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Characteristics, risk factors and clinical impact of penicillin and other antibiotic allergies in adults in the UK General Practice: A population-based cohort study

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SUMMARY

Objective: To assess the characteristics, risk factors and clinical impact of penicillin and other antibiotic allergy labels in general practice in the UK.
Design: Population-based cohort study.
Setting: Primary care in the UK, 2000–2018.
Participants: Adults aged 18–100 years who were registered with their general practice for at least 12 months between 01-Jan-2000 and 31-Dec-2018 and followed until 25-Sep-2019.
Main outcome measures: The main outcomes include the annual prevalence and incidence of penicillin and other antibiotic allergy labels. Multinominal logistic regression was used to examine the characteristics associated with receiving an allergy label to different antibiotics. Cox regression modelling was used to compare the risk of resistant infections (methicillin-resistant *Staphylococcus aureus* [MRSA] and vancomycin-resistant enterococci) as well as *Clostridioides difficile (C.difficile)* infection between patients with and without allergy labels. The monthly proportion of patients who had a penicillin allergy test, either before their allergy label was recorded or within one year, was calculated to assess any impact of NICE penicillin allergy assessment recommendations (Clinical guideline [CG183]) in September 2014.
Results: Both the prevalence and incidence of penicillin allergy label showed a pattern of initial growth followed by a decline. The prevalence reached a maximum of 8.25% in 2011, and the incidence peaked at 0.46% in 2004. Older age, being female, living in less deprived areas, belonging to a larger general practice, and having co-morbidities were associated with a higher chance of receiving a penicillin or other antibiotic allergy label. Patients with antibiotic allergy labels were more likely to receive alternative broad-spectrum antibiotics and had a higher risk of MRSA and *C.difficile* infections. The introduction of NICE drug allergy guideline did not alter the proportion of patients undergoing penicillin allergy assessment.
Conclusion: Penicillin and other antibiotic allergy labels are common and lead to radical change in the antibiotic prescribing practices and are associated with resistant and healthcare associated infections.

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Introduction

There is increasing evidence that a medical record of antibiotic allergy, so called 'allergy label' may not always be accurate or reflective of true allergies.[1–3] An estimated 3 million people have penicillin allergy labels in the UK.[4] National and international recommendations are advocating the use of formal testing to improve the quality of allergy recording,[5–8] but these have not been embedded in routine practice, even for the subset of patients that may have multiple allergies or are likely to require repeat courses of antibiotics due to long terms conditions. The presence of an allergy record has a negative influence on antibiotic prescribing and patient outcomes.[9] A published population-based study has described the prevalence of penicillin allergy and associated risk factors in the UK, but this included one year of data from a single healthcare record provider.[4] This study found that increased age, female sex, comorbidities, size of General Practice (GP), and lower deprivation scores were all associated with a higher risk of penicillin allergy labels, using the prevalence of penicillin allergy rather than the incidence for the analysis. The incidence of penicillin allergy labelling has not been described in the UK. Incidence data are required to plan current and future interventions to reduce inappropriate allergy recording. Assessment of the impact of an allergy label on prescribing in the NHS and health outcomes has been limited by difficulties addressing the problem of confounding by indication.[4,10–13] The National Institute for Health and Care Excellence (NICE) in the UK released a guideline on drug allergy (Clinical guideline [CG183]) in September 2014, which recommended formal allergy assessment under selected circumstances, but the effects of this guideline on allergy records remain unclear.[8]

The aims of this study were 1) to report the incidence and prevalence of penicillin (and other antibiotic) allergy label records among patients in primary care in the UK; 2) to examine the relationship between penicillin and other antibiotic allergy labels and patient characteristics, antimicrobial prescribing, and treatment-related outcomes; and, 3) to investigate the potential impact of NICE penicillin allergy assessment recommendations for GPs and service providers on acquisition of penicillin allergy labels on patient records.

Methods

Data source

A population-based cohort study was conducted using IQVIA Medical Research Data UK (IMRD), which incorporates data from The Health Improvement Network (THIN) database, a Cegedim Health Data database. Reference made to THIN is intended to be descriptive of the data asset licensed by IQVIA. IMRD includes longitudinal, de-identified electronic health records from over 800 UK general practices that use Vision software for electronic health records, representing 6% of the UK population.[14] Data in IMRD are demographically representative of the UK population.[15] Multiple diagnoses and lifestyle variables recorded in the IMRD database have been validated and widely used for pharmacoepidemiological research.[16] This work used de-identified data provided by patients as a part of their routine primary care.

Study population

Source population

The source study population included adults aged 18–100 years who were registered with their GP for at least 12 months between 01-Jan-2000 and 31-Dec-2018. Each individual was observed for antibiotic allergy label records over their observation period, starting from 01-Jan-2000, their 18th birthday, or 12 months after registration with the GP, whichever came later; until 31-Dec-2018, the last data collection date of the practice, date of transfer out of the practice, 101st birthday, or death, whichever came first. Within this population, we calculated the annual incidence and prevalence of penicillin and other antibiotic allergy label records over 2000–2018.

Penicillin population

Patients in the source study population who received a new prescription of penicillin between 2000 and 2018 were included for further comparative analyses on antibiotic allergy status (Fig. 1). A

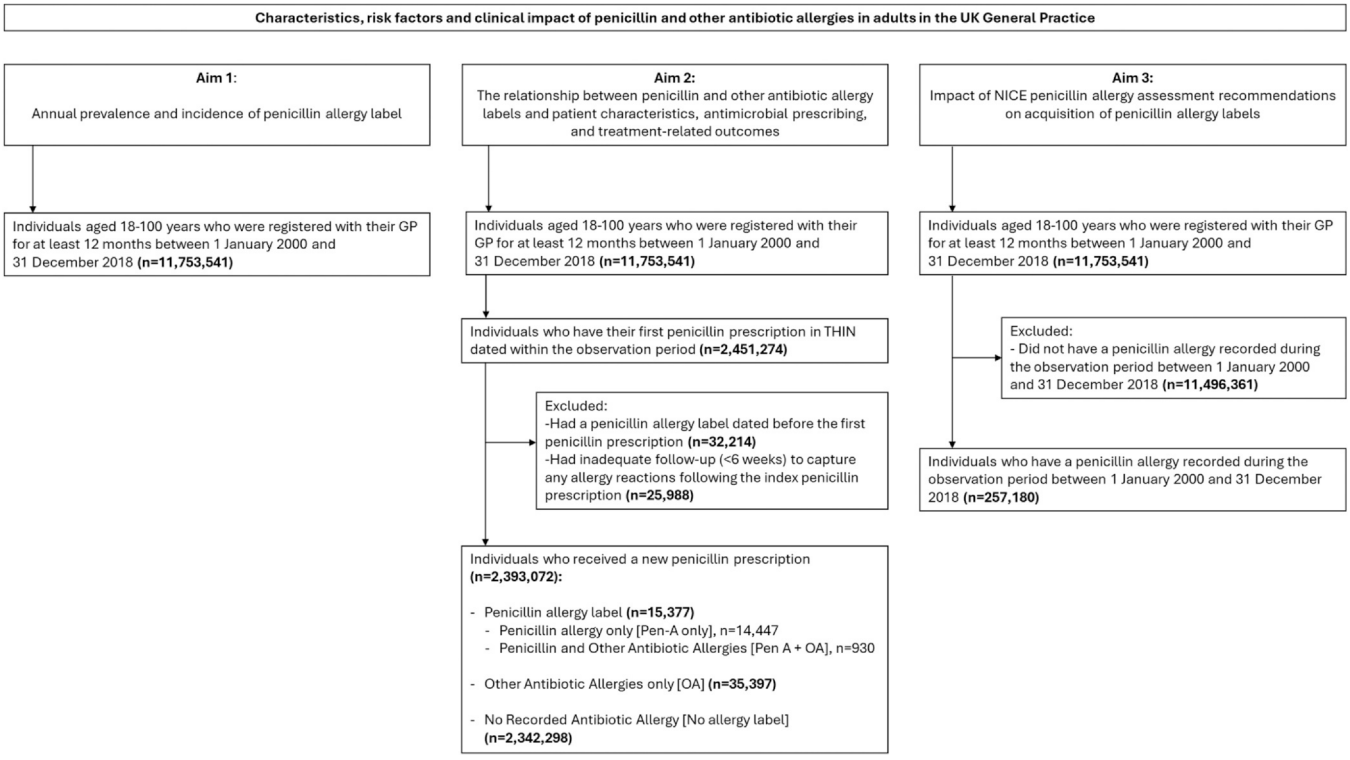

Fig. 1. Selection of study populations (Abbreviations: NICE=National Institute for Health and Care Excellence; IMRD=IQVIA Medical Research Data).

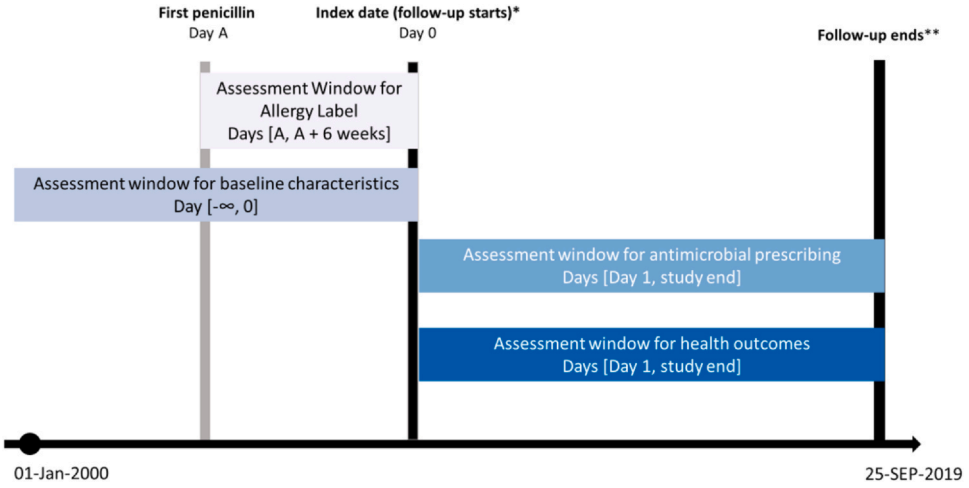

Fig. 2. Study design for comparative analyses. *At the start of follow-up, individuals were classified into having a penicillin allergy label, other antibiotic allergy label, or no allergy label. **Individual follow-up end date was defined as the earliest of 25-SEP-2019, date of which the patient reached 101 years old, death, transfer out of practice, changes in allergy label status, date of last collection of data from practice, or study aim-specific outcomes.

new prescription was defined as the first-recorded prescription of penicillin in the IMRD and was considered the "index penicillin prescription". Patients who had a penicillin allergy label record dated prior to the index penicillin prescription were excluded to ensure the capture of a new allergy reaction to penicillin.

At 6 weeks following the index penicillin prescription, patients were classified into four mutually exclusive groups based on their antibiotic allergy records[1]: those with a penicillin allergy label and without a concurrent allergy label to other antibiotics (Pen-A only)[2]; those with a penicillin allergy label as well as other antibiotics (Pen-A + OA)[3]; those with an allergy label for other antibiotics only (OA only); and[4] those without any antibiotic allergy records (No allergy label). The period of 6 weeks was based on the time to reaction in case of an allergy, as specified in the National Institute for Health and Care Excellence (NICE) guideline.[8] Patients were followed from the date immediately after the 6-week period (the index date) until the occurrence of an outcome, death, transfer out of practice, changes in allergy status, date of last data collection, 101st birthday, or study end (25-Sep-2019), whichever came first (Fig. 2).

Variables and measures

Allergy label records

Penicillin and other antibiotic allergy records were identified using read codes (Supplemental Table 1) and prescription-linked drug allergy records (Supplemental Table 2). Patients were considered to have penicillin or antibiotic allergy labels if they had any record of sensitivity, intolerance or anaphylaxis attributed to any penicillin (which included amoxicillin, ampicillin, penicillin V and G, flucloxacillin, piperacillin) and other antibiotic agents recorded in their electronic health record.

Variables for comparative analyses

Patient characteristics and indications for antibiotic use

Age, sex, index year, and comorbidities (asthma, smoking, cancer, diabetes, coronary heart disease, chronic obstructive pulmonary disease (COPD), stroke/transient ischaemic attack, chronic kidney disease, and peripheral arterial disease, identified using read codes[17,18] recorded any time before or on the index date were used to measure patient characteristics. The diagnoses recorded on the date of antibiotic prescription were retrieved to infer the possible indications for the antibiotic use, which are not directly recorded in the database. We identified the diagnoses for the common infection indications spanned the respiratory system, skin and wounds, urogenital tract, dental/mouth, gastro-intestinal system, eye, cardiovascular system, musculoskeletal system, cancer, prophylactic therapy, central nervous system, and miscellaneous, using read codes developed in previous studies.[17,18]

Outcome

Prescribing patterns of antibiotics (numbers of prescriptions), as well as treatment-related outcomes, were compared between different antibiotic allergy statuses. Treatment-related outcomes included *Clostridioides difficile* (*C. difficile*), methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE), identified using read codes.[19]

Statistical analysis

Incidence and prevalence of penicillin allergy

For each patient, the incidence of penicillin allergy was calculated by dividing the total number of the first-recorded penicillin allergy dated in a particular year by the total number of patients in IMRD in that particular year. The prevalence was calculated as the total number of patients who had received a penicillin allergy label record by the end of a particular year divided by the total number of patients in IMRD in that particular year (Fig. 1). We repeated the analyses for other antibiotic allergies.

Comparative analysis

Patient characteristics, prescribing patterns, and treatment-related outcomes were compared between patients with different antibiotic allergy statuses (Fig. 2).

Patient characteristics associated with allergy statuses

Descriptive statistics were used for reporting patient characteristics at the index date across four groups. Practice size and area-level measurement of socioeconomic status (Townsend scores) were also described. Multinominal logistic regression was used to identify any factors associated with receiving specific antibiotic allergy statuses, in terms of odds ratios and 95% confidence intervals (CIs).

Antibiotic prescribing patterns

For prescribing patterns, the groups of patients with an allergy record to penicillin only (Pen-A only) and those with a penicillin as well as other antibiotic allergy records (Pen-A + OA) were combined due to the low number of patients in the latter group. Zero-inflated

negative binomial regression model was used to estimate the incidence rate ratios (IRRs) comparing the number of specific antibiotic prescriptions between the three comparison groups (patients with a penicillin allergy label, other antibiotic allergy record, and without any antibiotic allergies recorded), adjusted for age, sex, index year, comorbidities, and indication for index penicillin prescription.

Additional analyses were conducted to investigate the impact of allergy labels on the likelihood of receiving specific types of antibiotics, among patients who experienced an infection commonly treated with penicillin. Patients who experienced an infection event related to the respiratory system, skin and wounds, and urogenital tract, all of which are the top three most common indications for penicillins, during follow-up were included in the analyses. Logistic regression model was used in which the dependent variable was having prescribed the specific antibiotic on the date of infection (yes/no), adjusted for age, sex, index year, and comorbidities at infection date.

For the treatment-related outcomes of *C. diff*, MRSA and VRE, we used Cox regression model to compare the risk of the outcomes between the three groups, adjusted for age, sex, index year, comorbidities, and indication for index penicillin prescription. In all analyses, a two-sided p-value < 0.05 was considered as statistically significant. Statistical Analysis System® v9.4 (SAS Institute Inc., Cary, North Carolina) was used for conducting statistical analyses.

Impact of NICE penicillin allergy assessment recommendations

A descriptive analysis was conducted to describe the proportion of patients who had a penicillin allergy test (Supplemental Table 3) recorded before or within one year after they received an allergy record, in order to investigate the potential impact of NICE penicillin allergy assessment recommendations on clinical practice (Clinical guideline [CG183]) in September 2014. A one-year time frame was selected to allow time between suspected penicillin allergy and formal referral and testing for penicillin allergy in specialist clinics. Patients who received a penicillin allergy label between 2000 and 2018 were included (Supplemental Figure 1). The proportion was calculated for each month using the formula below.

$$\frac{\text{Number of patients who received 1) a penillin allergy record in that month; and 2) a penicillin allergy test dated any time before or within 1 year after the allergy record}}{\text{Number of patients who received a penicillin allergy label in that month}} \times 100\%$$

Results

Patient characteristics

There were 11,753,541 adults aged 18–100 years who were registered with their GP for at least 12 months between 01-Jan-2000 and 31-Dec-2018. Of these, 2,393,072 patients were identified as having received a new penicillin prescription during the study period of 2000–2018, 15,377 patients with a new penicillin allergy label, 35,397 with recorded allergies to other antibiotics, and 2,342,298 with no allergy recorded (Fig. 1). The characteristics of patients are presented in Table 1.

Incidence and prevalence

The incidence of penicillin allergy label records gradually increased from 0.22% in 2000 to 0.46% in 2004, and then decreased over the following ten years to 0.2% and remained below this level until 2018 (Fig. 3). A gradual increase was noted in the prevalence from 4.77% in 2000 to a peak of 8.25% in 2011, and then reduced to 7.59% by 2018 (Fig. 3). A similar trend, but with lower proportions, was seen for records of other antibiotic allergies (Supplemental Table 4). The prevalence of allergy label records followed a similar trend as the proportion of any antibiotic prescriptions (Supplemental Figure 1 and Tables 4 and 5).

Patient factors, antibiotics prescribing, and outcomes associated with allergy records

Older, female patients, those from less deprived areas (lower Townsend score), those from larger GP practices and those with co-

Table 1
Patient characteristics at baseline.

Characteristics	Pen-A only (N=14,447)	Pen-A and OA (N=930)	OA only (N=35,397)	No allergy label (N=2,342,298)
Age in years, mean (SD)	53.5 (19.5)	58.2 (19.6)	53.7 (18.8)	48.7 (18.5)
Sex, female	8669 (60.0)	716 (77.0)	27,379 (77.3)	1,215,116 (51.9)
Townsend scores				
1 (least deprived)	3119 (21.6)	224 (24.1)	8036 (22.7)	442,918 (18.9)
2	2788 (19.3)	169 (18.2)	7258 (20.5)	414,967 (17.7)
3	2613 (18.1)	177 (19.0)	6534 (18.5)	412,190 (17.6)
4	2081 (14.4)	144 (15.5)	5125 (14.5)	359,971 (15.4)
5 (most deprived)	1367 (9.5)	81 (8.7)	2966 (8.4)	249,605 (10.7)
Unknown	2479 (17.2)	135 (14.5)	5478 (15.5)	462,647 (19.8)
Practice size				
0–4999	1226 (8.5)	77 (8.3)	3181 (9.0)	264,251 (11.3)
5000–9999	4863 (33.7)	307 (33.0)	12,112 (34.2)	827,179 (35.3)
10,000–14,999	5046 (34.9)	325 (34.9)	12,595 (35.6)	792,703 (33.8)
15,000–19,999	2112 (14.6)	137 (14.7)	4765 (13.5)	294,207 (12.6)
20,000 or above	1200 (8.3)	84 (9.0)	2744 (7.8)	163,958 (7.0)
Medical conditions				
Asthma	1641 (11.4)	154 (16.6)	5154 (14.6)	242,635 (10.4)
Smoker	1627 (11.3)	94 (10.1)	3388 (9.6)	241,894 (10.3)
Cancer	961 (6.7)	88 (9.5)	2678 (7.6)	113,641 (4.9)
Diabetes	1015 (7.0)	82 (8.8)	2222 (6.3)	127,336 (5.4)
Coronary heart disease	918 (6.4)	73 (7.8)	2280 (6.4)	120,902 (5.2)
COPD	315 (2.2)	30 (3.2)	817 (2.3)	37,633 (1.6)
Stroke/transient ischaemic attack	438 (3.0)	47 (5.1)	1171 (3.3)	54,348 (2.3)
Chronic kidney disease	717 (5.0)	64 (6.9)	1814 (5.1)	57,706 (2.5)
Peripheral arterial disease	190 (1.3)	17 (1.8)	393 (1.1)	22,151 (0.9)

Values are presented as N (%) unless otherwise specified. Abbreviations: Pen-A=penicillin allergy; OA=other antibiotic allergy; SD, standard deviation; COPD, chronic obstructive pulmonary disease.

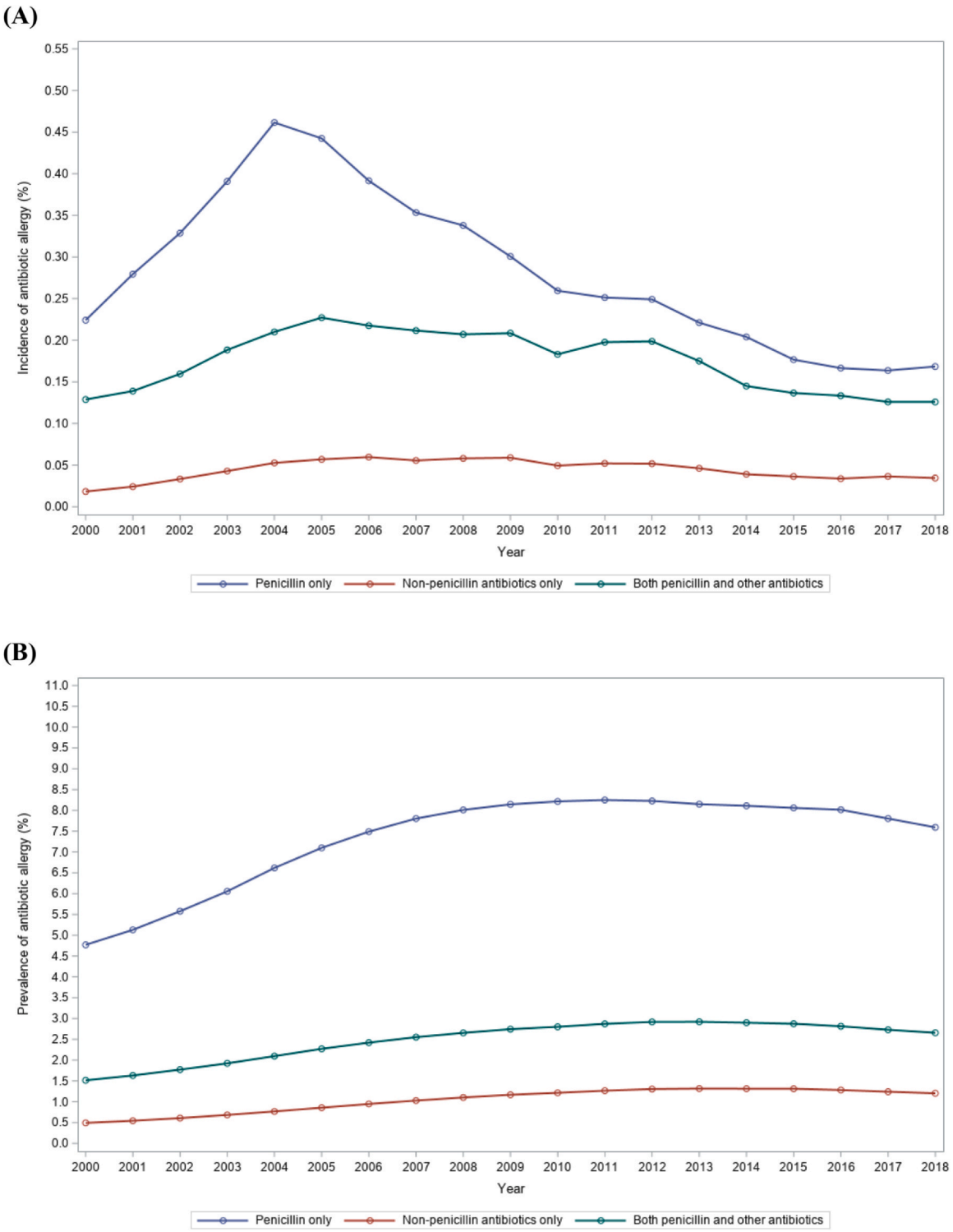

Fig. 3. Incidence (A) and prevalence (B) of people who received a record of antibiotic allergy, 2000–2018.

morbidities, were more likely to have an allergy record for penicillin and/or other antibiotics, compared to those with no allergies (Table 2 and Supplemental Table 6). The patient characteristics between patient with penicillin allergy and other antibiotic allergy groups were similar (Table 2). The complete case analyses that excluded people with unknown Townsend scores yielded similar results (Supplemental Table 7).

Out of all the antibiotics prescribed during follow-up, macrolides were the most commonly prescribed class in patients with a penicillin allergy label (n=8724, 57%), followed by tetracyclines (n=4462, 29%), trimethoprim (n=4030, 26%), cephalosporins (n=2609, 17%), and fluoroquinolones (n=2369, 15%). Continued prescription of penicillin antibiotics was noted for 15% of patients (2321/15,377) with a penicillin allergy label. Patients labelled with a penicillin allergy were found to be less likely to receive penicillin prescriptions (IRR=0.15; 95%CI=0.14–0.15) compared to those without any allergies, and were more likely to receive prescriptions for all other included antibiotic classes. The highest IRRs were observed for clindamycin (IRR=5.99; 95%CI=4.31–8.33) and macrolides (IRR=5.69; 95%CI=5.49–5.89) (Table 3). When restricted to those who had

Table 2
Comparison of patient characteristics at baseline. Pen-A=Penicillin Allergy; OA=Other Antibiotic Allergy.

	Adjusted odds ratios (95% confidence interval)[a]					
	Pen-A only	Pen-A + OA	OA only	Pen-A only	Pen-A + OA	Pen-A + OA only
Characteristics	Reference group=No allergy label			Reference group=OA only		Reference group=Pen-A only
Age, years	1.01 (1.01–1.01)*	1.02 (1.02–1.03)*	1.01 (1.01–1.01)*	1.00 (1.00–1.00)	1.01 (1.01–1.01)*	1.01 (1.01–1.01)*
Sex, female	1.41 (1.37–1.46)*	3.15 (2.70–3.67)*	3.22 (3.14–3.31)*	0.44 (0.42–0.46)*	0.98 (0.84–1.14)	2.23 (1.90–2.61)*
Townsend scores						
1 (least deprived)	1.21 (1.13–1.29)*	1.44 (1.12–1.87)*	1.47 (1.41–1.54)*	0.82 (0.76–0.88)*	0.98 (0.76–1.27)	1.20 (0.92–1.56)
2	1.15 (1.08–1.23)*	1.14 (0.87–1.49)	1.39 (1.33–1.46)*	0.82 (0.76–0.89)*	0.82 (0.62–1.07)	0.99 (0.75–1.30)
3	1.11 (1.04–1.18)*	1.24 (0.95–1.61)	1.29 (1.23–1.34)*	0.86 (0.80–0.93)*	0.96 (0.74–1.26)	1.12 (0.85–1.47)
4	1.03 (0.96–1.10)	1.18 (0.90–1.55)	1.17 (1.11–1.22)*	0.88 (0.81–0.95)*	1.01 (0.77–1.33)	1.15 (0.87–1.52)
5 (most deprived)	1.00	1.00	1.00	1.00	1.00	1.00
Unknown	0.94 (0.88–1.01)	0.85 (0.64–1.12)	0.94 (0.90–0.98)*	1.00 (0.93–1.09)	0.90 (0.68–1.19)	0.90 (0.67–1.19)
Practice size						
0–4999	1.00	1.00	1.00	1.00	1.00	1.00
5000–9999	1.24 (1.16–1.32)*	1.22 (0.95–1.57)	1.15 (1.11–1.20)*	1.07 (1.00–1.15)	1.06 (0.82–1.36)	0.99 (0.76–1.28)
10,000–14,999	1.32 (1.24–1.40)*	1.32 (1.03–1.70)*	1.23 (1.18–1.28)*	1.07 (1.00–1.15)	1.08 (0.84–1.39)	1.00 (0.78–1.30)
15,000–19,999	1.37 (1.28–1.48)*	1.38 (1.04–1.83)*	1.13 (1.08–1.19)*	1.21 (1.11–1.32)*	1.22 (0.91–1.62)	1.01 (0.75–1.35)
20,000 or above	1.40 (1.29–1.52)*	1.52 (1.11–2.08)*	1.16 (1.11–1.23)*	1.20 (1.09–1.32)*	1.31 (0.95–1.80)	1.09 (0.79–1.50)
Medical conditions						
Asthma	1.17 (1.11–1.24)*	1.92 (1.61–2.29)*	1.56 (1.52–1.61)*	0.75 (0.71–0.80)*	1.23 (1.02–1.47)*	1.63 (1.36–1.96)*
Smoker	1.02 (0.97–1.08)	0.95 (0.76–1.18)	0.88 (0.85–0.91)*	1.16 (1.09–1.24)*	1.07 (0.86–1.34)	0.93 (0.74–1.16)
Cancer	1.03 (0.96–1.10)	1.23 (0.98–1.55)	1.18 (1.14–1.23)*	0.87 (0.80–0.94)*	1.04 (0.83–1.31)	1.20 (0.95–1.52)
Diabetes	1.07 (1.00–1.15)*	1.23 (0.97–1.55)	1.00 (0.96–1.05)	1.07 (0.99–1.16)	1.23 (0.96–1.56)	1.14 (0.89–1.46)
Coronary heart disease	0.98 (0.91–1.05)	1.02 (0.79–1.32)	1.13 (1.08–1.18)*	0.87 (0.80–0.95)*	0.91 (0.70–1.18)	1.04 (0.80–1.36)
COPD	1.10 (0.98–1.23)	1.24 (0.85–1.81)	1.18 (1.10–1.27)*	0.93 (0.81–1.07)	1.05 (0.72–1.55)	1.13 (0.76–1.68)
Stroke/transient ischaemic attack	0.91 (0.83–1.01)	1.21 (0.89–1.64)	1.03 (0.97–1.10)	0.89 (0.79–1.00)*	1.17 (0.86–1.60)	1.32 (0.96–1.82)
Chronic kidney disease	1.28 (1.18–1.39)*	1.28 (0.97–1.68)	1.26 (1.20–1.33)*	1.01 (0.92–1.11)	1.01 (0.76–1.34)	1.00 (0.75–1.33)
Peripheral arterial disease	1.11 (0.96–1.28)	1.32 (0.81–2.15)	1.05 (0.95–1.16)	1.06 (0.88–1.26)	1.26 (0.76–2.07)	1.19 (0.71–1.98)

Abbreviations: Pen-A, penicillin allergy; OA, other antibiotic allergy; COPD, chronic obstructive pulmonary disease.
The odds ratios for index year are presented in supplemental material Supplemental Table 6. *p < 0.05.
[a] Multinominal logistic regression model was conducted using allergy label status as the dependent variable; and index year and the characteristics listed in this table as the independent variables.

experienced infection events in the respiratory system (ear, nose, throat), skin and wounds, and urogenital tract, a similar treatment pattern was observed (Table 4).

Patients with antibiotic allergy labels were more likely to have adverse clinical outcomes of *C. difficile infection* (hazard ratio [HR] = 1.21; 95% CI: 1.01–1.44) and MRSA infection or colonisation (HR = 1.66; 95% CI: 1.28–2.15), compared to those with no allergies (Table 5).

Compliance with NICE penicillin allergy assessment recommendations

There were 257,180 patients who received their first penicillin allergy label between 2000–2018 (Fig. 1), of which only 2851 (1.1%) had a record of an allergy test being performed within one year. Although an increasing trend was seen, there was no apparent impact of the publication of the NICE guidance in September 2014 (Fig. 4).

Discussion

Principal findings

The findings of this study indicate that both the prevalence and incidence of recorded penicillin allergy labels followed a trend of initially increasing and subsequently slowly decreasing. Incidence

Table 3
Antibiotic prescribing between patients with penicillin allergy label (Pen-A), other antibiotic allergy (Other-A), and without a label (No label).

	Pen-A	Other-A	No label	Pen-A vs No label	Other-A vs No label	Pen-A vs Other-A
N	15,377	35,397	2,342,298			
Follow-up years, median (IQR)	6.1 (2.7–10.3)	5.5 (2.3–10.0)	6.3 (2.6–11.2)			
Antibiotics	Number of patients / number of prescriptions			Adjusted incidence rate ratio (95%CI)[a]		
Penicillin	2321 / 6710	24,294 / 131,858	1,484,522 / 6,649,582	0.15 (0.14–0.15)	1.31 (1.29–1.32)	0.11 (0.11–0.12)
Macrolides	8724 / 35,441	7856 / 22,441	456,986 / 1,020,917	5.69 (5.49–5.89)	1.41 (1.37–1.45)	4.03 (3.86–4.21)
Trimethoprim	4030 / 12,938	7227 / 26,574	479,771 / 1,384,258	1.21 (1.16–1.26)	0.98 (0.95–1.00)	1.23 (1.18–1.30)
Tetracyclines	4462 / 15,322	7203 / 25,619	375,415 / 1,248,742	1.98 (1.88–2.08)	1.50 (1.45–1.55)	1.32 (1.24–1.40)
Cephalosporins	2609 / 8717	7157 / 31,258	252,686 / 607,706	2.07 (1.96–2.19)	2.89 (2.79–3.00)	0.72 (0.67–0.76)
Nitrofurantoin	2040 / 7059	7700 / 33,599	199,194 / 567,394	1.44 (1.35–1.53)	2.51 (2.42–2.60)	0.57 (0.53–0.62)
Quinolones	2369 / 6159	4957 / 14,225	198,426 / 401,795	2.35 (2.21–2.49)	2.45 (2.35–2.55)	0.96 (0.89–1.03)
Clindamycin	220 / 493	111 / 458	5555 / 13,280	5.99 (4.31–8.33)	1.71 (1.32–2.21)	3.51 (2.32–5.32)
Carbapenems[b]	* / *[c]	7 / 7	135 / 215	NA	NA	NA
Aztreonam[b]	0 / 0	0 / 0	6 / 6	NA	NA	NA

Abbreviations: IQR, interquartile range; CI, confidence interval.
[a] Zero-inflated negative binomial model was used to estimate the incidence rate ratios adjusted for age, sex, index year, comorbidities (asthma, smoker, cancer, diabetes, coronary heart disease, COPD, stroke/transient ischaemic attack, chronic kidney disease, peripheral arterial disease), indication for index prescription (respiratory system, skin and wounds, urogenital tract, dental/mouth, gastro-intestinal system, eye, cardiovascular system, musculoskeletal system, cancer, prophylactic therapy, central nervous system, miscellaneous).
[b] Unable to provide a reliable result estimate due to low number of prescription count.
[c] Small cell count of values 1-4 are suppressed to protect confidentiality.

Table 4
Indication-specific antibiotic prescribing between patients with penicillin allergy label (Pen-A), other antibiotic allergy (Other-A), and without a label (No label).

	Pen-A (N=15,377)	Other-A (N=35,397)	No label (N=2,342,298)	Pen-A vs No label	Other-A vs No label	Pen-A vs Other-A
Respiratory system (combined with ENT)				Adjusted odds ratios (95% CI)[a]		
Total	82,026	197,492	10,652,241			
Treatment, n (%)						
Penicillin	1869 (2.3)	43,029 (21.8)	2,414,251 (22.7)	0.08 (0.08–0.08)	0.97 (0.96–0.98)	0.08 (0.08–0.09)
Macrolides	13,053 (15.9)	7143 (3.6)	344,746 (3.2)	5.81 (5.70–5.92)	1.12 (1.09–1.15)	5.18 (5.03–5.34)
Trimethoprim	474 (0.6)	576 (0.3)	26,697 (0.3)	2.09 (1.91–2.29)	0.97 (0.89–1.05)	2.17 (1.92–2.45)
Tetracyclines	5342 (6.5)	6289 (3.2)	288,056 (2.7)	2.48 (2.41–2.55)	1.18 (1.15–1.21)	2.10 (2.02–2.18)
Cephalosporins	1734 (2.1)	2440 (1.2)	83,218 (0.8)	2.82 (2.68–2.96)	1.51 (1.45–1.57)	1.87 (1.75–1.99)
Nitrofurantoin	83 (0.1)	377 (0.2)	6033 (0.1)	1.44 (1.16–1.78)	2.44 (2.20–2.71)	0.59 (0.46–0.75)
Quinolones	1009 (1.2)	1347 (0.7)	45,620 (0.4)	2.93 (2.75–3.12)	1.62 (1.53–1.71)	1.81 (1.67–1.96)
Clindamycin	10(0)	11(0)	159(0)	8.08 (4.26–15.34)	3.66 (1.97–6.78)	2.21 (0.94–5.21)
Carbapenems[b]	0(0)	0(0)	7(0)	-	-	-
Aztreonam[b]	0(0)	0(0)	0(0)	-	-	-
None of the above/No antibiotics data	58,633 (71.5)	136,841 (69.3)	7,464,547 (70.1)	-	-	-
Skin and wounds				Adjusted odds ratios (95% CI)[a]		
Number of events	90,283	170,634	9,496,764			
Treatment, n (%)						
Penicillin	1171 (1.3)	15,406 (9)	943,348 (9.9)	0.13 (0.12–0.14)	0.94 (0.92–0.96)	0.14 (0.13–0.14)
Macrolides	6042 (6.7)	1773 (1)	90,896 (1)	8.01 (7.79–8.23)	1.10 (1.05–1.16)	7.25 (6.87–7.65)
Trimethoprim	279 (0.3)	373 (0.2)	20,700 (0.2)	1.24 (1.10–1.40)	0.79 (0.71–0.87)	1.57 (1.35–1.84)
Tetracyclines	1458 (1.6)	1989 (1.2)	112,863 (1.2)	1.69 (1.61–1.78)	1.10 (1.05–1.15)	1.54 (1.44–1.65)
Cephalosporins	636 (0.7)	707 (0.4)	19,046 (0.2)	3.32 (3.06–3.59)	1.89 (1.75–2.04)	1.75 (1.57–1.95)
Nitrofurantoin	85 (0.1)	483 (0.3)	6777 (0.1)	1.10 (0.89–1.36)	2.86 (2.61–3.14)	0.38 (0.30–0.48)
Quinolones	451 (0.5)	403 (0.2)	13,682 (0.1)	3.41 (3.10–3.74)	1.72 (1.56–1.90)	1.98 (1.73–2.26)
Clindamycin	143 (0.2)	54(0)	2952(0)	5.14 (4.34–6.08)	1.08 (0.83–1.42)	4.75 (3.47–6.49)
Carbapenems[b]	0(0)	0(0)	6(0)	-	-	-
Aztreonam[b]	0(0)	0(0)	0(0)	-	-	-
None of the above/No antibiotics data	80,130 (88.8)	149,691 (87.7)	8,296,254 (87.4)	-	-	-
Urogenital tract				Adjusted odds ratios (95% CI)[a]		
Number of events	29,666	93,010	3,552,261			
Treatment, n (%)						
Penicillin	224 (0.8)	7369 (7.9)	146,083 (4.1)	0.17 (0.15–0.20)	1.96 (1.92–2.01)	0.09 (0.08–0.10)
Macrolides	406 (1.4)	295 (0.3)	10,650 (0.3)	5.55 (5.02–6.14)	1.36 (1.21–1.53)	4.07 (3.50–4.74)
Trimethoprim	4478 (15.1)	8237 (8.9)	485,963 (13.7)	1.01 (0.98–1.04)	0.51 (0.50–0.53)	1.96 (1.89–2.04)
Tetracyclines	212 (0.7)	469 (0.5)	21,898 (0.6)	1.54 (1.35–1.77)	1.30 (1.19–1.43)	1.19 (1.01–1.40)
Cephalosporins	1115 (3.8)	6329 (6.8)	114,331 (3.2)	1.10 (1.03–1.17)	1.99 (1.93–2.04)	0.55 (0.52–0.59)
Nitrofurantoin	2093 (7.1)	9733 (10.5)	174,922 (4.9)	1.26 (1.20–1.32)	1.89 (1.85–1.93)	0.67 (0.63–0.70)
Quinolones	921 (3.1)	2914 (3.1)	74,143 (2.1)	1.78 (1.66–1.90)	2.13 (2.05–2.22)	0.83 (0.77–0.90)
Clindamycin	*(*)[c]	*(*)[c]	90(0)	4.00 (1.26–12.68)	0.83 (0.20–3.37)	4.84 (0.81–28.98)
Carbapenems[b]	0(0)	0(0)	22(0)	-	-	-
Aztreonam[b]	0(0)	0(0)	*(*)[c]	-	-	-
None of the above/No antibiotics data	20,335 (68.5)	58,264 (62.6)	2,536,226 (71.4)	-	-	-

Abbreviations: IQR, interquartile range; CI, confidence interval.
[a] Logistic regression model was used to estimate the odds ratios adjusted for age at disease, sex, disease year, comorbidities at disease date (asthma, smoker, cancer, diabetes, coronary heart disease, COPD, stroke/transient ischaemic attack, chronic kidney disease, peripheral arterial disease).
[b] Unable to provide a reliable result estimate due to low number of prescription count.
[c] Small cell count of values 1-4 are suppressed to protect confidentiality.

Table 5
Comparison of outcomes.

	Pen-A (N=15,377)	OA (N=35,397)	No label (N=2,342,298)	Pen-A vs No label	OA vs No label	Pen-A vs A
Outcomes	No. of events (incidence per 100 patient-years)			Adjusted hazard ratio (95%CI)[a]		
C diff.	122 (0.1)	333 (0.1)	12,870 (0.1)	1.21 (1.01–1.44)	1.51 (1.35–1.68)	0.80 (0.65–0.98)
MRSA	58 (0.1)	104(0)	4601(0)	1.66 (1.28–2.15)	1.45 (1.19–1.76)	1.15 (0.83–1.58)
VRE	0	0	*[b]	-	-	-

Abbreviations: C diff., *Clostridioides difficile*; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococcus. Pen-A, Penicillin Allergy; OA: Other Antibiotic Allergies; CI, Confidence Interval.
[a] Cox regression adjusted for age at index date, gender, index year, comorbidities at index date (asthma, smoker, cancer, diabetes, coronary heart disease, COPD, stroke/transient ischaemic attack, chronic kidney disease, peripheral arterial disease).
[b] Small cell count of values 1-4 are suppressed to protect confidentiality.

reached its peak at 0.46% in 2004, while prevalence reached its highest point at 8.25% in 2011. Older age, female gender, residing in less deprived areas, larger GP size, and having co-morbidities were associated with an increased likelihood of acquiring a penicillin or other antibiotics allergy label. Having a penicillin allergy label substantially influenced the selection of antibiotics, with patients documented as allergic more prone to encountering adverse clinical outcomes, specifically higher incidences of *C. difficile* and MRSA, even when accounting for indication. The publication of the NICE guidance appeared to have little to no noticeable effect on the percentage of patients with a recorded penicillin allergy test for their allergy documentation.

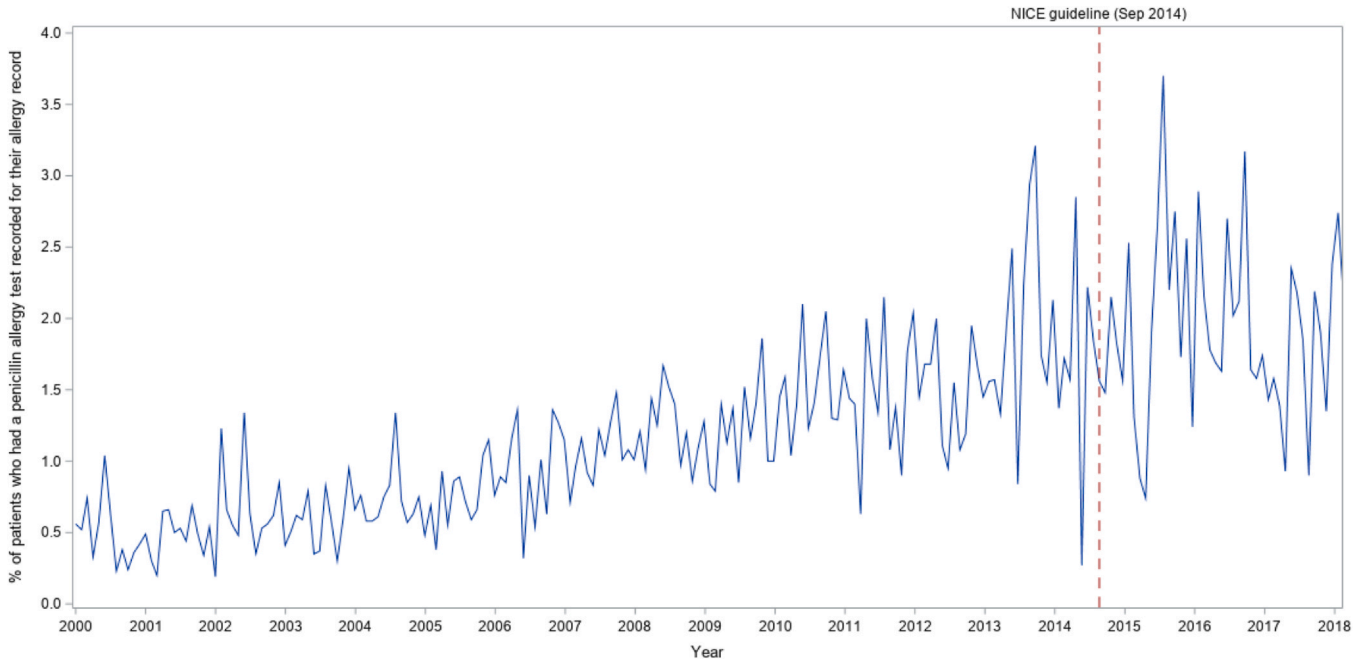

Fig. 4. Proportion of patients who had a penicillin allergy test recorded for their allergy record, 2000–2018. The proportion was calculated for each month using the formula: $\frac{\text{Number of patients who received 1) a penillin allergy record in that month; and 2) a penicillin allergy test dated any time before or within 1 year after the allergy record}}{\text{Number of patients who received a penicillin allergy label in that month}} \text{x}100\%$.

Comparison with other studies

We identified a prevalence of penicillin allergy that ranged from 4.77% to 8.25% over the 19-year study period. A previous study in the UK, West et al.,[4] reported a 5.9% prevalence of penicillin allergy in another English general practice database during 2013/14, which is lower than the rate of 8.15% seen during 2013/2014 in our study. This could be due to the different population profiles in the two different primary care electronic health record systems. A previous study in the US, Liang et al.,[20] reported a 9.2% prevalence of penicillin allergy in 2017, which is higher than the rate of 7.8% in this study. The difference could be attributed to the different healthcare systems and the different periods of follow-up within which to ascertain a new allergy label.

The increase in the allergy record prevalence and incidence during the first few years may be explained by the migration of patients onto electronic health record systems, while the gradual decline in the later years may reflect a parallel decline in antibiotic usage and reduced risk of adverse reactions due to reduced exposure: Our data indicated that the percentage of people who were prescribed an antibiotic decreased from 29.2% in 2012 to 25.1% in 2018. A previous study also suggested that there was a downward trend in antibiotic prescribing in primary care in the UK during 2014–2022.[21] This decline could be attributed to the relevant policies and programs aiming to reduce antimicrobial resistance through reduced prescribing, such as the NHS England Quality premium.[22]

Consistent with West et al.,[4] our findings, which were derived from a larger population and more recent data, also indicate that older patients, females, those living in less deprived areas, those registered with larger GP, and with co-morbidities were more prone to having a penicillin allergy label, suggesting these factors remained influential across time, and should be considered when investigating the impact of a penicillin allergy labels. In line with the previous study in the UK,[4] penicillin allergy was shown to be associated with an increased rate of prescribing of macrolide, trimethoprim, tetracycline, cephalosporin, nitrofurantoin, quinolone and clindamycin, with macrolides and tetracyclines most commonly prescribed, and clindamycin and macrolides having the highest rate ratios. Comparable findings have been seen in studies from the United States and the Netherlands.[23,24] Blumenthal et al.[23] found that the association between penicillin allergy label and alternative antibiotic use was stronger among patients treated with antibiotics for urinary tract infections (Odds Ratio=2.07) and for surgical procedure prophylaxis (Odds Ratio=7.31). In our study, the observed effect of a penicillin allergy label on antibiotic selection persisted even when specific infection indications were accounted for.

Of note, we discovered that 15% of patients labelled with a penicillin allergy still received penicillin prescriptions over a median follow-up period of 6.1 years (IQR 2.7–10.3 years), which may be for a number of reasons that require further research. For example, this may be reflective of the spurious allergy labelling of patients who report intolerances as allergies. GPs may therefore be making risk-benefit decisions or directly de-labelling patients. The concurrent prescription of penicillin to a patient with a patient allergy may also be considered a potential error in prescribing. West et al. reported that 4.2% of patients with labels with penicillin allergy still received penicillin prescriptions.[4] The difference in the percentage of patients who still received penicillin prescriptions may be attributed to the different follow-up periods and study periods in the two studies as well as the difference in the population profiles between the two studies. Another study in the UK reported a penicillin use rate of 248.23 per 1000 person years among those with penicillin allergy labels,[19] which is comparable to our findings.

Prior UK guidelines recommended that confirming or refuting a penicillin allergy should involve skin prick and intradermal testing, followed by an oral challenge if the initial tests are negative, with these procedures to be conducted by allergists and immunologists in specialised clinics.[8,25] Given the labour-intensive, time-consuming nature of penicillin allergy assessment and the requirement for specialist involvement, the substantial demand for allergy services and testing exceeds the capacity even in major centres.[25,26]

Consequently, the majority of patients labelled with a penicillin allergy are unable to access testing.[26,27] A recent systematic review encompassing 69 studies has demonstrated that patients with penicillin allergy labels can be safely de-labelled by non-allergy specialists using a variety of methods which included, on their medical history alone, after negative skin testing followed by an oral challenge or following a successful direct oral penicillin challenge without prior skin testing.[28] In 2022, The British Society for Allergy and Clinical Immunology (BSACI) updated its recommendations regarding the direct oral penicillin challenge to endorse penicillin allergy de-labelling services by non-allergists in a hospital setting.[29] While the recommendations are intended for patients in a hospital setting, the guidelines also indicate that primary care physicians can remove a penicillin allergy label when the patient's history is inconsistent with a penicillin allergy.[29] Given the timeframe of this study, it is probable that GPs may have reviewed the patients' allergy status prior to the update of the guideline. Previous research found that healthcare workers were motivated to address the challenge of eradicating inaccurate penicillin allergy labels,[30,31] with some professionals feeling confident in removing these labels when patients provided a clear history indicating a non-allergic reaction.[32] Many penicillin allergy labels were assigned during childhood following an adverse reaction while taking penicillin, often amidst diagnostic uncertainty and unclear causal attribution, resulting in erroneous allergy identification.[3] Often, these reactions, such as nausea, vomiting, diarrhoea, or the documented reason of "family history of penicillin allergy", do not indicate a true allergy to penicillin.[3,33] For this specific group of patients, GPs were likely to directly de-label them after weighing the benefits of prescribing penicillin against the risk of an adverse reaction.

The publication of the NICE guideline in September 2014 did not lead to a noticeable immediate rise in the proportion of patients undergoing allergy assessment for their allergy labels. The observed upward trend over time might be due to enhanced knowledge and awareness stemming from both this NICE guideline and the earlier guideline on anaphylaxis.[34] In addition, although we have added the one-year time frame after the allergy record to allow time for referral and testing, the publication of the NICE guideline may have had some impact on testing outside of that time frame.

There has been evidence that allergy-labelled patients were more likely to experience infections with *C. difficile*, MRSA, or VRE.[19,35–38] We were unable to assess the impact of allergy label on VRE as there was only a small number of VRE cases identified but we confirmed the increased risk of these infections in penicillin allergy-labelled patients as well as those with other antibiotic allergies. The main reason why having a penicillin allergy label leads to resistant infections is likely through the use of alternative broad-spectrum antimicrobials that favour the resistance selection of these organisms.[24,39] In addition, penicillin allergy labels are linked to lengthened hospital stays.[40] Extended hospital stays are likely a significant factor in the higher rates of resistant infections. Frequent readmissions, prolonged hospital stays, and intensive care unit admissions have all been identified as risk factors for acquiring multidrug-resistant bacteria.[41] The longer patients stay in the hospital, the more opportunities there are for cross-infection, leading to a higher risk of spreading resistant organisms among patients.[36]

Strengths and limitations

To our knowledge, this study represents the first population-based study to report the incidence of penicillin allergy in the UK. The major strengths of this study were its longitudinal analysis and large sample size. In addition, we linked the indication of antibiotic therapy to allergy records and influence on prescribing.

This study has limitations. The database itself does not contain information about antibiotics prescribed from sources other than primary care, such as hospitals and emergency departments. It is possible that new allergies that may have occurred during hospitalisation may not be communicated to the GP and outpatient data for referrals to allergy assessment to confirm suspected diagnosis of allergy to penicillin may also be limited. Additionally, patients may have been tested beyond the one-year time frame applied in the study between suspected penicillin allergy and formal testing for penicillin allergy in specialist clinics. Second, there was uncertainty about whether the indications recorded on the day of the prescription were actually related to the antibiotic use. Third, the 2004 peak in penicillin allergy incidence could be attributed to improved documentation from the Quality and Outcomes Framework (QOF) implementation. Additionally, the effect of healthcare data migration could also skew the results. Finally, the study was unable to evaluate the effects of allergy labels on hospitalisation or mortality rates because of data limitations.

Conclusions and implications

Penicillin allergy labels are common with a prevalence of 8% and an incidence of 0.5% in this population. Previously identified risk factors for penicillin allergy, such as older age, female sex, deprivation (lower Townsend score), and co-morbidities, were confirmed. There was no evidence that NICE recommendations had affected rates of penicillin allergy assessment. Penicillin allergy is a common contraindication to the use of this critical class of antibiotics, forcing clinicians to use alternative treatments, and putting patients at increased risk of AMR or adverse effects. Access to penicillin allergy de-labelling services is vital to ensure patients are not denied penicillin treatments unnecessarily.[42] Prioritising allergy de-labelling is essential to decrease the use of antibiotics listed in the WHO Watch and Reserve group,[43] a strategy endorsed by the UK Department of Health and Social Care as part of its national policy.[42] Given the limited capacity for allergy assessment, there is a demand for de-labelling services for antibiotic allergies by non-allergists, which have been shown to be both effective and safe.[28,44] There is a need for future research on the effects of de-labelling over extended follow-up periods, necessitating enhancements to existing electronic healthcare databases.

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Author contributions

(1) The conception and design of the study (YJ, PH, JS, RW, WL), or acquisition of data (YJ, WL), or analysis and interpretation of data (all authors), (2) drafting the article or revising it critically for important intellectual content (all authors), (3) final approval of the version to be submitted (all authors).

Declaration of interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

NP is a NIHR/ HEE CDRF studying non-allergist penicillin allergy de-labelling in secondary care (Clinical Doctoral Research Fellowship). He is co-lead on the BSAC MOOC on non-allergist penicillin allergy de-labelling (British Society Antimicrobial Chemotherapy Massive Open Online Community) and on the Study

Steering Committee and UK co-ordinator for the international National Antibiotic Allergy Network (iNAAN) study.

JATS has research funding from the NIHR and Wellcome Trust in relation to penicillin allergy. He is a member of the British Society for Allergy and Clinical Immunology allergy working party. He is co-lead on the BSAC MOOC on non-allergist penicillin allergy de-labelling (British Society Antimicrobial Chemotherapy Massive Open Online Community) and a BSAC council member.

PH is a co-investigator in the NIHR Alabama study https://www.fundingawards.nihr.ac.uk/award/RP-PG-1214–20007 and contributed to British Society of Antimicrobial Chemotherapy Massive Open Online Course on Penicillin Allergy https://www.futurelearn.com/courses/understanding-penicillin-allergy-assessment-and-delabelling.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106367.

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