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"Warning: allergic to penicillin:" Association between penicillin allergy status in 2.3 million NHS general practice electronic health records, antibiotic prescribing, and health outcomes.

RM West[1], CJ Smith,[1] SH Pavitt,[2] CC Butler,[3] P Howard,[4] C. Bates,[5] S Savic,[4] JM Wright,[1] J Hewison,[1] JAT Sandoe.[4*]

1. Leeds Institute for Health Sciences, University of Leeds, Leeds, UK. LS2 9LU.
2. School of Dentistry, University of Leeds, Leeds, UK. LS2 9LU.
3. University of Oxford Primary Care Clinical Trials Unit, Oxford, UK. OX2 6GG.
4. Faculty of Medicine and Health, University of Leeds and Leeds Teaching Hospitals NHS Trust, Leeds, UK. LS13EX.
5. TPP House, Leeds, UK. LS18 5PX.

Corresponding author email j.sandoe@leeds.ac.uk, tel

Running title – Penicillin allergy records: prevalence and impact

Abstract

Background. The prevalence of reported penicillin allergy(PenA) and the impact these records have on health outcomes in the UK general population are unknown. Without such data, justifying and planning enhanced allergy services is challenging.

Objectives. Determine:1) prevalence of PenA records; 2) patient characteristics associated with PenA records; 3) impact of PenA records on antibiotic prescribing/health outcomes in primary care.

Methods. Cross sectional/retrospective cohort studies using patient-level data from electronic health records. Cohort study: exact matching across confounders identified as affecting PenA records. Setting: English NHS general practices between 1st April 2013 and 31st March 2014. Participants: 2.3 million adult patients. Outcome measures: prevalence of PenA; antibiotic prescribing, mortality, methicillin resistant *Staphylococcus aureus*(MRSA) infection/colonisation, *C. difficile* infection.

Results. PenA prevalence: 5.9% (interquartile range,3.8-8.2%). PenA records were more common in older people, females, those with co-morbidity and were affected by General practitioner (GP) practice. Antibiotic prescribing varied significantly: penicillins were prescribed less frequently in those with PenA record (relative risk (RR)0.15), macrolides(RR4.03), tetracyclines(RR1.91) nitrofurantoin(RR1.09), trimethoprim(RR1.04), cephalosporins(RR2.05), quinolones(RR2.10), clindamycin(RR5.47) and total number of prescriptions were increased in patients with PenA record. Risk of: re-prescription of a new antibiotic class within 28 days(RR 1.32); MRSA infection/colonisation(RR1.90), and; death during the year subsequent to 1st April 2013 increased(RR1.08) in those with PenA records.

Conclusions. PenA records are common in the general population and associated with increased/altered antibiotic prescribing and worse health outcomes.

Clinical implications: We estimated incorrect PenA records affect 2.7 million people in England. Establishing true PenA status (e.g. oral challenge testing) would allow more people to be prescribed first-line antibiotics potentially improving health outcomes.

49

Introduction

Many patients have a record of penicillin allergy (PenA),[1,2,3,4] but, when formally tested, only a small proportion are found to have a true PenA.[1,5,6] "False" PenA labels can arise for a number of reasons, including skin reactions to the penicillin that do not constitute a serious allergy risk, adverse effects that have been misclassified as an allergy and misidentification of infection symptoms. When antibiotic treatment is considered necessary, clinicians generally prescribe second-line antibiotic classes for these patients,[7] that may not be as effective, may impact more negatively on antimicrobial resistance and might not be as safe. For example, increased risk of cardiovascular mortality has been reported following therapy with antibiotics often used as alternatives to penicillins clarithromycin,[8] azithromycin,[9,10] and levofloxacin[9] and the risk of MRSA infection is increased following cephalosporin[11,12] clindamycin[13] and fluoroquinolone[12] prescribing. A recent analysis of general practice data has found a significant increased risk of MRSA and *Clostridioides difficile* infection in patients with a PenA record, partly attributed to changes in antibiotic prescribing.[14]

PenA testing is available and reliable, so many patients who are falsely labelled as penicillin allergic could have their status safely reversed. However, PenA testing is available but not commonly carried out in general practice, partly due to GP uncertainty about referral criteria and knowledge about the test.[15] Existing hospital allergy services are unable to meet the current demand for allergy testing.

Precise estimates of the prevalence of PenA records and their impact on the general population in the United Kingdom (UK) are not available. It is unclear the extent to which the worse patient outcomes attributed to PenA might be explained by comorbidity, age, or

75 other factors. If a record of PenA was associated with such increased risks, then
76 confirmation of allergic status in advance of need for antibiotics (a “pre-emptive” strategy)
77 in primary care may have important benefits for these individuals and for antibiotic
78 stewardship.
79
80 To support a “pre-emptive” testing strategy, we set out to: 1) determine the prevalence of
81 PenA in UK general practice records; 2) establish patient characteristics associated with a
82 recorded PenA and; 3) investigate the impact on antibiotic prescribing decisions and
83 health outcomes.
84

Methods

Ethics approval

The study was approved by the School of Medicine Research Ethics Committee, University of Leeds(REF:SoMREC/13/101). The protocol/data request also approved by the Project Committee at ResearchOne. *ResearchOne* is a research database that consists of de-identified clinical and administrative data drawn from the electronic patient records of ~6 million patients on SystmOne.[16] ResearchOne has received a favourable opinion from NHS Research Ethics Committee North East–Newcastle and North Tyneside 1 (REF: 11/NE/0184) and an opinion from the National Information Governance Board and Secretary of State for Health that no recommendation of support for Section 251 approval is required as there is no disclosure of identifiable data (National Research Ethics Service Research Ethics Committee North East REC reference number 11/NE/0184).

Study Design

This study comprised three parts:

(1) Cross-sectional study of adult patients in ResearchOne based on their electronic health records at 1st April 2013. Aim: to identify factors associated with the record of a PenA, allowing for clustering within practice.

(2) Retrospective cohort study with patients matched by the factors identified in Part 1. Patients were followed for one year until 31st March 2014 to establish the associated impact of a PenA record on several health outcomes.

(3) A retrospective cohort study which included only patients prescribed at least one antibiotic during the study year 1st April 2013 to 31st March 2014. Patient cohorts with and without PenA record were matched by the factors identified in Part 1.

Setting and source data

Data comprised an extract from NHS general practices in England whose routine clinical data was included in ResearchOne at 29th June 2016. ResearchOne has been mainly used in quality improvement research and to develop a frailty index.[17] Patient records included historical contributions from 400 general practices. The one-year study period began 1st April 2013. Matched case control studies used a subset of the extract.

Participants

All adults (18-100 years old) with records on ResearchOne at the date of extraction. Eligible patients included those that had died since 1st April 2013. Patients over 100 years of age were excluded to reduce the risk of inadvertent identification.

Variables

Variables included: PenA records and antibiotic prescriptions from the following classes: penicillins, cephalosporins, clindamycin, macrolides, tetracyclines, nitrofurantoin, trimethoprim, quinolones, carbapenems and aztreonam; date of prescription and all prescriptions of drugs within the period 1st April 2013 to 31st March 2014. Additional variables included: age, gender, date of death, index of multiple deprivation (IMD),[18] smoking status and practice identifier (anonymised). The IMD is the official measure of relative deprivation for neighbourhoods in England. England can be divided into 32,844 neighbourhoods each with around 1500 residents (650 households) and these are ranked from 1 (most deprived area) to 32,844 (least deprived) based on an aggregated measure of seven dimensions of deprivation.[18] It is common practice to use the fifths of deprivation to give a summary of the deprivation where patients live, moving from the most deprived 20% through to the most affluent 20%. Comorbidities were included where data are routinely collected and where an impact on antibiotic prescribing or outcome from antibiotic

prescribing might be anticipated. Clinical codes for these comorbidities were determined using the business rules defined in the NHS Quality Outcomes Framework (QOF).[19] These included: cancer, coronary heart disease (CHD), chronic kidney disease (CKD), COPD, peripheral arterial disease (PAD), asthma, diabetes, stroke, and transient ischaemic attack (TIA). Any new record of the following pathogens during the year of study was extracted: *C. difficile*, VRE, and MRSA; no attempt was made to distinguish colonisation from infection. Codes used were READ Codes (Version 3) - CTV3[20] and those used for the data extract are shown in appendix 1; if any of these codes were present, the variable was considered to be present, otherwise they were considered to be not present.

PenA records were defined using READ codes specified by the research team. Patients were considered to have PenA record if they had either a record of "sensitivity" or "allergy" to any penicillin class antibiotic agent (amoxicillin, ampicillin, penicillin V and G, flucloxacillin, piperacillin) recorded in their electronic health records on 1st April 2013. We combined allergy and sensitivity records because these terms are often used interchangeably.[1]

Health Outcomes

We ascertained if there was a record of a prescription of a subsequent antibiotic of a different class in the 28 days following the prescription of an index antibiotic agent; this has been used previously as a proxy marker of 'lack of treatment response'.[21] Mortality and healthcare associated infection (MRSA, *Clostridioides difficile* infection (CDI) and VRE) at any time during the one year study period were included as additional health outcomes.

Selection Bias

Data for all patients available on ResearchOne who fulfilled the inclusion criteria were used for the analyses.

Sample size

The sample comprised data for all patients on ResearchOne who fulfilled inclusion criteria. We estimated a population of 2 million with a prevalence of 10% would yield an estimate of prevalence with a standard error of 0.02%.

Statistical methods (including quantitative variables)

Part 1: Cross sectional study

Adjusted and unadjusted OR were calculated from cross tabulation of PenA records with potential factors affecting these records, and 95% CI reported. For convenience, continuous variables (age, GP practice list size and area deprivation (IMD) were categorised. This reduced the risk of inadvertent identification further during analysis, enabled handling of non-linear effects, and made interpretation of results easier. Adjusted OR were calculated from a logistic regression model which included a random intercept term to account for clustering of patients within general practice. The intra-class correlation coefficient is reported to enable the assessment of clustering.

Part 2: Retrospective cohort study for associated health impacts

Two patient cohorts were formed according to the PenA records at 1st April 2013 and patients in the cohort with a penicillin allergy record were then exact matched to patients in the cohort without a PenA record. Exact matching was undertaken according to the factors identified in Part 1: age, sex, ethnicity, IMD, comorbidities: asthma, cancer, CHD, CKD,

185 COPD, diabetes, PAD, smoking, stroke, TIA, and the proportion of patients with PenA
186 record within the general practice. Any continuous variables were finely categorised to
187 allow the exact matching process. All patients in the PenA cohort were then matched,
188 according to all the factors above; multiple subclasses were formed which differed only in
189 their PenA status. This meant that each PenA patient could be matched to multiple
190 patients without a PenA record, who shared the same characteristics. Practices were also
191 categorised according to the percentage of patients within them with a PenA record, and
192 these categories were used in the exact matching as an additional factor. Following
193 matching, each binary outcome, MRSA, *C. difficile*, 1-year mortality, was modelled within a
194 binomial model using a log link and including all of the matching factors as covariates as
195 well as PenA record. This is the currently recommended approach, which demands the
196 controlling of factors even after matching.[22] RR was reported from exponentiated
197 coefficients along with 95% CI. The number of antibiotic prescriptions was modelled as a
198 negative binomial regression with the same set of covariates. The incidence RR was
199 calculated by exponentiating the coefficients. Patients were only counted once in this
200 analysis. A propensity score matched model was used for a sensitivity analysis.
201
202 Part 3: Retrospective cohort study for antibiotic prescribing
203 A subset comprising all patients prescribed at least one antibiotic in the year 1/4/2013-
204 31/3/2014 was used because only those having an infection requiring antibiotic treatment
205 were considered with respect to type of antibiotic prescribed. Exact matching using the
206 method of Part 2 was applied to the subset. Outcomes of interest were the prescription of
207 specific antibiotic classes and were modelled by a binomial model with a log link function.
208 Then exponentiated coefficients gave the RR of each antibiotic class. A value of the RR
209 risk greater than 1.000 meant that, according to the fitted model, the antibiotic class was

more likely to be prescribed to those with a PenA record than those without, after controlling for age, sex, ethnicity, IMD, smoking status, comorbidities (asthma, cancer, CHD, CKD, COPD, diabetes, PAD, stroke, TIA), and the proportion of patients with PenA record within the general practice.

Results

Participants

2,350,803 adult patients met inclusion criteria and comprised the initial population for cross sectional analysis (Tables 1 and 2).

Prevalence of penicillin allergy records.

139,437 patients had a PenA record, giving a prevalence for the population of 5.9% (95% CI5.9-6.0%).

Characteristics of patients with a penicillin allergy record.

Women were more likely to have a recorded PenA, even after adjustment for possible confounders (Table 1). The prevalence increased significantly with increasing age (Table 1). Rates of PenA varied considerably by general practice (IQR 3.8-8.2%); from the random intercept term, the calculated intra-class correlation (ICC) revealed that 7.2% of the variation in PenA records could be attributed to general practice. After adjustment, IMD status had a small but significant impact, and with more affluent patients more likely to have a record of allergy. The exception was patients with 'unknown' IMD status, which was associated with lower odds of a record of PenA; IMD status was not available for 11.1% of patients. The selected comorbidities were all associated with small but significantly increased odds of having a PenA record, with asthma having the highest (Table 2).

Exact matching

Part 2: 130,571 of 139,437 patients with a record of PenA were matched with 1,892,835 of 2,211,366 patients. Exact matching results are shown in Table 3. Part 3: For those

patients treated with an antibiotic, 45,831 with a record of PenA were matched with 409,687 patients with no record.

Penicillin allergy records and antibiotic prescribing

In the exact matched analysis, patients with a PenA record received approximately 5% more antimicrobial prescriptions than those without a PenA record during the 12-months follow-up (Table 3). Macrolides, tetracyclines, cephalosporins, quinolones, clindamycin, nitrofurantoin and trimethoprim were all prescribed significantly more frequently in patients with a PenA record (Table 4). As expected, carbapenems and aztreonam were prescribed infrequently. Antibiotic prescribing patterns in the total population are shown in Tables S1 and S2.

Penicillin allergy record and health outcomes

Compared to patients without a PenA record, those with a record had significantly increased risk of: death in the following year; re-prescription of a new antibiotic class within 28 days and MRSA infection/colonisation (Tables 3, 5 and S3). A PenA record was associated with 6 in 1000 more deaths and 1 in 1000 more patients with MRSA. There was a non-statistically significant increase in risk of CDI. There were only two patients with VRE records and these were not analysed further. The propensity score matched sensitivity analysis found equivalent results (data not shown).

Discussion

Key results

A record of PenA affected 1 in 17 general practice patients, with considerable variation between practices. PenA records were associated with increasing age, being female, and co-morbidity. After matching for demographic factors and co-morbidities, a PenA record was associated with more antibiotic prescriptions, a different profile of antibiotic prescribing, a higher rate of re-prescription of a new antibiotic class within 28 days, greater MRSA burden and increased risk of death. There was little evidence of an impact on CDI, when confounding factors were taken into consideration.

Strengths and weaknesses

Use of routinely collected clinical data carries risk of bias, but exact matching was used to reduced this. Such studies are affected by data quality, so we purposefully chose conditions that are included in QOF because they are linked to health services payments and likely to be consistently and well recorded across general practices. There may be conditions that affect PenA recording that we have not included. The main concern with the use of exact matching is bias due to lack of matches; in this study the matching rate was very high (94%), minimising risk of bias due to lack of matches.

Drug reactions can be recorded in different ways on SystmOne, and hence appear in ResearchOne, as either “sensitivities” or “allergies” so they were considered interchangeable in the analysis. This might be an over-simplification, but from GP stakeholder consultations and literature these terms seemed to be used interchangeably.[23] In addition, when patients move to a new GP there is a potential problem with the

286 correctness and completeness of the data migration process between GP systems with
287 respect to recorded allergies and sensitivities. For example, migration might omit
288 sensitivities, or might import at a coarser granularity. The more patient records move
289 between practices, the more they are subject to any issues associated with these
290 migration processes. IMD was not recorded in 11% of patients and this was associated
291 with a lower rate of PenA records; we think that this may relate to patients whose
292 postcodes were missing, invalid or newly assigned, or patients without a permanent
293 residence but it is possible that it reflects generally poor record keeping. While this might
294 result in an underestimate of the overall prevalence of PenA records it did not affect the
295 exact matching analysis.
296
297 We did not standardise the counting of antibiotic prescriptions to average daily quantities
298 (ADQs) but we were primarily concerned with choice of agent in this analysis, rather than
299 dose-related effects. Methods of testing for, diagnosing, and communicating MRSA and *C.*
300 *difficile* infection vary between laboratories, but we could not see any reason why this
301 would have a selective effect on either our patient groups. We know that there is
302 inconsistency and a lack of consensus on what information is transferred from hospital
303 records to general practice electronic health records. For this reason, we also collected all
304 MRSA positive results and did not attempt to distinguish between MRSA colonisation and
305 infection.
306
307 *ResearchOne* data are likely to be representative of the general population because they
308 came from a large number (400) of general practices in England. The similarity of our
309 findings when compared with recent data from The Health Improvement Network (THIN)[14]

provides important validation of the use of these clinical databases in applied research, as these databases derive from different electronic health record systems.

Prevalence of penicillin allergy records

An allergy to penicillin has previously been reported in 4.5-15.6% of patients, depending on location and population, but none of these studies were a based on a general adult population.[1,2,3,4,24,25] Our estimate of prevalence is lower than the National Institute of Health and Care Excellence (NICE) estimate of 10%[1] probably because hospital patients are enriched for those with co-morbidites. The observed variation in recording of PenA between general practices, raises the possibility of under recording and therefore an underestimate of its prevalence. There are differences in the reported prevalence of PenA between the United States of America (US), which generally reports prevalence of over 10%,[2,3,24] and the UK and Europe where a lower prevalence has been reported,[4,25] but these studies were generally small (single institution) or undertaken in select patient groups. The importance of this figure lies in the number of patients who are likely to have a true allergy to penicillin; probably fewer than 10% of those with an record of PenA.[1] With a 5.9% prevalence of PenA records, an estimated 3 million UK adults are affected.

Patient characteristics associated with a penicillin allergy record

Older women with co-morbidities were more likely to have a PenA record, while area deprivation (IMD) was associated with a reduced risk. General practice list size also had an effect, with increased records in medium size practices. Studies that explore the health impacts of penicillin records clearly need to account for these confounding factors. All the factors identified increase the possibility of being prescribed an antibiotic and, presumably,

335 the chance of having a reaction that is recorded as an allergy or sensitivity. All the selected
336 comorbidities that we felt were likely to impact on infection risk were associated with a
337 small but significant increased risk of a PenA record. Our assumption of increased
338 infection risk was borne out by higher rates of all antibiotic prescriptions in patients with all
339 the selected conditions (data not shown).
340
341 *Effects on antibiotic prescribing*
342 Even after matching for age, sex, IMD, smoking and comorbidities (asthma, cancer, CHD,
343 CKD, COPD, diabetes, PAD, stroke, TIA) and prevalence of PenA records at the general
344 practice, a PenA record was associated with altered and increased antibiotic prescribing.
345 In keeping with previous mainly hospital-based studies, macrolides and tetracyclines were
346 the most commonly prescribed antibiotics for patients with a PenA record,[26] while the
347 biggest impact (increase in relative risk) of the record was on clindamycin, tetracyclines
348 and quinolones, similar to a recent primary care-based analysis from the Netherlands,
349 which also found patients with a PenA record had a higher likelihood of receiving more
350 than one antibiotic prescription (OR 2.56, 95% CI 2.05–3.20).[7] This raises questions about
351 the relative clinical effectiveness of non-penicillins and the possibility that patients with a
352 PenA record receive less effective agents with more treatment failures. An alternative
353 explanation is that patients with a PenA record are more prone to infection and also
354 treatment failure. We attempted to account for this by controlling for comorbidities that are
355 associated with an increased risk of infection but the increased rate of antibiotic
356 prescribing remained. Trimethoprim and nitrofurantoin prescribing were included as a
357 reference point because we initially thought these would not be affected by PenA status.
358 The small but significant increase of trimethoprim RR might be accounted for by use in
359 infections other than urinary tract infection (e.g. respiratory tract infections[21]) in patients

with a PenA record. Higher rates of nitrofurantoin prescribing in patients with a PenA record may indicate health seeking behaviour.

Effects on health outcomes

The observed increase in all-cause mortality in patients with a PenA record, even after matching for age, gender and comorbidity was surprising given the low mortality from infections managed in general practice. Increased mortality has been described previously in a US hospital-based study which found a 1.6-fold higher risk of dying during hospitalisation associated with a PenA record (crude OR 1.56, 95% CI 1.20-2.04),[27] and it has been suggested that a PenA record might result in suboptimal therapy, particularly for hospitalised patients, where for example, penicillins are considered treatment of choice for *Staphylococcus aureus* bloodstream infection.

Healthcare associated infection pathogens.

MRSA and CDI rates were low as would be expected in a general practice population but the risk of MRSA colonisation/infection was higher among those with a PenA record. There were no records of VRE, confirming this as a pathogen whose relevance is currently restricted to secondary care. A recent study using THIN, a UK electronic health record database of general practice patients, also found an increased risk of MRSA in patients with a PenA of similar magnitude (multivariable adjusted hazard ratio 1.69).[14] In the US, penicillin allergic hospital patients were found to have 23.4% (95% CI, 15.6% to 31.7%) more *C. difficile*, 14.1% (95% CI, 7.1% to 21.6%) more MRSA, and 30.1% (95% CI, 12.5% to 50.4%) more VRE infections than expected compared with control subjects.[3] Many factors affect the risk of MRSA infection, including antibiotic prescribing practices.[28] Observational studies show an association between MRSA colonisation/infection and

various classes of antibiotics:-cephalosporins,[11,12] carbapenems,[13] clindamycin[13] and fluoroquinolones,[12] so there is a plausible, potential mechanism for the increased risk. The THIN analysis found that half the increased risk of MRSA was mediated through fluoroquinolone, clindamycin and macrolide prescribing. While we saw a non-statistically significant increased risk of CDI in patients with a PenA (RR 1.22), the THIN analysis found a significantly increased risk of CDI (adjusted hazzard ratio 1.26), perhaps because of the longitudinal nature of that study allowing longer follow-up for each patient.[14]

Penicillin prescribing

Patients who report a PenA are not usually prescribed penicillins[5] so finding that nearly 1 in 25 patients with a PenA record had been prescribed a penicillin, subsequent to the date of their allergy record, was unexpected. Possible explanations include: Data entry errors or GPs consciously “over-ruling” PenA alerts, perhaps because a patient may have an allergy to a specific agent but can tolerate other penicillins. Re-prescription of a new antibiotic class within 28 days was associated with a PenA record, this has been used a marker of treatment response failure in some studies but there are other explanations why this may have occurred, for example, it is possible that patients returned when they noticed a penicillin had been prescribed, or experienced an adverse reaction, or were non-compliant.

Conclusions

The prevalence of PenA records in adults in general practice suggests there are three million affected patients in the UK. Identifying patients without a current PenA (e.g. by a pre-emptive penicillin allergy testing strategy) has the potential to improve antibiotic prescribing, enabling more patients to receive first line therapy for infections. This

antimicrobial stewardship strategy has potential to improve clinical outcomes and help contain antibiotic resistance. Current services are unlikely to cope with the increased demand that additional testing would require so service provision needs to be reviewed; a safe streamlined testing pathway is under evaluation* to avoid over-burdening the existing allergy service.

Conflicts of Interest

C Bates is employed by TPP, the company that owns SystmOne electronic health record system. CC Butler is a NIHR Senior Investigator . None of the other authors have any conflicts of interest to declare.There are no other relationships or activities that could appear to have influenced the submitted work..

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Characteristic	Penicillin allergy record	No penicillin allergy record	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Overall count	139,437 (5.9%)	2,211,366		
Gender				
Male	51,754 (4.4%)	1,115,192	1.00 (Ref.)	1.00
Female	87,683 (7.4%)	1,096,157	1.72 (1.70-1.74)	1.72 (1.70-1.74)
Age				
18–24	10,160 (4.0%)	245,248	1.00	1.00
25–34	17,611 (4.3%)	390,920	1.09 (1.06-1.11)	1.10 (1.07-1.13)
35–44	22,321 (5.7%)	373,061	1.44 (1.41-1.48)	1.42 (1.38-1.45)
45–54	25,760 (6.2%)	392,976	1.58 (1.55-1.62)	1.49 (1.45-1.54)
55–64	22,205 (6.5%)	318,181	1.68 (1.64-1.73)	1.50 (1.46-1.53)
65–74	20,338 (7.2%)	263,051	1.87 (1.82-1.91)	1.50 (1.46-1.54)
75–100	21,042 (8.5%)	227,929	2.23 (2.17-2.28)	1.59 (1.55-1.64)
IMD (fifths)				
Most deprived	22,075 (5.3%)	396,076	1.00	1.00
Deprived	24,618 (5.9%)	393,822	1.12 (1.10-1.14)	1.04 (1.02-1.06)
Average	27,993 (6.7%)	389,731	1.29 (1.27-1.31)	1.07 (1.05-1.09)
Affluent	27,380 (6.6%)	390,678	1.26 (1.23-1.28)	1.07 (1.04-1.09)
Most affluent	27,178 (6.5%)	390,902	1.25 (1.22-1.27)	1.07 (1.04-1.10)
Unknown	10,193 (3.9%)	250,157	0.73 (0.71-0.75)	Dropped
Practice list size				

0–5,000	15,656 (5.4%)	275,288	1.00	1.00
5,000–9,999	52,556 (5.9%)	834,541	1.11 (1.09-1.13)	1.05 (0.98-1.12)
10,000–14,999	49,688 (6.3%)	739,903	1.18 (1.16-1.20)	1.17 (1.08-1.26)
15,000–19,999	15,037 (6.2%)	229,617	1.15 (1.13-1.18)	1.19 (1.05-1.34)
20,000–75,000	6,285 (4.6%)	129,614	0.85 (0.83-0.88)	0.99 (0.84-1.17)
Unknown	215 (8.2%)	2,403	1.57 (1.37-1.81)	Dropped

Table 1. Characteristics of patients with and without a penicillin allergy record in a sample of antibiotic treated general practice patients in England. *The adjusted analysis was undertaken with complete cases only, that is those with complete data for all covariates; IMD, index of multiple deprivation.

Condition	Penicillin allergy record	No penicillin allergy record	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
No conditions	43,199 (4.6%)	886,940	1.00	1.00
1 condition	58,041 (5.9%)	929,994	1.28 (1.27-1.30)	-
2 conditions	24,226 (8.1%)	275,509	1.81 (1.78-1.84)	-
3 or more	13,971 (10.5%)	118,923	2.41 (2.36-2.46)	-
Asthma	25,052 (8.9%)	255,637	1.68 (1.65-1.70)	1.58 (1.56-1.61)
Cancer	9,827 (8.9%)	100,723	1.59 (1.56-1.62)	1.18 (1.15-1.21)
CHD	8,845 (9.1%)	88,748	1.62 (1.58-1.66)	1.23 (1.20-1.26)
CKD	11,228 (9.5%)	106,585	1.73 (1.69-1.76)	1.18 (1.15-1.21)
COPD	8,130 (10.7%)	67,587	1.96 (1.92-2.01)	1.41 (1.37-1.45)
DM	11,280 (8.1%)	127,784	1.44 (1.41-1.46)	1.18 (1.16-1.21)
PAD	1,647 (9.5%)	15,712	1.67 (1.59-1.76)	1.16 (1.10-1.22)
Smoker	74,720 (6.5%)	1,078,500	1.21 (1.20-1.23)	1.11 (1.10-1.13)
Stroke	2,782 (9.2%)	27,591	1.61 (1.55-1.68)	1.15 (1.11-1.20)
TIA	2,437 (9.8%)	22,328	1.74 (1.67-1.82)	1.19 (1.13-1.24)

Table 2: Counts, percentages and odds ratios of penicillin allergy record compared to patient disease registration. *The adjusted analysis was undertaken with complete cases only, that is those with complete data for all covariates. The analysis adjusted for all

variables listed in tables 1 and 2. CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; TIA, transient ischaemic attack; PAD, peripheral arterial disease.

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	Relative risk	95% CI	p
Antibiotic prescribing			
Any antibiotic	1.05	1.04-1.06	<0.001
Health outcomes, absolute number (%)			
Mortality	1.08	1.03-1.14	0.002
CDI	1.22	0.80-1.87	0.359
MRSA	1.90	1.50-2.41	<0.001

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546 Table 3: Health outcomes in the exact-matched cohort of general practice patients, with
547 (n= 130571) and without (n= 1,892,835) a record of penicillin allergy. CDI, *Clostridioides*
548 *difficile* infection. MRSA, Methicillin resistant *Staphylococcus aureus*; aHR, adjusted
549 hazard ratio.

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	Relative risk	95% Confidence interval	p
Antibiotic			
Clindamycin	5.47	4.83-6.20	<0.001
Macrolide	4.03	3.99-4.08	<0.001
Quinolone	2.10	2.02-2.19	<0.001
Cephalosporin	2.05	1.99-2.12	<0.001
Tetracycline	1.91	1.88-1.94	<0.001
Nitrofurantoin	1.09	1.07-1.11	<0.001
Trimethoprim	1.04	1.03-1.06	<0.001
Penicillin	0.15	0.14-0.15	<0.001
Carbapenem	-	-	-
Monobactam	-	-	-
Health outcomes			
Re-prescription of a new antibiotic class within 28 days	1.33	1.31-1.35	<0.001

552 Table 4: Antibiotic prescribing patterns in an exact-matched cohort of general practice
553 patients, prescribed antibiotics, with and without a record of penicillin allergy.

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Health outcome	Penicillin allergy	No penicillin allergy	P value
	139,437	2,211,366	
Re-prescription of a new antibiotic class within 28 days	10,111 (7.3%)	89,191 (4.0%)	<0.001
Mortality, absolute number (%)	2056 (1.5%)	2,0521 (0.9%)	<0.001
CDI, absolute number (%)	26 (0.0%)	256 (0.0%)	0.027
MRSA, absolute number (%)	95 (0.1%)	674 (0.0%)	<0.001

Table 5. Health outcomes in the total cohort of general practice patients, with and without a record of penicillin allergy. CDI, *Clostridioides difficile* infection. MRSA, Methicillin resistant *Staphylococcus aureus*.

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