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MAJOR ARTICLE

Penicillin Allergy Testing Is Cost-Saving: An Economic Evaluation Study

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(See the Editorial Commentary by Mattingly and Heil on pages 939-41.)

Background. Having a penicillin allergy label is associated with the use of less appropriate and more expensive antibiotics and increased healthcare utilization. Penicillin allergy testing results in delabeling most allergy claimants and may be cost-saving. This study aimed to project whether penicillin allergy testing in patients reporting a penicillin allergy is cost-saving.

Methods. In this economic evaluation study, we built decision models to project the economic impact of 2 strategies for a patient with a penicillin allergy label: (1) perform diagnostic testing (drug challenges, with or without skin tests); and (2) do not perform diagnostic testing. The health service perspective was adopted, considering costs with penicillin allergy tests, and with hospital bed-days/outpatient visits, antibiotic use, and diagnostic testing. Twenty-four base case decision models were built, accounting for differences in the diagnostic workup, setting (inpatient vs outpatient) and geographic region. Uncertainty was explored via probabilistic sensitivity analyses.

Results. Penicillin allergy testing was cost-saving in all decision models built. For models assessing the performance of both skin tests and drug challenges, allergy testing resulted in average savings (in United States [US] dollars) of $657 for inpatients (US: $1444; Europe: $489) and $2746 for outpatients (US: $256; Europe: $6045). 75% of simulations obtained through probabilistic sensitivity analysis identified testing as the less costly option.

Conclusions. Penicillin allergy testing was projected to be cost-saving across different scenarios. These results are devised to inform guidelines, supporting the adoption of policies promoting widespread testing of patients with a penicillin allergy label.

Keywords. drug allergy; drug challenge; economic evaluation; penicillin allergy.

A penicillin allergy is more commonly reported than an allergy to any other drug class [1]. Studies performed in general populations identify that up to 5% of individuals claim to be allergic to penicillins, and this percentage often rises to >10% in studies assessing outpatients or inpatients [2–4]. Most penicillin allergy claimants do not have a true penicillin allergy [5, 6]. Multiple studies have shown that performing diagnostic tests results in delabeling most (>90%) patients reporting penicillin allergies, allowing them to be safely treated with penicillins. This is particularly important, as patients with a penicillin allergy label often receive less adequate antibiotics (with penicillin allergy testing recommended as part of antibiotic stewardship [7]), which not only results in worse clinical outcomes, but also in an increased healthcare burden. Patients with a penicillin allergy label have been reported to receive more expensive antibiotics [8, 9], have longer hospital stays [10, 11], are more frequently readmitted [12], and have a higher frequency of outpatient visits [13]. There is perception that penicillin allergy testing may be cost-saving in specific populations [14–16], though supportive data are sparse. Studies to date have largely assessed inpatients and did not explore the uncertainties associated with their estimates [8, 10].

Therefore, in this economic evaluation study, we used different sources to build decision models aiming to assess whether penicillin allergy testing is cost-saving. We explored the uncertainty of costs and consequences estimates by simulation methods and by building distinct models accounting for regional, patient setting, and test performance differences.

METHODS

Model Structure

This is a partial economic evaluation study, because it is primarily focused on costs, and it follows Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines [17]. We built decision models projecting whether penicillin allergy testing would be cost-saving. That is, we projected whether the costs of testing patients claiming to be allergic to

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penicillins would be lower than the underlying potential savings in hospital bed-days, outpatient visits, and antibiotic use. We adopted the health system perspective, considering direct medical costs. Estimates are expressed in United States (US) dollars ($) as of December 2017.

The population of this study consisted of patients with a penicillin allergy label, for whom 2 alternative scenarios were compared: performing vs not performing penicillin allergy diagnostic testing. In the first scenario, all patients are subject to a diagnostic workup—if positive, patients are treated as truly allergic; if negative, patients are considered to be tolerant to penicillins and treated as nonallergic (such assumption was explored in univariate sensitivity analyses). In the second scenario, testing for penicillin allergy is not performed, with all patients being treated as allergic to penicillins irrespective of whether they have a true allergy.

Patients whose initial reaction consisted of a severe cutaneous adverse reaction (< 1 in 10 000 exposures [18]), where any testing or re-exposure is contraindicated [19], were excluded from these scenarios.

We built and analyzed 24 different base case ("main") decision models (see Figure 1 for an example), accounting for differences/variants in the diagnostic workup, setting (inpatients vs outpatients), and geographical region (Figure 2). The diagnostic workflows encompassed sequential performance of skin testing and drug challenge (DC; ie, drug provocation testing), or direct performance of DC without prior skin tests. The former workflow was based on current recommendations [18, 19] and consisted of skin tests being performed to all individuals—if positive, patients were considered to be truly allergic to penicillins; if negative, individuals were subject to a subsequent DC (a positive DC indicated that the patient is truly allergic to penicillins, while a negative DC indicated penicillin tolerance). On the other hand, models involving direct performance of DC (which is recommended in American and British pathways for low-risk patients [20]) consisted of (1) sole performance of DC for all patients, or (2) direct performance of DC only among patients reporting a nonimmediate reaction, with the remaining individuals receiving sequential testing (skin tests followed by DC).

Both for models involving sequential testing and for models consisting of direct DC, we built series of models assessing inpatients and series assessing outpatients. For inpatients, we compared the costs of the 2 alternatives considering the hospitalization period and the possibility of 30-day readmissions. For outpatients, we took into account the frequency of ambulatory visits and antibiotic use for a period of 5 years after penicillin allergy testing. To account for regional differences, we developed variants for each model specifically including data from the US, Europe, and Portugal (an example European country for which we had access to the most information).

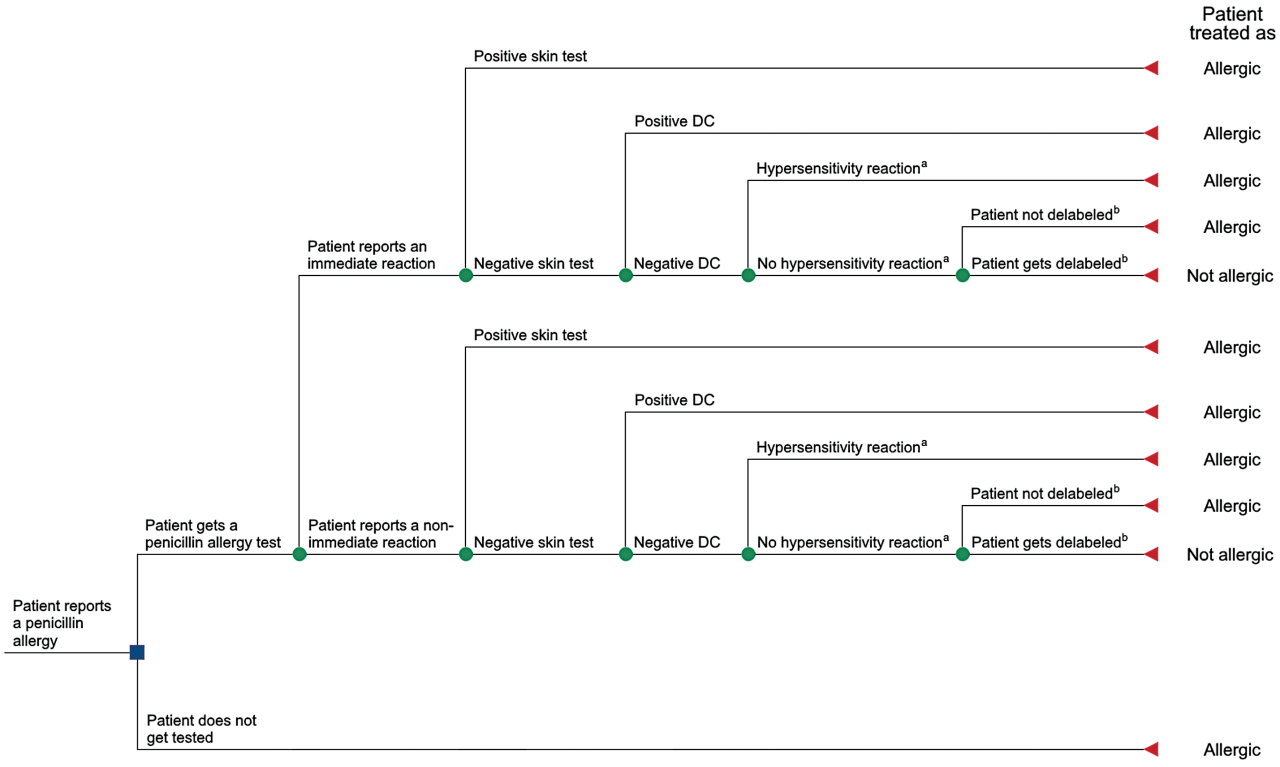

Figure 1. Example of a decision tree: comparison between penicillin testing and not testing among inpatients. [a]Hypersensitivity reaction to penicillins during treatment (ie, perceived false-negative drug challenge. [b]In the base case scenario, we assumed that all patients with negative results were delabeled. Abbreviation: DC, drug challenge.

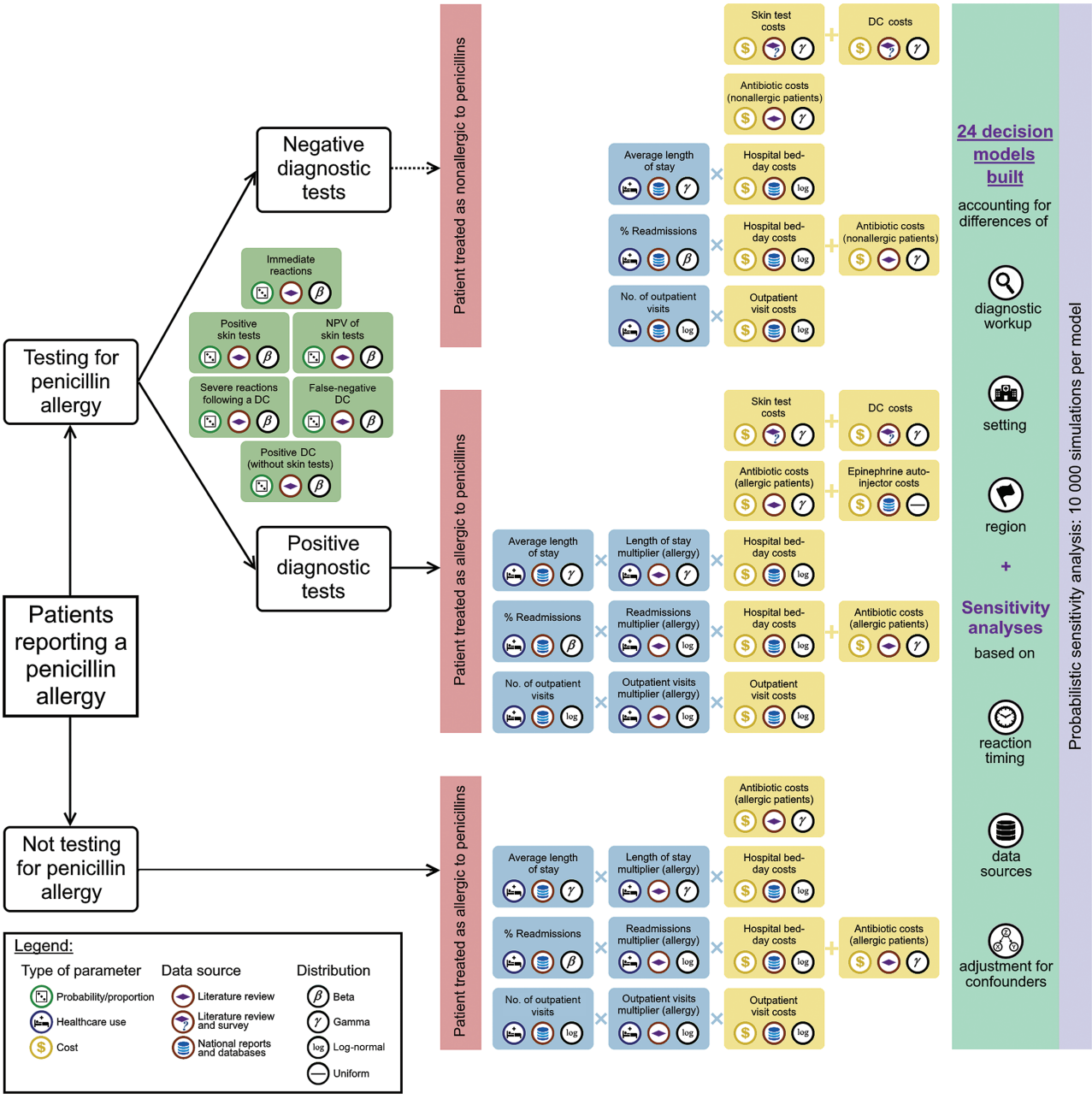

Figure 2. Graphical description of the methods and sources used for building decision models. Abbreviations: DC, drug challenge; NPV, negative predictive value.

Model Inputs

A full description on model inputs can be found in the Supplementary Methods. This includes information sources, statistical methods, and assumptions on how proportions/probabilities, healthcare use, and costs were estimated. In addition, Figure 2 and Table 1 summarize variables tested with their corresponding data sources.

Data Analysis

For each decision model, we projected the respective incremental net benefit, defined as the cost difference between testing and not testing for penicillin allergy. An incremental net benefit > 0 identified testing as the less costly alternative.

These analyses were based on base case input values ("most likely input values") for all variables in every decision model (Table 1). However, all these estimates have an associated uncertainty, which we addressed through sensitivity analyses. We performed univariate/1-way deterministic sensitivity analyses on the percentage of patients with negative tests who must be treated as nonallergic for penicillin allergy testing to become cost-saving, because, in clinical practice, a substantial percentage of patients with negative testing are not appropriately

Table 1. Decision Models' Inputs and Respective Distributions

Variable	Distribution Parameters			Distribution	Source
	Mean	SD	Median		
A. Proportions					
Immediate reactions					
Inpatients					
All regions	0.220	0.0539	…	Beta	[21]
US	0.210	0.0837	…	Beta	[21]
Europe	0.146[a]	0.1897[a]	…	Beta	[21]
Portugal	0.146[b]	0.1897[b]	…	Beta	[21]
Outpatients					
All regions	0.271	0.1889	…	Beta	[21]
US	0.224	0.1058	…	Beta	[21]
Europe	0.306[a]	0.2168[a]	…	Beta	[21]
Portugal	0.329[a]	0.1750[a]	…	Beta	[21]
Positive skin tests					
Nondiscriminated reaction timing					
Inpatients					
All regions	0.065	0.0548	…	Beta	[21]
US	0.058	0.0592	…	Beta	[21]
Europe	0.077[a]	0.2718[a]	…	Beta	[21]
Portugal	0.077[b]	0.2718[b]	…	Beta	[21]
Outpatients					
All regions	0.115	0.0995	…	Beta	[21]
US	0.109[a]	0.1261[a]	…	Beta	[21]
Europe	0.106	0.0775	…	Beta	[21]
Portugal	0.105	0.0400	…	Beta	[21]
Immediate reactions					
Inpatients					
All regions	0.044	0.0316	…	Beta	[21]
US	0.041[a]	0.0316[a]	…	Beta	[21]
Europe	0.044[c]	0.0316[c]	…	Beta	[21]
Portugal	0.044[c]	0.0316[c]	…	Beta	[21]
Outpatients					
All regions	0.144	0.0917	…	Beta	[21]
US	0.041[a]	0.0316[a]	…	Beta	[21]
Europe	0.176	0.0943	…	Beta	[21]
Portugal	0.176[b]	0.0943[b]	…	Beta	[21]
Nonimmediate reactions					
Inpatients					
All regions	0.128[a]	0.2398[a]	…	Beta	[21]
US	0.128[c]	0.2398[c]	…	Beta	[21]
Europe	0.128[c]	0.2398[c]	…	Beta	[21]
Portugal	0.128[c]	0.2398[c]	…	Beta	[21]
Outpatients					
All regions	0.051	0.0412	…	Beta	[21]
US	0.051[c]	0.0412[c]	…	Beta	[21]
Europe	0.068	0.0510	…	Beta	[21]
Portugal	0.068[b]	0.0510[b]	…	Beta	[21]
Negative predictive value of skin tests					
Nondiscriminated reaction timing					
Inpatients					
All regions	0.992	0.0020	…	Beta	[21]
US	0.993	0.0010	…	Beta	[21]
Europe	0.962[a]	0.0533[a]	…	Beta	[21]
Portugal	0.962[b]	0.0533[b]	…	Beta	[21]
Outpatients					
All regions	0.959	0.0265	…	Beta	[21]
US	0.975	0.0173	…	Beta	[21]

Table 1. Continued

Variable	Distribution Parameters			Distribution	Source
	Mean	SD	Median		
Europe	0.955	0.0283	…	Beta	[21]
Portugal	0.970	0.0105	…	Beta	[21]
Immediate reactions					
Inpatients					
All regions	0.937	0.0566	…	Beta	[21]
US	0.941	0.0548	…	Beta	[21]
Europe	0.937[c]	0.0566[c]	…	Beta	[21]
Portugal	0.937[c]	0.0548[c]	…	Beta	[21]
Outpatients					
All regions	0.940	0.0400	…	Beta	[21]
US	0.941	0.0548	…	Beta	[21]
Europe	0.940	0.0469	…	Beta	[21]
Portugal	0.940[b]	0.0469[b]	…	Beta	[21]
Nonimmediate reactions					
Inpatients					
All regions	0.990	0.0059	…	Beta	[21]
US	0.990[c]	0.0059[c]	…	Beta	[21]
Europe	0.990[c]	0.0059[c]	…	Beta	[21]
Portugal	0.990[c]	0.0059[c]	…	Beta	[21]
Outpatients					
All regions	0.951	0.0300	…	Beta	[21]
US	0.990	0.0059	…	Beta	[21]
Europe	0.947	0.0265	…	Beta	[21]
Portugal	0.929	0.0742	…	Beta	[21]
Severe reactions following a DC					
Nondiscriminated reaction timing					
Outpatients					
All regions	0.0016	0.0007	…	Beta	[21]
US	0.002	0.0010	…	Beta	[21]
Europe	0.0014	0.0006	…	Beta	[21]
Portugal	0.0014[b]	0.0006[b]	…	Beta	[21]
Immediate reactions					
Outpatients					
All regions	0.0006	0.0005	…	Beta	[21]
US	0.0006[c]	0.0005[c]	…	Beta	[21]
Europe	0.0005	0.0004	…	Beta	[21]
Portugal	0.0005[b]	0.0004[b]	…	Beta	[21]
Nonimmediate reactions					
Outpatients					
All regions	0.0007	0.0006	…	Beta	[21]
US	0.0007[c]	0.0006[c]	…	Beta	[21]
Europe	0.0007	0.0006	…	Beta	[21]
Portugal	0.0007[b]	0.0006[b]	…	Beta	[21]
False-negative DC					
Nondiscriminated reaction timing					
Inpatients					
All regions	0.0097	0.0066	…	Beta	[21]
US	0.012	0.0100	…	Beta	[21]
Europe	0.0097[c]	0.0066[c]	…	Beta	[21]
Portugal	0.0097[c]	0.0066[c]	…	Beta	[21]
Outpatients					
All regions	0.017	0.0100	…	Beta	[21]
US	0.011	0.0029	…	Beta	[21]
Europe	0.007	0.0024	…	Beta	[21]
Portugal	0.017[a]	0.0235[a]	…	Beta	[21]
Immediate reactions					

Table 1. Continued

Variable	Distribution Parameters			Distribution	Source
	Mean	SD	Median		
Inpatients					
All regions	0.007	0.0066	…	Beta	[21]
US	0.007[c]	0.0066[c]	…	Beta	[21]
Europe	0.005	0.0045	…	Beta	[21]
Portugal	0.005[b]	0.0045[b]	…	Beta	[21]
Outpatients					
All regions	0.012	0.0100	…	Beta	[21]
US	0.012[c]	0.0100[c]	…	Beta	[21]
Europe	0.011	0.0100	…	Beta	[21]
Portugal	0.011[b]	0.0100[b]	…	Beta	[21]
Nonimmediate reactions					
Inpatients					
All regions	0.041	0.0283	…	Beta	[21]
US	0.041[c]	0.0283[c]	…	Beta	[21]
Europe	0.037	0.0332	…	Beta	[21]
Portugal	0.037[b]	0.0332[b]	…	Beta	[21]
Outpatients					
All regions	0.048	0.0300	…	Beta	[21]
US	0.048[c]	0.0300[b]	…	Beta	[21]
Europe	0.048	0.0400	…	Beta	[21]
Portugal	0.048[c]	0.0400[c]	…	Beta	[21]
Positive DC without prior skin tests					
Nondiscriminated reaction timing					
Inpatients					
All regions	0.048[a]	0.8246[a]	…	Beta	[22–37]
US	0.016[a]	0.2164[a]	…	Beta	[22, 25, 27, 28, 30, 36]
Europe	0.045[a]	0.1507[a]	…	Beta	[26, 32, 34, 35, 37]
Portugal	0.045[b]	0.1507[b]	…	Beta	[b]
Outpatients					
All regions	0.056[a]	0.7708[a]	…	Beta	[23–26, 28–31, 33–37]
US	0.017[a]	0.3132[a]	…	Beta	[25, 28, 30, 36]
Europe	0.055[a]	0.6976[a]	…	Beta	[26, 34, 35, 37]
Portugal	0.055[b]	0.6976[b]	…	Beta	[b]
Severe reactions following a DC without prior skin tests					
Nondiscriminated reaction timing					
Inpatients					
All regions	0.006[a]	1.3256[a]	…	Beta	[22–37]
US	0.003[a]	0.5153[a]	…	Beta	[22, 25, 27, 28, 30, 36]
Europe	0.009[a]	0.6929[a]	…	Beta	[26, 32, 34, 35, 37]
Portugal	0.009[b]	0.6929[b]	…	Beta	[b]
Outpatients					
All regions	0.006[a]	1.2244[a]	…	Beta	[23–26, 28–31, 33–37]
US	0.004[a]	0.7044[a]	…	Beta	[25, 28, 30, 36]
Europe	0.005[a]	0.6303[a]	…	Beta	[26, 34, 35, 37]
Portugal	0.005[b]	0.6303[b]	…	Beta	[b]
B. Health services use					
Baseline average length of stay, d					
All regions	6.3	16.7	…	Gamma	[38–42]
US	4.5	9.8	…	Gamma	[38]
Europe	6.7	19.2	…	Gamma	[39–42]
Portugal	7.6	15.5	…	Gamma	[42]
Increase in LOS (multiplier) for patients with a penicillin allergy label[d]					
All regions	1.066	0.0578	…	Gamma	[10–12, 43–54]
US	1.099	0.0786	…	Gamma	[10, 43–46, 48, 53]
Europe	1.084	0.0066	…	Gamma	[11, 12, 52]
Portugal	1.088	0.0067	…	Gamma	[11, 52]

Table 1. Continued

Variable	Distribution Parameters			Distribution	Source
	Mean	SD	Median		
Baseline frequency of readmissions (proportion)					
All regions	0.095	0.0316	…	Beta	[38, 55–58]
US	0.139	0.024[e]	…	Beta	[38]
Europe	0.080	0.0141	…	Beta	[55–58]
Portugal	0.068	0.0173[e]	…	Beta	[56]
Increase in readmissions rate (multiplier) for patients with a penicillin allergy label (log-normal scale)[d]					
All regions	0.238	0.0541	…	Log-normal	[12, 45, 46, 50, 59]
US	0.224	0.0858	…	Log-normal	[45, 46]
Europe	0.189	0.0800	…	Log-normal	[12]
Portugal	0.189[b]	0.0800[b]	…	Log-normal	[b]
Baseline No. of outpatient visits within 5 y					
All regions	32.90	…	38.50	Log-normal	[60–63]
US	20.67	…	23.15[e]	Log-normal	[62, 63]
Europe	38.34	…	41.17	Log-normal	[61, 63]
Portugal	18.15	…	20.33[e]	Log-normal	[61, 63]
Increase in outpatient visits' frequency (multiplier) for patients with a penicillin allergy label[d]					
All regions	0.585[f]	0.5098[f]	…	Log-normal	[13, 15, 64, 65]
US	0.160[f]	0.0877[f]	…	Log-normal	[15, 64, 65]
Europe	5.28[f]	…	1.67[f]	Log-normal	[13]
Portugal	5.28[b]	…	1.67 [b]	Log-normal	[b]
C. Costs (2017 US dollars)					
Hospital bed-day ("daily hotel costs")					
All regions	684	…	543	Log-normal	[63, 66–69]
US	1728	…	1167[e]	Log-normal	[63, 66, 67]
Europe	433	…	256	Log-normal	[63, 66, 68]
Portugal	322	…	217[e]	Log-normal	[63, 66, 68]
Outpatient visit					
All regions	58	…	61	Log-normal	[63, 66]
US	103	…	96[e]	Log-normal	[63, 66]
Europe	40	…	32	Log-normal	[63, 66]
Portugal	32	…	30[e]	Log-normal	[63, 66]
Antibiotics for hospitalized patients with no penicillin allergy label[d]					
All regions	245	139	…	Gamma	[8, 9, 47, 48, 51, 59, 70–77]
US	260	167	…	Gamma	[8, 9, 48, 71, 73, 76]
Europe	212	61	…	Gamma	[70, 72, 75, 77]
Portugal	212[b]	61[b]	…	Gamma	[b]
Antibiotics for hospitalized patients with penicillin allergy label[d]					
All regions	461	216	…	Gamma	[8, 9, 47, 48, 51, 59, 70–77]
US	513	217	…	Gamma	[8, 9, 48, 71, 73, 76]
Europe	432	177	…	Gamma	[70, 72, 75, 77]
Portugal	432[b]	177[b]	…	Gamma	[b]
Antibiotics for outpatients with no penicillin allergy label[d,g]					
All regions	37	32	…	Gamma	[64, 65, 78, 79]
US	37	32	…	Gamma	[64, 65, 78, 79]
Europe	37[c]	32[c]	…	Gamma	[c]
Portugal	37[c]	32[c]	…	Gamma	[c]
Antibiotics for outpatients with penicillin allergy label[d,g]					
All regions	59	45	…	Gamma	[64, 65, 78, 79]
US	59	45	…	Gamma	[64, 65, 78, 79]
Europe	59[c]	45[c]	…	Gamma	[c]
Portugal	59[c]	45[c]	…	Gamma	[c]
Epinephrine auto-injector					
All regions	Uniform distribution (range, $62–$730)				[80–82]

Table 1. Continued

Variable	Distribution Parameters			Distribution	Source
	Mean	SD	Median		
US	Discrete values: $375; $494; $730				[80]
Europe	Uniform distribution (range, $50–$100)				[81, 82]
Portugal	Discrete values: $62; $6				[82]
Skin tests					
Literature search-retrieved amounts					
Inpatients					
All regions	86	39	…	Gamma	[10, 21, 71, 83–85]
US	102	39	…	Gamma	[10, 71, 83, 84]
Europe	64	27	…	Gamma	[21, 85]
Portugal[h]	74	29	…	Gamma	[86]
Outpatients					
All regions	106	41	…	Gamma	[10, 21, 71, 83–85]
US	120	40	…	Gamma	[10, 71, 83, 84]
Europe	87	33	…	Gamma	[85, 86]
Portugal[h]	96	38	…	Gamma	[86]
Survey-retrieved amounts					
Inpatients					
All regions	77	55	…	Gamma	[86]
US	135	53	…	Gamma	[86]
Europe	72	53	…	Gamma	[86]
Portugal	74	75	…	Gamma	[86]
Outpatients					
All regions	83	65	…	Gamma	[86]
US	107	37	…	Gamma	[86]
Europe	81	67	…	Gamma	[86]
Portugal	94	108	…	Gamma	[86]
Drug challenges					
Literature search-retrieved amounts					
Inpatients					
All regions	80	13	…	Gamma	[10, 83–86]
US	78	18	…	Gamma	[10, 83, 84]
Europe	81	5	…	Gamma	[85, 86]
Portugal[h]	84	1	…	Gamma	[86]
Outpatients					
All regions	94	16	…	Gamma	[10, 83–86]
US	91	19	…	Gamma	[10, 83, 84]
Europe	101	2	…	Gamma	[85, 86]
Portugal[h]	102	1	…	Gamma	[86]
Survey-retrieved amounts					
Inpatients					
All regions	171	142	…	Gamma	[86]
US	173	38	…	Gamma	[86]
Europe	171	148	…	Gamma	[86]
Portugal	127	150	…	Gamma	[86]
Outpatients					
All regions	273	245	…	Gamma	[86]
US	208	59	…	Gamma	[86]
Europe	279	255	…	Gamma	[86]
Portugal	193	228	…	Gamma	[86]

Abbreviations: DC, drug challenge; LOS, length of stay; SD, standard deviation; US, United States.

[a]Beta distribution parameters estimated by means of program evaluation and review technique methods.

[b]In the absence of satisfactory specific Portuguese data, parameters from existent European studies were used.

[c]In the absence of satisfactory specific regional data, parameters from all regions were used.

[d]Supplementary Figure 1 illustrates the selection process resulting in the identification of the included studies.

[e]Estimates based on the average ratios obtained for the remaining regions.

[f]Data for all regions and for US models were obtained by means of meta-analysis of several studies. Regarding Europe, only 1 study was available.

[g]One-year estimate.

[h]Corresponds to estimates obtained by means of formal cost assessments; survey-obtained data were solely used in the context of "survey-retrieved amounts."

delabeled in medical records, get relabeled, and/or are incorrectly treated as being penicillin allergic [9, 87]. In addition, we performed probabilistic sensitivity analyses via Monte Carlo simulation methods. That is, for each mode, we ran 10 000 simulations with variables not assuming base case input values, but rather any allowed value according to their distribution of probabilities (Table 1). From the probabilistic sensitivity analyses performed, we retrieved the proportion of simulations identifying penicillin allergy testing as cost-saving, and the average and median incremental net benefits. Therefore, for each model, we determined whether penicillin allergy testing was cost-saving under base case assumptions, and how many simulations identified penicillin allergy testing as cost-saving when the values of variables varied under a distribution of probabilities. To identify the variables more strongly associated with higher or lower incremental net benefits, we performed univariable linear regressions with the dependent variable corresponding to the incremental net benefits obtained in the set of simulations resulting from each decision model. Decision models and sensitivity analyses were performed using TreeAgePro 2019 (TreeAge Software, Williamstown, Massachusetts), while all other statistical analyses were performed using software R (version 3.5.0).

Additional Sensitivity Analyses

In addition to our base case models, we performed additional sensitivity analyses with models (1) not discriminating allergic reaction timing (ie, not distinguishing immediate from nonimmediate reactions), (2) taking into account the possibility of delabeling patients solely based on the clinical history, (3) using alternative data sources [88], or (4) restricting inputs to studies that controlled for confounding by matching or multivariable analyses (Supplementary Methods).

RESULTS

In all decision models built, under base case analyses, performing penicillin allergy testing was associated with lower costs than not testing (incremental net benefits >0) (Tables 2 and 3 and Figure 3). For models in which the penicillin allergy diagnostic workup encompassed the sequential performance of skin testing and DC, the average incremental net benefit for inpatients was $657 ($1444 for the US vs $489 for Europe), while for outpatients it was $2746 (US: $256; Europe: $6045). For inpatients, an average minimum of 23.0% individuals with negative tests need to be effectively delabeled so that penicillin allergy testing becomes cost-saving (US: 10.4%; Europe: 21.3%); for outpatients, this percentage decreases to 16.2% (US: 46.4%; Europe: 2.9%).

In probabilistic sensitivity analyses, 70.2% of all simulations identified penicillin allergy testing as the less costly strategy (Table 2; Supplementary Figure 2). In all decision models, testing was cost-saving in more than half of simulations.

For models in which skin tests were only performed in patients reporting immediate reactions (with direct DC performed in the remaining patients) (Table 3), the average incremental net benefit was $823 for inpatients (US: $1792; Europe: $595) and $2849 for outpatients (US: $355; Europe: $6178). In probabilistic sensitivity analyses, penicillin allergy testing was the less expensive option in 76.9% of simulations.

For models in which DC were directly performed in all patients irrespective of the reported reaction timing (Table 3), the average incremental net benefit was $656 for inpatients (US: $1343; Europe: $429) and $3122 for outpatients (US: $417; Europe: $6745). The minimum percentage of patients needing to be delabeled so that penicillin allergy testing becomes cost-saving was 13.7% for inpatients (US: 5.5%; Europe: 15.9%) and 7.0% for outpatients (US: 18.8%; Europe: 1.5%). In probabilistic sensitivity analyses, penicillin allergy testing was found to be the less costly strategy in 78.8% of simulations.

Results were similar when performing additional sensitivity analyses (1) not distinguishing immediate from nonimmediate reactions, (2) considering the possibility of delabeling patients solely based on the clinical history, (3) using alternative sources [86, 89], or (4) restricting inputs to studies that controlled for confounding (Supplementary Tables 1–4).

Supplementary Figure 3 shows the results of the linear regression models performed to identify the variables whose increase was more strongly associated with higher incremental net benefits.

DISCUSSION

In this economic evaluation study, we projected that penicillin allergy testing would be cost-saving for both inpatients and outpatients in the US and Europe, with an incremental net benefit ranging between $256 and $6745. In addition, in probabilistic sensitivity analyses with variables varying according to a distribution of probabilities, more than three-fourths of simulations identified penicillin allergy testing as cost-saving. However, these results are based on existing evidence and on model-based simulation methods. While those are representative scenarios of the most usual practices, unstudied scenarios cannot not be excluded, especially since penicillin allergy testing is highly heterogeneous [86] and antibiotic utilization patterns vary globally. On account of that, it is expected that in some institutions (eg, those in which patients reporting a penicillin allergy are systematically treated with cephalosporins), penicillin allergy testing does not result in such substantial inpatient savings. While highlighting the need for complementary context-based economic assessments, this does not diminish the importance of our study, as, in current clinical practice, aztreonam and non-β-lactams are more frequently chosen in patients reporting a penicillin allergy [9, 59, 75].

Table 2. Results of Decision Models Testing Performing Versus Not Performing Sequential Diagnostic Testing[a] in Patients With a Penicillin Allergy Label

Model Characteristics						Probabilistic Sensitivity Analysis Results			
Setting/Type of Patients	Region	Cost Associated With Performing Allergy Tests[b,c]	Cost Associated With Not Performing Allergy Tests[b,c]	Incremental Net Benefit[b,d]	Minimum % Delabeled So That Testing Is Cost-saving[e]	% of Simulations With Testing as Best Strategy	Average Incremental Net Benefit	Median Incremental Net Benefit (25th–75th Percentile)	% Delabeled So That Testing is the Best Strategy in > 50% of Simulations[f]
Inpatients	All	$5004	$5379	$375	28.9%	66.8%	$361	$115 (–$53 to $356)	56%
	US	$14 005	$15 449	$1444	10.4%	78.0%	$1492	$277 ($29 to $892)	37%
	Europe	$5825	$6314	$489	21.3%	72.2%	$491	$116 (–$14 to $318)	53%
	Portugal	$4218	$4536	$319	31.2%	72.4%	$328	$124 (–$13 to $333)	54%
Outpatients	All	$3580	$5887	$2308	8.2%	83.1%	$2368	$1178 ($269–$3035)	15%
	US	$3049	$3307	$256	46.4%	72.6%	$258	$166 (–$20 to $426)	57%
	Europe	$3493	$9538	$6045	2.9%	60.1%	$6291	$513 (–$456 to $3882)	29%
	Portugal	$1662	$4037	$2375	7.4%	56.7%	$2375	$157 (–$300 to $1610)	51%

Abbreviations: $, United States dollars; US, United States.

[a]Corresponding to skin testing followed, if negative, by a drug challenge.

[b]Base case analyses results.

[c]Sum of costs involving (1) performance of penicillin allergy tests and (2) consequences (as expressed in monetary units) resulting from healthcare use.

[d]An incremental net benefit > 0 indicates that penicillin allergy testing is cost-saving.

[e]Corresponds to the minimum percentage of patients with negative penicillin allergy testing that needs to be effectively treated as nonallergic so that testing becomes cost-saving (incremental net benefit > 0).

[f]Corresponds to the minimum percentage of patients with negative penicillin allergy testing that needs to be effectively treated as nonallergic so that at least half of simulations performed by probabilistic sensitivity analysis identify penicillin allergy testing as cost-saving.

The proportion of cost-saving simulations was higher for models using US-based data, whereas European models tended to result in higher incremental net benefits. This difference reflects the higher hospitalization costs and the lower frequency of ambulatory visits observed in the US. In addition, it reflects the uncertainty related to the relative lack of European studies assessing the consequences of having a penicillin allergy label. Indeed, the particularly high incremental net benefits obtained with models assessing European outpatients are likely explained by the existence of only a single Dutch study that compared the frequency of outpatient visits among patients with and without a penicillin allergy label, and which found large differences [13]. When using American data for that variable, European models yield lower incremental net benefits, but higher percentages of simulations identifying testing as the best strategy—for sequential performance of skin testing and DC, an incremental net benefit of $128 was observed, with 61% of simulations identifying testing as the best strategy; these values go up to $183 and 72% when direct DC is performed in outpatients reporting nonimmediate reactions, and to $237 and 78% when direct DC is performed in all outpatients.

As expected, since direct DC is less costly than a full diagnostic evaluation [83], the percentage of cost-saving simulations was higher for models performing direct DC. We estimated that, for each false-positive skin test, an average of $1022 for inpatients and $3601 for outpatients would be saved if DC had been performed instead. These estimates are lower than those of studies assessing specific populations [16], reflecting the incorporation of information from multiple sources. However, direct DC is currently only advisable for "low-risk patients." These correspond to individuals reporting mild reactions or a clinical history poorly compatible with a true allergic reaction, in whom the frequency of severe events following a direct DC is deemed to be <1% [89]. Nevertheless, there is accumulating evidence suggesting that direct DC can be safely performed in broader contexts [22, 36].

In addition to skin tests and DC, the European Network for Drug Allergy recommends the performance of in vitro tests for patients reporting immediate reactions. In our decision models, penicillin allergy testing remained cost-saving even considering the additional quantification of specific immunoglobulin E (IgE). In fact, 68.9% of simulations identified testing as the least expensive strategy when considering a percentage of positive IgE results of 13.5%, and average quantification costs of $46 for inpatients and $71 for outpatients [21, 85]. However, data on the accuracy and costs of IgE quantification are limited [90].

The base case scenario in our model assumed that all patients with a negative diagnostic workup would be treated as nonallergic. Nevertheless, current evidence suggests that as many as half of the patients with negative results may not get correctly delabeled (or get erroneously relabeled) [9, 87]. For the sequential performance of skin tests and DC to be cost-saving,

Table 3. Results of Decision Models Testing Performing Versus Not Performing Direct Drug Challenges[a] in Patients With a Penicillin Allergy Label

Model Characteristics							Probabilistic Sensitivity Analysis Results			
Patient Type	Cases in Which a Direct DC Was Performed	Region	Cost Associated With Performing Allergy Tests[b,c]	Cost Associated With Not Performing Allergy Tests[b,c]	Incremental Net Benefit[b,d]	Minimum % Delabeled So That Testing is Cost-saving[e]	% of Simulations With Testing as Best Strategy	Average Incremental Net Benefit	Median Incremental Net Benefit (25th–75th Percentile)	% Delabeled So That Testing Is the Best Strategy in >50% of Simulations[f]
Inpatients	NIR	All	$4888	$5379	$492	16.6%	76.4%	$492	$197 ($10–$472)	33%
		US	$13 657	$15 449	$1792	5.2%	86.0%	$1764	$418 ($134–$1063)	19%
		Europe	$5719	$6314	$595	14.0%	81.3%	$582	$183 ($39–$406)	35%
		Portugal	$4123	$4536	$414	19.9%	82.2%	$410	$192 ($44–$424)	36%
	All	All	$4851	$5362	$511	13.5%	78.4%	$521	$224 ($29–$501)	26%
		US	$9291	$10 634	$1343	5.5%	86.4%	$1339	$412 ($150–$934)	16%
		Europe	$3495	$3924	$429	15.9%	83.7%	$432	$187 ($50–$388)	31%
		Portugal	$2870	$3211	$341	19.8%	84.0%	$342	$196 ($53–$394)	30%
Outpatients	NIR	All	$3518	$5887	$2369	5.4%	84.6%	$2368	$1292 ($323–$3020)	10%
		US	$2952	$3307	$355	27.8%	84.0%	$358	$260 ($70–$537)	35%
		Europe	$3360	$9538	$6178	2.0%	61.4%	$5809	$552 (−$395 to 3867)	20%
		Portugal	$1542	$40 367	$2495	5.1%	59.4%	$2670	$246 (−$253 to $1842)	40%
	All	All	$3480	$6124	$2644	3.8%	85.7%	$2665	$1443 ($380–$3466)	7%
		US	$2890	$3307	$417	18.8%	88.1%	$410	$309 ($115–$578)	23%
		Europe	$2793	$9538	$6745	1.5%	62.8%	$6566	$664 (−$393 to $4520)	15%
		Portugal	$1355	$4037	$2682	3.8%	61.5%	$2767	$291 (−$232 to $1948)	28%

In cases not reporting a nonimmediate reaction, skin tests were performed and, if negative, followed by a drug challenge.

Abbreviations: $, United States dollars; NIR, nonimmediate reaction; US, United States.

[a]Direct drug challenges correspond to drug challenges without prior skin tests.

[b]Base case analyses results.

[c]Sum of costs involving (1) performance of penicillin allergy tests and (2) consequences (as expressed in monetary units) resulting from healthcare use.

[d]An incremental net benefit >0 indicates that penicillin allergy testing is cost-saving.

[e]Corresponds to the minimum percentage of patients with negative penicillin allergy testing that needs to be effectively treated as nonallergic so that testing becomes cost-saving (incremental net benefit >0).

[f]Corresponds to the minimum percentage of patients with negative penicillin allergy testing that needs to be effectively treated as nonallergic so that at least half of simulations performed by probabilistic sensitivity analysis identify penicillin allergy testing as cost-saving.

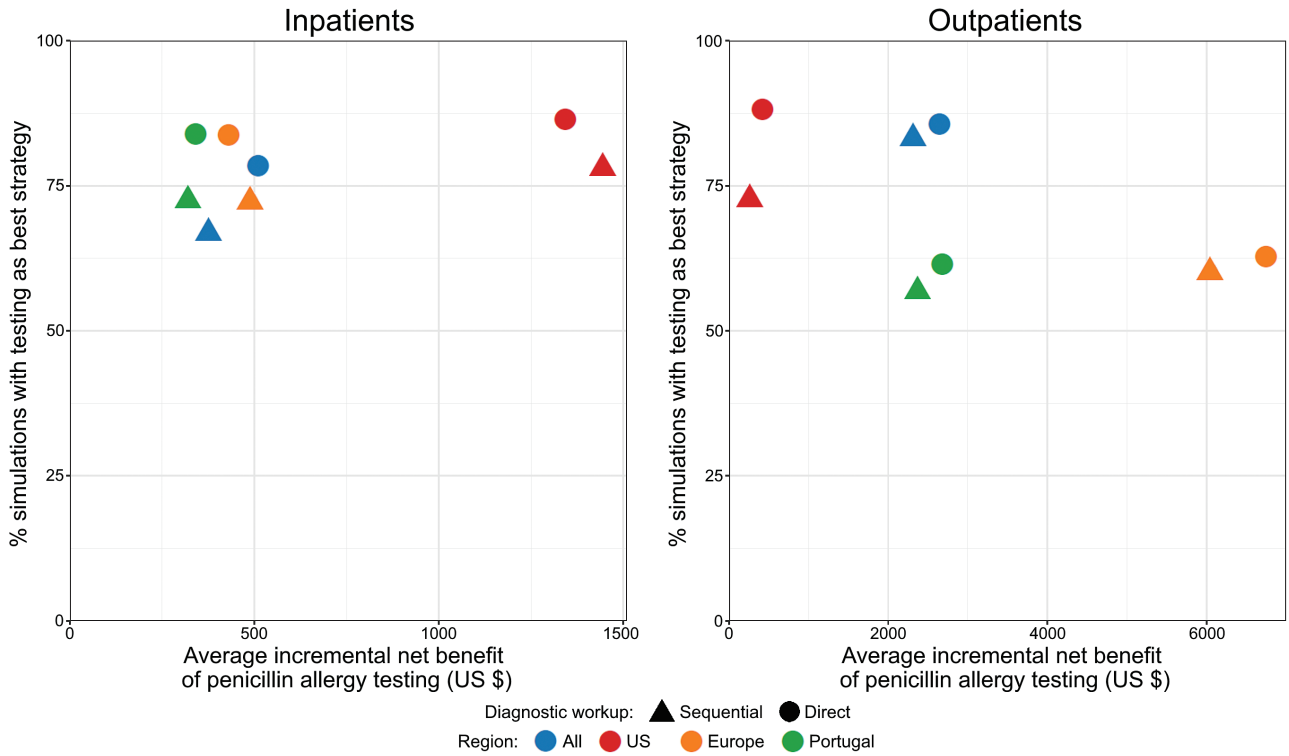

Figure 3. Summary of the results of economic decision models by setting and region. Incremental net benefits (difference of net benefits, with an incremental net benefit >0 indicating that penicillin allergy testing is cost-saving) obtained through use of fixed values were plotted against the percentage of simulations (obtained via probabilistic sensitivity analysis) identifying penicillin allergy testing as cost-saving. Sequential diagnostic workup corresponds to the performance of skin tests followed, if negative, by drug challenges. Direct diagnostic testing corresponds to the direct performance of drug challenges without prior skin tests (either in all patients or only in those reporting nonimmediate reactions). Abbreviation: US, United States.

a minimum of 30%–60% of inpatients (depending on whether base case input values or the results of probabilistic sensitivity analyses are being considered) and 10%–50% of outpatients would need to be effectively delabeled. These percentages notably decrease to 15%–30% in inpatients and 5%–30% in outpatients when considering direct DC only. It is thus possible that penicillin allergy testing is cost-saving even when less than half of the patients with negative tests are treated as nonallergic, although this depends on the setting in which testing is performed. This issue highlights the importance of delabeling patients with a negative diagnostic workup, and of opting for direct DC at least in "low risk" patients.

This study has some limitations. We adopted the health services perspective, as we were not able to assess such costs as those related to transportation, patient and caregiver time, and productivity. Productivity costs would be particularly difficult to measure accurately, not least on account of the paucity of information regarding the sociodemographic composition of patients with a penicillin allergy label seeking healthcare (average wages probably not being good indicators of productivity losses among those patients [3]). In addition, the lifelong burden of having a penicillin allergy label was not fully considered. In fact, for inpatients, our models only took into account that specific hospitalization and any possible readmission within the next month after discharge, ignoring potential savings in subsequent hospitalizations or in the use of ambulatory care. For outpatients, we assessed a 5-year time horizon and did not consider the possibility of hospitalizations during that period. These choices reflected the time horizon of primary studies that evaluated the healthcare use of patients with a penicillin allergy label, with only a few having a follow-up period of more than a year [15]. However, demonstrating savings adopting the health services perspective and with these short follow-up periods is a conservative strategy. True savings are likely far greater than those projected, particularly if patient productivity/time gains are accounted for (ie, for most outpatients, productivity/time loss for testing would be compensated by larger future gains related to decreased healthcare use), transportation savings, and a potential lifelong delabeling. Such savings were also greater when considering—as indicated in some pathways [20] – the possibility of delabeling some patients based on clinical history alone, notably those whose clinical history is incompatible with that of a true allergic reaction (Supplementary Table 2).

Another important limitation results from the fact that literature-based evidence was obtained by studies that often

adopted different methodologies and definitions. Such heterogeneity mirrors the diversity in the practice of penicillin allergy testing and may explain differences in the results obtained across different studies. We tried to minimize the impact of that variability by defining distributions of probabilities for each variable, based on which we performed probabilistic sensitivity analysis. In addition, most evidence was obtained by retrospective studies for which confounding may have been incompletely controlled. Patients with a penicillin allergy label are known to be demographically different and have more comorbidities than those without such label [3]. Additionally, among patients with a penicillin allergy label, those who get tested tend to have more morbidity than the remainder and tend to be those who need testing prior to planned/required antibiotic use. Therefore, it is not possible to causally prove that increased healthcare use among patients with a penicillin allergy label is necessarily because of such label. Nevertheless, we performed sensitivity analyses restricted to studies that at least partially addressed confounding. In those analyses, penicillin allergy testing was still projected to be cost-saving, although with smaller incremental net benefits for US patients. Further prospective follow-up studies are needed to more accurately assess the impact of delabeling patients claiming a penicillin allergy label.

This study has also several strengths. This is the first economic evaluation study based on decision analytic modeling assessing whether penicillin allergy testing is cost-saving across methods of testing, settings, and regions. Our input parameters were obtained from diverse information sources, including scientific literature, administrative databases, and technical reports. In addition, when estimating parameters based on the literature, we performed systematic or comprehensive searches of the literature with the aim of obtaining data from the largest number of relevant studies. Data from these different studies were then pooled by means of meta-analysis, so that the more precise studies provided a larger contribution to our estimates. We performed probabilistic sensitivity analyses to explore the uncertainty associated with our estimates. Finally, we performed ancillary sensitivity analyses, with penicillin allergy testing projected to be cost-saving even under more conservative assumptions.

In conclusion, penicillin allergy testing was projected to be cost-saving across an array of testing strategies and scenarios. While not precluding the need for context-based assessments, this study provides evidence that verification of reported penicillin allergy has economic advantages. If patients are successfully delabeled and are treated as not penicillin-allergic, advantages may be even higher than the presented incremental net benefits. These results are devised to inform guidelines, supporting the adoption of policies promoting generalized penicillin allergy testing on economic grounds, in addition to clinical grounds.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. K. G. B. has a clinical decision support tool for inpatient β-lactam allergy evaluation used at Partners HealthCare Systems and licensed to Persistent Systems. E. M. has received research grants from ALK (the sellers of Pre-Pen in the United States) and has consulted for and is serving on a data and safety monitoring board for Audentes. All other authors report no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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