

# Represcription of penicillin after allergic-like events

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**Objective:** We sought to determine the frequency of represcription of penicillin to individuals with penicillin allergy and the risk of a second reaction in those who had a previous reaction.

**Methods:** A retrospective cohort study was conducted within the UK General Practice Research Database. All patients who had received a prescription for penicillin were identified. Within that source population, records of patients who had received at least 2 prescriptions for penicillin at least 60 days apart were selected and examined for allergic-like (hypersensitivity) events on the day of or within 30 days after a prescription.

**Results:** At least one prescription for penicillin was given to 3,375,162 patients. Of 6212 (0.18%) patients who experienced an allergic-like event after the initial prescription, 48.5% were given a second prescription compared with 59.8% of those without an initial allergic-like event (risk ratio, 0.81; 95% CI, 0.79-0.83). Two or more prescriptions for penicillin were given to 2,017,957 patients. Three thousand fourteen (0.15%) patients experienced an allergic-like event after the first prescription, and 57 (1.89%) of those had another event after the second prescription. The unadjusted odds ratio of an allergic-like event after the second prescription for those who experienced an allergic-like event after the first prescription, compared with those who had no initial event was 11.2 (95% CI, 8.6-14.6). Adjusting for confounding had no substantive effect on this result.

**Conclusion:** The risk of an allergic-like event after penicillin is markedly increased in those who have had a prior event, although the absolute difference is small (1.72%). Represcription of penicillin to such patients is more frequent than anticipated. (*J Allergy Clin Immunol* 2004;113:764-70.)

**Key words:** Drug allergy, adverse drug reaction, drug hypersensitivity, penicillin, anaphylaxis, urticaria, angioedema, toxic epidermal necrolysis

The overall frequency of  $\beta$ -lactam allergy has been reported as approximately 2% per course,<sup>1-3</sup> with the rate after re-exposure in patients with a previous allergy estimated to be as high as 60%.<sup>4-6</sup> Anaphylaxis is estimated to occur in 0.01% to 0.05% of all penicillin courses.<sup>2</sup> Much of this information comes from small case series of inpatients. However, the great majority of antibiotics are prescribed for outpatients.<sup>7</sup> Although 10% to 15% of adults report a history of penicillin allergy, little is known about how often patients with a history of allergy are re-exposed to penicillin.<sup>1,2,8,9</sup>

A national task force recently emphasized the importance of research to improve prevention and management of drug hypersensitivity reactions.<sup>10</sup> Understanding the risk of readministration in outpatients is important for several reasons. First, outpatients might be different from inpatients in their risk of reaction after re-exposure. Second, with the increase in antimicrobial resistance of bacteria, particularly multidrug resistance, therapeutic options are increasingly limited. Readministering penicillin to individuals with an allergic history might be necessary, although the risks and benefits of this practice must be fully understood. Third, avoidance of an antibiotic because of a history of an allergy might result in a patient receiving an antibiotic that is less effective or more toxic than necessary. Fourth, it is necessary to understand how often represcription occurs and to understand its associated risk to reduce medical errors and to protect patients.

To address these concerns, we conducted a retrospective cohort study using the United Kingdom General Practice Research Database (GPRD), a database of electronic primary care medical records and prescriptions. We used the database to describe the frequency of events consistent with drug hypersensitivity (allergic-like) reactions. We determined the risk of allergic-like events after the next prescription of penicillin for those who had had an event after the first prescription compared with the risk for those who had not. This electronic record allowed us to identify prescriptions, and therefore for this analysis, we assumed the prescription was filled and taken as prescribed.

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#### Abbreviations used

BNF: British National Formulary  
GPRD: United Kingdom General Practice Research Database  
OR: Odds ratio  
TEN: Toxic epidermal necrolysis  
UTS: Up to standard

## METHODS

A retrospective cohort study was performed by using the GPRD.<sup>11-13</sup> Fig 1 outlines the protocol schematically.

### Data source: GPRD

GPRD data are the actual outpatient medical records from 687 general practitioner practices, are geographically representative of England and Wales, and comprise 6% of this population. The electronic data record includes demographic information, prescription drug information, and indications for all new prescriptions, clinical events and diagnoses, preventive care (eg, screening and intervention programs), hospital admissions, and cause of death, as entered by the general practitioner. Diagnoses are recorded by using the Oxford Medical Indexing System codes that are cross-referenced to READ diagnostic codes.<sup>12,14</sup> Prescriptions are recorded by using 2 drug code schemes (Multilex and Prescription Prescribing Authority of the National Health Service).<sup>12,14</sup>

Contributing general practitioners are required to meet specific recording standards to be considered up to standard (UTS).<sup>15-17</sup> Prior studies have suggested that the clinical information in the GPRD is of high quality for epidemiologic studies.<sup>13,15,18-25</sup>

The UTS data provide a window of observation for patients. It is possible that patients had medical events before entering or after leaving a GPRD-participating practice, before or after their physician's participation in GPRD was terminated, or after September 2001. Such events were not captured in this study. For this project, historical events recorded in the electronic record were included as potential confounders, but prescriptions and events consistent with drug hypersensitivity were identified only from the UTS time periods.

### Study population

The source population consisted of all individuals in the GPRD UTS database from 1987 through September 2001 who received a prescription for a penicillin (Fig 1). Within that population, we defined a cohort of patients who received at least 2 penicillin prescriptions at least 60 days apart. This cohort was used for the primary analyses. The study group consisted of patients who experienced an allergic-like event on the day of or within the 30 days after the first penicillin prescription. The comparison group consisted of patients who did not have such an event in that time period. The outcome was an allergic-like event on the day of or within 30 days after the second penicillin prescription.

The GPRD database provides the date prescriptions were given to the patient; the date of initiation of treatment is unknown. Similarly, events are recorded at the time of subsequent contact with the patient; the onset of symptoms is not recorded. Because of this temporal imprecision, we selected a broad 30-day window after a prescription for the time in which an allergic-like event could occur. We conservatively chose 60 days as the minimum interval between the 2 penicillin prescriptions to be sure that any allergic-like event after the first event had resolved before the second prescription.

## Identification of penicillins

We identified penicillins from the British National Formulary (BNF code 5.1.1) classification (Table E1 of the online supplemental material).<sup>26</sup>

## Identification of allergic-like events: The study outcome

We grouped READ and Oxford Medical Indexing System codes for events consistent with allergic reactions: anaphylaxis, urticaria, angioedema, erythema multiforme, laryngeal spasm, dermatitis attributed to a drug, toxic epidermal necrolysis (TEN), and adverse drug reactions attributed to a medication (Table E1 in the Online Repository at [www.mosby.com/jaci](http://www.mosby.com/jaci)). As a group, we termed all these codes the "narrow" group.

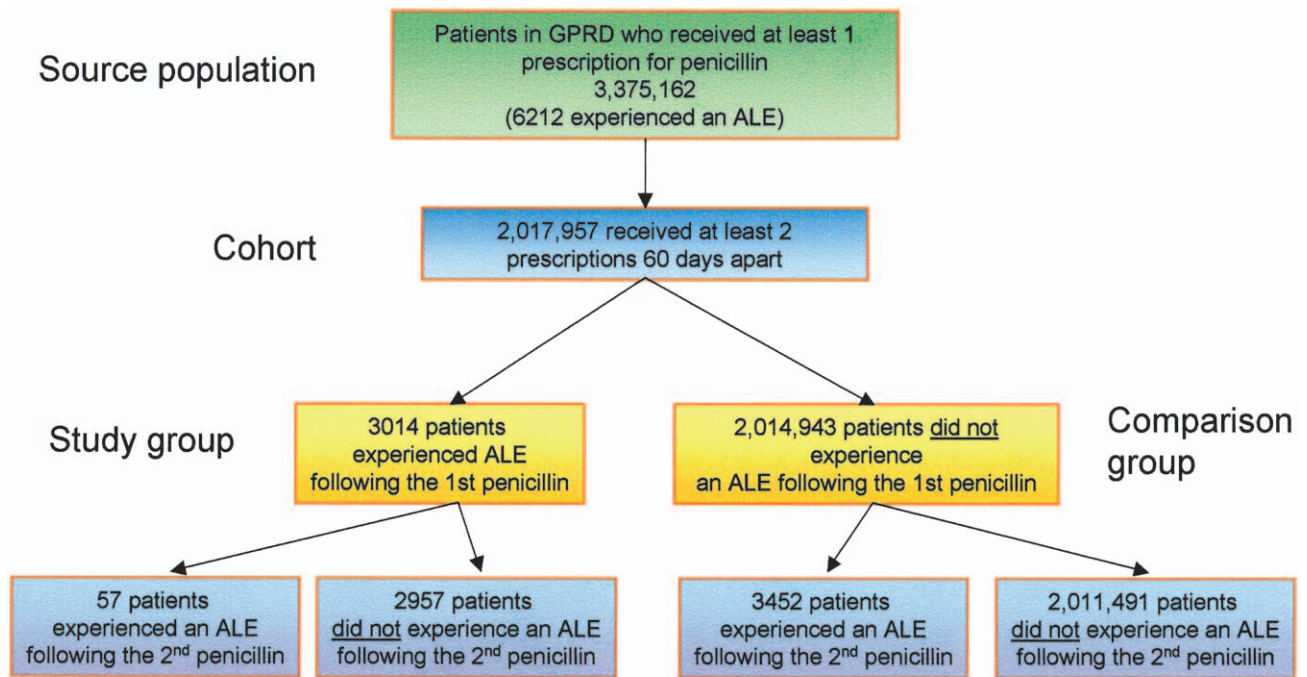
We defined an expanded group of codes for allergic-like events, which we called the "broad" group. This group included the "narrow" group codes plus codes for bronchospasm, asthma, and eczema, as well as a larger group of codes defining reactions to specific medications (Table E2 in the Online Repository). Although bronchospasm can be a manifestation of an immediate allergic reaction, it can also be a manifestation of underlying asthma that worsened during a respiratory tract infection for which penicillin was prescribed. Similarly, although an eczematous rash could represent a drug hypersensitivity reaction, it can be a manifestation of underlying chronic dermatitis that became infected and for which a penicillin antibiotic was prescribed. For these reasons, we used the broad group of codes for secondary analyses. Events of other types (eg, thrombocytopenia, neutropenia, hepatic dysfunction, and renal dysfunction) were excluded because they are not specific for an allergic drug reaction.

## Data analysis

The source population was selected by using Knowledge Manager, a patient-level data warehouse and analysis tool developed for exploring the GPRD. The data set was defined from Knowledge Manager and downloaded for analysis performed with SAS Version 8.1 (SAS Institute, Inc, Cary, NC) and STATA Release 7.0 (StataCorp, College Station, Tex).

An initial analysis was performed reviewing the occurrence of allergic-like events within 30 days after a first prescription for penicillin and the patients' risk of receiving a second penicillin prescription. For those who received a second prescription, the unadjusted odds ratio (OR) with 95% CIs was computed for the risk of an allergic-like event after a second penicillin prescription in patients who had experienced an allergic-like event with the first exposure compared with the risk for those who did not have an event after the first prescription. Because the outcome under investigation in this study was a rare event, the OR is a close estimate of the risk ratio.<sup>27</sup> For these primary analyses, we used the narrow group of codes for allergic-like events.

Logistic regression was used to test for potential confounding, testing each potential confounder (eg, prior history of urticaria) one at a time. Confounders that changed the point estimate of the OR of interest by 15% or more were to be included in the final adjusted model.<sup>28</sup> Age and sex were tested as effect modifiers of the relationship between the risk of an allergic-like event after the first penicillin prescription and the odds of an allergic-like event after the second penicillin prescription. We chose to analyze our data for these effect modifiers because it has been reported that children are less likely to have adverse drug reactions than older individuals.<sup>29</sup> It also has been reported that females are at greater risk for such events.<sup>30</sup> The ORs were compared for age-specific and sex-specific strata by using the Breslow-Day test for homogeneity of the OR to test for effect modification.<sup>31</sup>



ALE= Allergic-like event  
GPRD=General Practice Research Database

FIG 1. Schematic representation of the study protocol.

Age was considered both as a continuous and categorical variable to allow for the nonlinear effect of age. The categorical representation was based on the age frequency distribution (0-2, 3-17, 18-39, 40-59, and  $\geq 60$  years). Other potential confounders, listed in Table E3 in the Online Repository, included the occurrence before the first penicillin prescription of acute processes that have manifestations similar to an acute hypersensitivity reaction. Included were diseases that are associated with a rash resembling an adverse drug reaction. We also adjusted for a prior history of allergic-like medical events that together constitute the events under study, both singly and as a group, under both the narrow and the broad definitions of allergic-like events (Table E2). We adjusted for the current use (within 30 days before the second penicillin prescription) of drugs known or suspected to be associated with or indicative of hypersensitivity-allergic reactions (Table E3). Finally, we accounted for the nonindependent nature of multiple patients from the same general practitioner's practice (ie, clustering). This was accomplished by using the Huber-White sandwich estimator<sup>32,33</sup> for the variance of the model parameter estimates.

We performed several sensitivity analyses. First, we repeated the crude analysis by using the broad group of codes for allergic-like events. Second, we computed the OR and 95% CI for risk of an allergic-like event after the second penicillin prescription within 10 (rather than 30) days after the first penicillin prescription, within 10 (rather than 30) days after the second prescription, and after limiting both follow-up periods to 10 days. Third, we excluded those patients who did not have 30 days of follow-up after the second penicillin prescription.

We received approval from the Scientific and Ethical Advisory Group of the GPRD. The University of Pennsylvania Institutional Review Board reviewed the protocol and determined that it met the criteria for exempt status.

## RESULTS

The source population consisted of 3,375,162 patients who had received at least one prescription for penicillin (Fig 1). Six thousand two hundred twelve (0.18%) patients from this source population experienced an allergic-like event after the initial penicillin prescription. Of those with an allergic-like event after the initial penicillin prescription, 48.5% were given a second prescription for penicillin, whereas 59.8% of those without an initial allergic-like event received a second prescription (risk ratio, 0.81; 95% CI, 0.79-0.83). Thus the probability of their receiving a second penicillin prescription after an initial event was reduced by approximately 20% compared with the probability in those who had not experienced an event. Patients who experienced an allergic-like event after the initial penicillin prescription remained in the UTS GPRD database for a median of 1355 days (interquartile range, 1627 days); patients who did not experience an allergic-like event remained in the database

**TABLE I.** Description of patients who received at least 2 penicillin prescriptions as recorded in the GPRD between January 1987 and September 2001

Characteristic	Study group* N = 3,014 n (% of 3,014)		Comparison group† N = 2,014,219‡ n (% of 2,014,219)	
	Male	Female	Male	Female
Age (y)				
0-2	168 (5.6)	144 (4.8)	126,433 (6.3)	108,826 (5.4)
3-17	409 (13.6)	447 (14.8)	217,178 (10.8)	232,971 (11.6)
18-39	257 (8.5)	586 (19.4)	213,074 (10.6)	348,160 (17.3)
40-59	148 (4.9)	349 (11.6)	160,725 (8.0)	218,700 (10.9)
≥60	175 (5.8)	331 (11.0)	160,873 (8.0)	227,279 (11.3)
Total	1,157 (38.4)	1,857 (61.6)	878,283 (43.6)	1,135,936 (56.4)
Median days (interquartile range) between 1st and 2nd penicillin	363 (546)		335 (524)	
Median days (interquartile range) between 1st penicillin and follow-up in GPRD	1823 (1541)		1724 (1495)	

\*The study group consists of those patients who experienced an allergic-like event following the first prescription for penicillin.

†The comparison group consists of patients who did not have an allergic-like event following the first prescription for penicillin.

‡Age data missing on 724 patients.

a median of 1264 days (interquartile range, 1583 days). This difference was statistically significant ( $P < .0001$ ).

The cohort used for the primary analysis was the 60% of the source population who had received a second penicillin prescription. These 2,017,957 patients are described in Table I. Of this cohort, 3014 (0.15%) experienced an event consistent with an allergic reaction; these patients constituted the study group (Fig 1). The comparison group consists of the 2,014,943 patients who did not have an allergic-like event after their first penicillin prescription. Because of the very large number of patients, the study group and comparison groups differed statistically with respect to age and sex ( $P < .0001$ ). However, these differences are very small and do not represent substantial clinical differences (Table I). There was a significant difference in the time interval from first to second prescriptions for penicillin. Patients who experienced no allergic-like event after the first prescription received a second prescription in a shorter time period (mean, 335 days; interquartile range, 524 days) compared with those who had allergic-like events (mean, 363 days; interquartile range, 546 days;  $P < .0003$ ).

Approximately three fourths of the penicillin prescriptions were for amoxicillin. Table II describes the allergic-like events after the first or second prescription of penicillin. Of 3014 patients who had an allergic-like event after the first penicillin prescription, only 57 (1.89%) had such an event after the second penicillin prescription. Urticaria was the most frequent allergic-like event, accounting for approximately three fourths of the events. Anaphylaxis was infrequent, accounting for 0.53% of the first and 0.91% of the second events or a rate of 16 per 2,017,957 (8 per million) and 32 per 2,017,957 (16 per million) prescriptions of penicillin.

Fifty-seven patients had an allergic-like event after both prescriptions of penicillin (Table E4 in the Online

**TABLE II.** Description of the allergic-like event following the first and second penicillin prescriptions

Event type*	First penicillin (N = 3014) N (column %)	Second penicillin (N = 3509) N (column %)
Anaphylaxis	16 (0.53)	32 (0.91)
Angioedema	106 (3.52)	131 (3.73)
Laryngospasm	19 (0.63)	18 (0.51)
Urticaria	2275 (75.48)	2589 (73.78)
Erythema multiforme	237 (7.86)	220 (6.27)
TEN	6 (0.20)	11 (0.31)
Dermatitis due to an ingested drug	11 (0.36)	11 (0.31)
Adverse drug reaction to an ingested drug	344 (11.41)	497 (14.16)
Total	3014	3509

\*As cited in the GPRD medical record.

Repository). Forty-two (74%) patients had urticaria after either the first or second prescription, and 21 (37%) had urticaria after both prescriptions. Only one of the 57 patients had anaphylaxis after both prescriptions. Fifteen of the 16 patients who had anaphylaxis after the first prescription and all 6 patients who had TEN had no allergic-like events after the second prescription (Tables II and E4). There were no deaths, and it did not appear that any patients were hospitalized as a result of these events.

The unadjusted OR of an allergic-like event after the second prescription of penicillin for those who had experienced an allergic-like event after the first prescription compared with those who had no initial event was 11.2 (95% CI, 8.6-14.6). Adjusting one at a time for disease-associated confounders, the OR changed by more than 15% for a history of urticaria before the first prescription and for a history of any of the events

**TABLE III.** ORs and 95% CIs of the risk of an allergic-like event following the second penicillin prescription after an allergic-like event following the first penicillin

Variable	OR	95% CI
Unadjusted OR using "narrow" definition of an allergic-like event*	11.2	8.6, 14.6
Accounting for GP practice	11.2	8.7, 14.6
Adjusting for prior urticaria	9.1	7.0, 11.9
Adjusting for history of prior allergic-like event	8.8	6.8, 11.5
Sensitivity analyses		
OR using a broad definition of an allergic-like event†	9.9	9.8, 10.0
Allergic-like event 0 to 10 d after the 1st prescription, up to 30 d after the 2nd	10.7	7.6, 15.3
Allergic-like event 0 to 30 d after the 1st prescription, up to 10 d after the 2nd	10.7	7.6, 15.1
Allergic-like event 0 to 10 d after both prescriptions	11.1	7.1, 17.2
Excluding patients without 30 d of follow-up after 2nd penicillin	11.3	8.7, 14.7

\**Narrow*: These are codes for anaphylaxis, urticaria, angioedema, erythema multiforme, laryngeal spasm, dermatitis attributed to a drug, TEN, and adverse drug reactions attributed to a medication.

†*Broad*: These codes include the narrow codes plus codes for bronchospasm, asthma, and eczema, as well as a larger group of codes defining reactions to specific medications (Table E2 in the Online Repository).

constituting the narrow definition of an allergic-like event. Adjusting for a history of urticaria, age, and sex, the OR reduced to 9.1 (95% CI, 7.0-11.9). Adjusting for a prior history of any event consistent with the narrowly defined group of allergic-like events and for age and sex reduced the OR to 8.8 (95% CI, 6.8-11.5; Table III).

By using the broad group of codes to define allergic-like events, the unadjusted OR was 9.9 (95% CI, 9.8-10.0), which is not a substantive change from the primary analysis. With this broad group of codes, the incidence of a penicillin-associated event with the first administration of the antibiotic increased from 0.18% to 9%, a 50-fold difference. Interestingly, by using the broad rather than the narrow codes, the probability of getting a second penicillin prescription was slightly higher in the group with an event after the initial prescription (risk ratio, 1.130; 95% CI, 1.127-1.133) compared with patients who did not have an allergic-like event after the first prescription. Accounting for general practitioner practice did not meaningfully change the OR of the basic primary result (Table III). There was no substantive difference in the ORs and 95% CIs when limiting the interval from prescription to allergic-like event of either the first or second penicillin to 10 days or when excluding patients who were not in the database for a full 30 days after the second prescription for penicillin (Table III).

Age was not a confounder or a risk factor, but it was an effect modifier ( $P = .009$ ). There was substantial variation in risk of an allergic-like event across age categories, with

the younger and older patients having the lower risk (Table E5 in the Online Repository).

## DISCUSSION

We used a large, electronic, medical-record database to determine the frequency of represcription of penicillin to allergic individuals and to compare the risk of a second event in those who had had a previous allergic-like event with those who had not. Of more than 3 million patients who had received at least one penicillin prescription, only a small percentage (0.18%) experienced an allergic-like event by using a narrow definition. Nearly half of those allergic patients were subsequently given another prescription for a penicillin. The probability of their receiving a second penicillin prescription after an initial event was reduced by approximately 20% compared with the probability in those who had not experienced an event.

Of the more than 2 million patients in the cohort who received 2 or more prescriptions for penicillin, the risk for having an allergic-like event was approximately 9 times greater for those who had an allergic-like event after the first penicillin prescription compared with those who had not experienced such an event after the first prescription. However, only 1.89% of the patients who had an event after the first prescription for penicillin experienced another event after the second prescription.

These results suggest that allergic-like events, those consistent with a hypersensitivity reaction, occur less frequently than previously thought, at least among outpatients. Urticaria was the most frequent allergic-like event, representing approximately three fourths of all events. The most serious events, anaphylaxis and TEN, accounted for about 0.5% and 0.2% of the initial events. The overall rate of anaphylaxis per course of penicillin is also much less frequent than reported in the literature (0.01%-0.05%).<sup>2</sup>

The availability of a large, population-based, medical record provides a unique opportunity to address the clinically important issues surrounding penicillin allergy. It is important to emphasize that we studied clinical events and not patient reports of allergy. Most studies of drug allergy have focused on hospitalized patients, a group that might have a different reaction rate than outpatients. Our study is focused on outpatients, a large and important patient group. It is in the outpatient setting that patients are most likely to be labeled as allergic to penicillin.<sup>7</sup> Also, our study attempts to consider all allergic-like events and is not limited to dermatologic events. Thus we are attempting to capture the more serious clinical events related to drug hypersensitivity occurring in the outpatient population.

Our results must be interpreted with caution. First, it is possible that our choice of codes omits codes consistent with hypersensitivity reactions. It also is possible that we included codes for events other than those consistent with a hypersensitivity reaction. We attempted to choose codes conservatively for the narrow group, omitting codes that might suggest nonunique causes. Repeating our analysis with a broader group of codes supports our result,

although the incidence of events increases from 0.18% to 9%. It is likely that 9% is an overestimate and that the true incidence is bounded by these 2 values. Of note, the fact that those with the broader codes after a first prescription for penicillin were more likely to be prescribed a second penicillin prescription than those without those codes and that this was very different from those with the narrower codes suggests that the broad codes (eg, asthma) are capturing events that are not attributed by their physicians to the penicillin prescriptions. Yet the fact that the OR for a subsequent event is completely consistent between the 2 indicates that some of the events captured by the expanded code might indeed be attributable to penicillin.

Another limitation is the difficulty in studying time from prescription to the clinical event consistent with a hypersensitivity reaction. Medical records are used to record patient contacts with their physician; it is possible that events were not reported immediately, not diagnosed, or both. Also, it is possible that prescriptions were not filled, not filled promptly, or once filled, the penicillin was not taken. To validate our methods, we repeated our analysis with a second time interval of 0 to 10 days, examining the effect of the shorter surveillance period after both the first and second penicillin prescriptions and after either the first or the second prescription. These additional analyses did not substantively change the results.

Undercounting of severe reactions might have occurred because it is possible that patients who had a previous very severe reaction before entering the GPRD UTS database might be more likely to avoid future prescriptions for penicillin and therefore not be captured in our database. For example, it is logical to assume that most patients who had TEN or anaphylaxis associated with a penicillin prescription did not receive a second prescription. Similarly, it could be hypothesized that patients who had a very severe event after the first prescription are less likely to receive a second prescription and therefore were not included in our study group. Finally, the generalizability of the GPRD to other countries is not completely clear, given differences in population demographics.

We emphasize that because the GPRD is an outpatient medical record, the use of intravenous preparations is underrepresented. The route of prescription has been reported to influence the rate of reaction.<sup>29</sup> Our study cannot assess this possible risk factor. We could not adjust for the use of nonsteroidal anti-inflammatory medications because over-the-counter use was not recorded. However, to be a confounder, nonsteroidal anti-inflammatory drug use concomitant with the second penicillin prescription would need to have differed between those who had a prior allergy after penicillin and those who did not have a prior allergy after penicillin, which seems unlikely.

In these times of concern about patient safety and medical errors, our findings might be cause for concern. It appears that far more patients than expected received a prescription for penicillin after an event consistent with a hypersensitivity reaction. At the same time, although the risk of a second event was markedly increased, serious

outcomes were relatively rare. That is, although the OR was approximately 10, the risk difference was very small ( $1.89\% - 0.17\% = 1.72\%$ ). Furthermore, the older and younger patients did not have the same risk as the more middle-aged patients. All of these findings suggest the need for further research.

In summary, this study confirms that the risk of an allergic-like event after penicillin is markedly increased (about 10-fold) in those who have had such a prior event, although the absolute difference is small (1.72%). These results should be interpreted cautiously because the analysis did not include patients who might have had a reaction before entering the database. Nevertheless, it is striking that patients who had an allergic-like event after penicillin frequently received subsequent penicillin prescriptions.

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