided by Health & Social Care Information Centre (HSCIC). Prescribing data is aggregated at GP practice level by month and includes the GP practice code and practice postcode, drug prescribed, the total number of items of the drug (prescription items) and the total Defined Daily Dose (DDD). Prescribing data will be collated on the commonly prescribed antibiotics in the community, which include:

- Ampicillin / amoxicillin
- Trimethoprim
- Cephalexin
- Co-amoxiclav
- Ciprofloxacin
- Nitrofurantoin

The dataset will not include patient level demographic data.

2. Antimicrobial susceptibility test (AST) data for the period 01 January 2010 to 31 December 2013 will be obtained from the PHE laboratory surveillance systems (AmSurv/SGSS). This system monitors AST data submitted from NHS diagnostic microbiology laboratories in the West Midlands. These data are at patient level and include the organism and the antibiotic susceptibility test results. The patient demographic data includes DOB, sex, patient postcode, and GP practice. Patient demographics will be used to de-duplicate results and then removed from the dataset. AST data will be aggregated by General Practice.
3. General Practice characteristics such as; practice location, practice list size and the number of general practitioners per practice will be obtained from the HSCIC database.
4. Regional, Upper-tier Local authority and Clinical Commissioning Group level population denominators will be obtained from the Office for National Statistics (ONS) based on 2001 and 2011 census data.

Analysis

1. Antibiotic prescribing data

Antibiotic items prescribed will be aggregated for individual GP practices by quarter and annually for each of the four years in the study period. Practice list size will be obtained from HSCIC and practices with list sizes less than 500 will be excluded. The number of antibiotic items dispensed per 1000 registered patients will be calculated for each practice and aggregated to the corresponding UTLA area and region. Similar calculations will be performed to obtain the total DDDs for each practice and aggregated for these organisations or geographic areas. A descriptive analysis will be performed describing variation in antibiotic prescribing across the region by General Practice and region.

2. Antibiotic Resistance data

Antimicrobial resistance (AMR) data for *E. coli* isolated from urine specimens submitted by GPs in the West Midlands will be extracted from the AMR reporting database for 2010-2014. A descriptive analysis will be performed on these data to describe antibiotic non-susceptibility proportions in *E. coli* isolated from community specimens to selected antibiotics. Repeat specimen reports received from the same

patient with matching results within the same year will be excluded. The percentage of *E. coli* listed as non-susceptible for each antibiotic being studied will be calculated quarterly/annually for each GP practice, Local Authority (LA) area and for the region.

3. Multi-level modelling

Antibiotic prescribing and antibiotic non-susceptibility for each General practice will be selected based on biological plausibility of an exposure/non-susceptibility relationship and to enable comparisons with other international studies (Table 1). For each of the prescribing / non-susceptibility combination a datasheet will be created showing quarterly data for 2010-2013. The *E. coli* non-susceptibility to each antibiotic will be compared with antibiotic prescribing data for the same antibiotic or one that may select non-susceptibility for that antibiotic for the same quarter or the previous quarters (up to four lagged quarters).

We will use multiple regression methods to examine the relationship between antibiotic use and *E.coli* non-susceptibility. The effect of characteristics such as practice size, numbers of GPs within a practice, urban/rural settings of practice and seasonality will be included within the statistical models as potential explanatory variables. An iterative process will be applied to each prescribing / non-susceptibility combination to build individual statistical models to measure the association of prescribing on the number of non-susceptible *E. coli* urine isolates from the community.

To allow for variability between General Practices and between Local Authorities, these variables will be modelled as random effects within the statistical models. Adjusted odd ratios will be used to measure the association of the explanatory variables, with a *P* value of ≤ 0.05 being considered statistically significant.

The number of *E. coli* reports non-susceptibility to a specific antibiotic will be the outcome variable and a binomial distribution will be assumed.

All statistical analyses will be performed using STATA v13 (StataCorp, USA).

Bias and limitation

- Implementation of the AmSurv system began in 2009. Complete regional coverage was not achieved until late 2012. Therefore all regional AMR data was only captured for 2013 in this study period. However over 50% of laboratories were reporting in 2010 and all but one laboratory reporting by 2012.
- The prescribing data provided by HSCIC is based on dispensed prescriptions and is aggregated at GP practice level. Therefore individual level data on age, sex or medical indication is not known.
- Urine specimens sent from the community for microbiological examination may represent cases with initial treatment failures, more complicated medical histories and

severe infections [6], therefore the observed levels of resistance are likely to overestimate the true levels of resistance in our population.

- Testing methods and antibiotics tested in first-line panels may vary between laboratories.
- This is an ecological study and therefore is not able to examine individual patient-level data or related risk factors.

Table 1: Antibiotic combinations evaluated

| <i>Escherichia coli</i> non-susceptibility | Prescribed antibiotic |
|--|------------------------|
| Ampicillin / amoxicillin | ampicillin/amoxicillin |
| | co-amoxiclav |
| | fluoroquinolones |
| Cephalexin | cephalosporins |
| | fluoroquinolones |
| | trimethoprim |
| | nitrofurantoin |
| Co-amoxiclav | co-amoxiclav |
| | ampicillin/amoxicillin |
| Ciprofloxacin | ampicillin/amoxicillin |
| | fluoroquinolones |
| | co-amoxiclav |
| | cephalosporins |
| Trimethoprim | trimethoprim |
| Nitrofurantoin | nitrofurantoin |
| | cephalosporins |

3.7 Study milestones

- Data gathering and initial analysis complete – by end of December 2015
- Model building complete - by end of April 2016
- Final draft of manuscript complete – by June 2016
- Final draft – by end of July 2016

Reference List

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4. Ironmonger D, Edeghere O, Bains A, Loy R, Woodford N, Hawkey PM: **Surveillance of antibiotic susceptibility of urinary tract pathogens for a population of 5.6 million over 4 years.** *J Antimicrob Chemother* 2015, **70**: 1744-1750.
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