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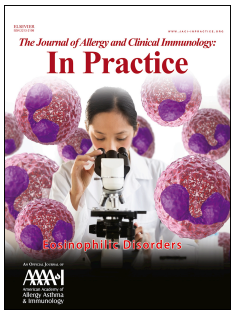

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Readiness for **PEN**icillin allergy testing: **P**erception of **A**llergy **L**abel (PEN-PAL) Survey

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Clinical Implications: Patients reporting penicillin allergy believe their allergy to be permanent, would take penicillins if tested negative, but are rarely referred for penicillin testing, leading to differential antibiotic utilization.

Keywords: Penicillin; allergy; testing; de-labeling; PEN-PAL

Although 8-20% of patients are reported to carry a penicillin allergy label (PAL), more than 95% of these individuals will be negative on standardized penicillin allergy (PA) testing[1-3]. Patients with a PAL are subject to adverse health outcomes, including increased nosocomial infections, surgical site infections, prolonged time to administration of emergent antibiotics, prolonged hospitalizations, and hospital readmissions[4-6]. PA testing has been shown to be safe, facilitates antibiotic stewardship, and data suggests it is likely to be cost effective [1,7,8]. While much is published regarding the worse outcomes of a PAL and approaches to remove a PAL[9], little is known about PA patients' willingness to undergo PA testing. Therefore, we conducted the "Readiness for **PEN**icillin allergy testing: **P**erception of **A**llergy **L**abel (PEN-PAL)" survey to ascertain beliefs, perceptions, and experiences of a current self-reported PA patient population and to identify potential barriers to testing.

A survey (**Figure E1 in the Online Repository**) was created using REDCap (Research Electronic Data Capture), an established secure web-based application for creating and managing online surveys and databases. Of note, the only mandatory question was whether the patient reported either a current penicillin allergy, reported a historical penicillin allergy which was removed, or reported no penicillin allergy. The participants were free to omit answers to all other questions if they did not recall the answer or if they chose not to answer, and thus, the denominator of responses varied slightly by question. An email with the survey was sent to 18,943 adult patients (≥18 years of age) pre-consented to receive IRB-approved study advertisements in the context of the MyResearch at Vanderbilt (MRAV) program,

with three reminder emails, from late October 2019 to early December 2019. Additional details regarding REDCap and MRAV can be found in the **EMethods in the Online Repository.**

For continuous variables, median and interquartile range were calculated. Statistical comparisons were performed between the three penicillin allergy status groups. For categorical variables, Fisher's exact test or Pearson's chi-squared statistic were used. Wilcoxon rank-sum test was used to compare continuous variables. Statistical analysis was performed using Stata 15.0.

18,943 eligible participants of MRAV, 5284(28%) completed the survey. 1047(20%) reported a current PA, 4091(77%) reported no PA, and 146(3%) reported a historical PA which was removed. Participants reporting a current PA were more likely to be female (Pearson, $P<0.005$) (**Table 1**).

Patients reporting a current PAL experienced their index reaction at a median age of 16 [IQR 6-30] with most reactions occurring $\geq$10 years ago (915/1040, 88%). The three most common types of reactions were rash only (510/1037, 49%), an unknown reaction (141/1037, 14%), or "anaphylaxis" (139/1037, 13%), and all reactions recalled are detailed in **Table E1 in the Online Repository**. Of the 116/998(12%) who endorsed receiving epinephrine, 77(66%) recalled the index reaction of "anaphylaxis" and 39(34%) received epinephrine but didn't recall the index reaction of "anaphylaxis." Following the index reaction, of those who recalled their highest level of care required (805/1034, 78%), most required only an outpatient visit, phone call, or self-discontinued penicillin (612/805, 76%), while few utilized the emergency department (106/805, 13%), inpatient floor (62/805, 8%), or the intensive care unit (17/805, 2%).

Antibiotic utilization differed among those reporting a current PA and the other groups (**Figure 1)**. Compared to no reported PA, participants reporting a current PA less frequently recalled receiving penicillin** (subsequent to index reaction) (11% vs 70%), amoxicillin** (24% vs 79%),

amoxicillin/clavulanate** (12% vs 46%), and cephalexin* (40% vs 45%), and more frequently recalled receiving fluoroquinolones** (11% vs 7%), macrolides** (15% vs 6%), tetracyclines** (8% vs 4%), clindamycin** (6% vs 1%), sulfa antimicrobials* (6% vs. 4%), and vancomycin* (2% vs 1%) (Pearson chi-squared *$P<0.05$, **$P<0.005$). Compared to participants reporting a historical PA which was removed, participants reporting a PA less frequently recalled receiving penicillin** (subsequent to index reaction) (11% vs 47%), amoxicillin** (24% vs 63%), and amoxicillin/clavulanate** (12% vs 35%), and more frequently recalled receiving clindamycin* (11% vs 6%), tetracyclines* (8% vs 2%), and macrolides* (15% vs 8%) (Fisher's exact test *$P<0.05$, **$P<0.005$) **(Figure 1)**. Furthermore, 198/1040(19%) with a PAL had taken and tolerated a penicillin, but continued to self-report their PAL.

Participants reporting a current PA often discussed their PA with a primary care provider (639/1035, 61%), but that conversation rarely comprised of the negative consequences of a PA (73/1040, 7%), and the minority were offered referral to an allergist for PA testing (38/1040, 4%). Regarding surgeries in PA patients, 869/1039(81%) reported both a PA and a surgery since their index reaction, and majority of these (747/861, 87%) had a pre-operative discussion of their PA with a provider. The minority of these participants perceived their PA had an adverse effect on their medical care (167/1040, 16%). Most (799/989, 81%) believed their PA to be permanent, and many believed it "likely" or "very likely" to react to penicillin today (397/1039, 38%). Despite this, a high proportion (813/1016, 80%) would take penicillin for an indicated cause if an allergist tested them and found it to be safe. Overall, 561/1024 (55%) were interested in PA testing.

This survey is the first which attempts to capture a large population-based sample of attitudes and experiences of a current reported PA patient, and while the survey link was only sent to those accessing care at a tertiary medical center, we believe that the conclusions are generalizable to a population level. Limitations of the study which we do not believe will significantly change conclusions are that many of the answers involve the participants recollection of reaction details and medications, and we did not ask

the participants whether they had other antibiotic allergies, which may independently alter the antibiotics received.

We identified educational points for both patients and providers. Notably, >80% of those with a current PA perceived their PA as permanent. However, if the reported histories of rash only, "my family member told me I'm allergic but I don't recall," gastrointestinal distress, unknown history, and family history of penicillin allergy were applied to a recently validated penicillin allergy risk stratification scheme[9,10], 71% of our PA participants' reported histories would be categorized as low risk, and thus likely to tolerate a single-dose amoxicillin oral challenge today. Most (561/1024, 55%) with a current PAL were interested in PA testing, and the majority (813/1016, 80%) indicated they would take a penicillin if testing was negative. Despite this, primary care doctors rarely referred our participants for PA testing (38/1040, 4%).

Self-reported antibiotic utilization was different between those with and without a current PAL. PAL participants recalled significantly fewer β-lactam prescriptions and increased prescriptions of antibiotics associated with potentially reduced treatment efficacy. Those with a current PAL also recalled fewer β-lactam prescriptions than those with a historical PAL which was removed, highlighting the importance of PAL testing in guiding antibiotic prescribing patterns.

PAL patients believed their PAL to be permanent and several retained a PAL despite proven tolerance. Although they expressed interest in formal allergy assessment, and most would take penicillin if tested negative, they were rarely referred, leading to differential antibiotic utilization in favor of broader spectrum and potentially less effective therapy.

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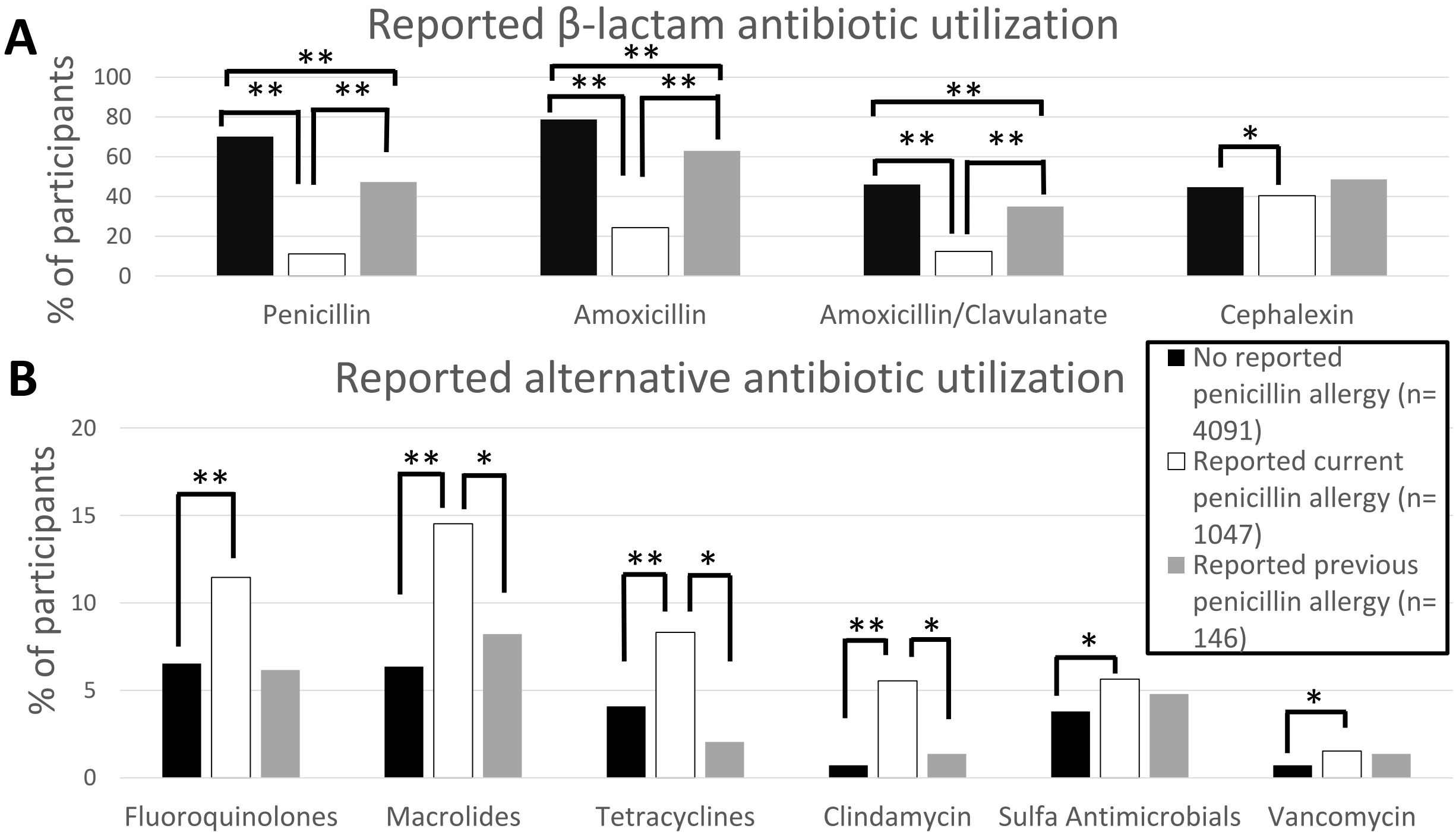
Figure 1: Reported antibiotic utilization, by penicillin allergy status. A) Participants reporting a current PA less frequently reported utilization of penicillin** (after index reaction, when applicable), amoxicillin**, amoxicillin/clavulanate**, and cephalexin*. **B)** Participants reporting a current PA more frequently reported utilization of fluoroquinolones**, macrolides**, tetracyclines**, clindamycin**, sulfa antimicrobials*, and vancomycin* (* $P<0.05$, ** $P<0.005$, no bar= *NS*).

Table 1: Demographics of PEN-PAL Survey Participants

Demographic	No Penicillin Allergy (n=4091)	Current Penicillin Allergy (n=1047)	Removed Penicillin Allergy (n= 146)	*P* value
Median Age [IQR]	62 [51-70]	61 [51-69]	64 [51-71]	NS
Gender No. (%)				
Male	1599 (39)	275 (26)	45 (31)	<0.005
Female	2464 (60)	769 (73)	99 (68)	
Other	2 (0)	0 (0)	1 (1)	
Declined to answer	26 (1)	3 (0)	1 (1)	
Race No. (%)				
White	3720 (92)	972 (93)	136 (93)	NS
African American	167 (4)	44 (4)	3 (2)	
Other	177 (4)	26 (2)	7 (5)	
Declined to answer	27 (1)	5 (0)	0 (0)	


A
Reported β-lactam antibiotic utilization
% of participants
100
80
60
40
20
0
**
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**
*
Penicillin
Amoxicillin
Amoxicillin/Clavulanate
Cephalexin
B
Reported alternative antibiotic utilization
% of participants
20
15
10
5
0
**
**
*
**
*
**
*
*
*
Fluoroquinolones
Macrolides
Tetracyclines
Clindamycin
Sulfa Antimicrobials
Vancomycin
No reported penicillin allergy (n= 4091)
Reported current penicillin allergy (n= 1047)
Reported previous penicillin allergy (n= 146)

ETable 1: Index reactions recalled by those reporting a penicillin allergy (n= 1037)

Reaction	Number (%)
Rash only	510 (49)
"A family member told me; I don't remember"	141 (14)
Anaphylaxis	139 (13)
Swelling	68 (7)
GI Distress	47 (5)
Unknown	34 (3)
Hives	33 (3)
Family history of penicillin allergy	5 (0.5%)
Other	60 (6)

Online Repository

EMethods

REDCap

Study data were collected and managed using REDCap electronic data capture tools hosted at Vanderbilt University Medical Center[E1,E 2]. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

MyResearch at Vanderbilt

MyResearch at Vanderbilt (MRAV) is a participant repository recruitment tool available to Vanderbilt researchers that reaches over 18,000 My Health at Vanderbilt users that have previously confirmed they would like to be contacted directly for research. This repository provides investigators a forum for advertising for volunteers for a specific study. Email notifications are limited to IRB approved language, describe study specifics and provide contact information. To utilize this initiative, investigators complete a MyResearch Access Request that is reviewed to ensure the recruitment tool and requested number of contacts are appropriate.

References:

E1. Harris P, Taylor R, Thielke R, Payne J, Gonzalez N, Conde J. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009; 42:377-81.

E2. Harris P, Taylor R, Minor B, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform 2019; 95:103208.

EFigure 1: PENPal Survey Questions

EFigure 1: PENPal Survey Questions

1. **Sole mandatory question:** Do you have a penicillin allergy?
    a. Yes
    b. No
    c. I had a penicillin allergy, but it has since been disproven
2. Age: (list age)
3. Sex
    a. Male
    b. Female
    c. Other
4. Race/ethnicity
    a. White
    b. African American
    c. Latino
    d. Asian
    e. Mixed
    f. Other
        i. List other Race/Ethnicity
5. Do you recall needing antibiotics for any reason in your lifetime?
    a. Yes
    b. No
6. Which antibiotics have you taken without issue in your lifetime? Choose all that apply, only choose if you are confident
    a. I have confidently taken none of these specifically listed here
    b. Penicillin
    c. Amoxicillin (Amoxil)
    d. Amoxicillin/Clavulanic acid (Augmentin)

e. Cephalexin (Keflex)

f. Ceftriaxone (Rocephin)

g. I have taken an antibiotic not on this list

i. Which other antibiotics not listed in the previous question have you taken without issue in your lifetime?

h. Unsure

7. **(Answered by those reporting to be female only)** Are you currently or have you ever been pregnant?

a. Yes

b. No

8. **(Answered by those reporting to be female and penicillin allergic only)** Do you perceive your penicillin allergy affected your pregnancy, delivery, or time while nursing/breastfeeding in any way?

a. Yes

b. No

c. I became allergic to penicillin after my last pregnancy

i. Please list how you perceive your penicillin allergy affected your pregnancy, delivery, or time while nursing/breastfeeding

9. **(Answered by those reporting to be female only)** Did you require antibiotics while pregnant, during delivery, or when you were nursing/breastfeeding?

a. Yes

b. No

i. Please list the antibiotics you confidently remember taking while pregnant, during delivery, or when you may have been nursing/breastfeeding

Remainder of questions answered by those reporting to be currently penicillin allergic only

10. How many years ago did you acquire your penicillin allergy?

a. Less than one year ago

b. Greater than one, but less than five years ago

c. Greater than five, but less than ten years ago

d. Greater than 10 years ago

e. I did not personally have a reaction to penicillin

f. Not sure

11. Around what age did you acquire your penicillin allergy? (List age)

12. What was your reaction to penicillin?

a. Rash only

b. Anaphylaxis

c. Gastrointestinal distress only

d. My family member told me I'm allergic. I do not remember the reaction

e. I avoid penicillin because of a family member who did not tolerate penicillin

f. Unknown

g. Other

i. Please list other reaction

13. During the event leading to your penicillin allergy, what was the most involved level of care you required?

a. It was stopped without talking to a provider

b. A health care practitioner recommended stopping it over the phone

c. Urgent Care/Primary Care doctor visit

d. Emergency Room

e. Inpatient hospitalization, not requiring the intensive care unit

f. Inpatient hospitalization, requiring the intensive care unit

g. The penicillin allergy label was acquired based on a reaction that occurred with a relative

h. Do not remember

14. Did your reaction to penicillin require epinephrine (otherwise known as epi, epipen) injection?

a. Yes
b. No

15. If you were prescribed penicillin today, how likely would it be for you to have a reaction to it?
    a. Very likely
    b. Likely
    c. Unsure
    d. Unlikely
    e. Very unlikely
16. Do you recall needing antibiotics for any reason SINCE ACQUIRING YOUR PENICILLIN ALLERGY?
    a. Yes
    b. No
17. Did you provider discuss your penicillin allergy prior to prescribing those antibiotics
    a. Yes
    b. No
18. Which antibiotics have you taken without issue SINCE ACQUIRING YOUR PENICIILIN ALLERGY? Choose all that apply, only choose if you are confident.
    a. I have confidently taken none of these specifically listed here
    b. Penicillin
    c. Amoxicillin (Amoxil)
    d. Amoxicillin/Clavulanic acid (Augmentin)
    e. Cephalexin (Keflex)
    f. Ceftriaxone (Rocephin)
    g. I have taken an antibiotic not on this list
        i. Which other antibiotics not listed in the previous question have you taken without issue SINCE ACQUIRING YOUR PENICILLIN ALLERGY?
    h. Unsure

19. Has your primary care provider talked to you about your penicillin allergy?
    a. Yes
    b. No
20. Has your primary care provider offered to refer you for penicillin allergy testing?
    a. Yes
    b. No
21. Has any provider ever reported to you that your penicillin allergy is affecting your medical treatment?
    a. Yes
    b. No
22. Have you had a surgery since acquiring your penicillin allergy?
    a. Yes
    b. No
23. In the time leading up to your surgery, did a health care practitioner ask you about your penicillin allergy?
    a. Yes
    b. No
24. Do you believe that your penicillin allergy is permanent?
    a. Yes
    b. No
25. If your regular healthcare provider wanted to prescribe penicillin, and an allergist tested you and found it to be safe, would you take it?
    a. Yes
    b. No
        i. If not, please list why
26. Would you be interested in being referred for penicillin allergy evaluation?
    a. Yes
    b. No