

Original Article

The impact of antibiotic allergy labels on antibiotic exposure, clinical outcomes, and healthcare costs: A systematic review

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Abstract

Objective: A growing body of evidence suggests that antibiotic allergy labels as documented in medical records are a risk factor for poor clinical outcomes. In this systematic review, we aimed to determine how antibiotic allergy labels influence 3 domains: antibiotic use and exposure, clinical outcomes, and healthcare-related costs.

Design: We performed a systematic review to identify studies reporting outcomes in patients with antibiotic allergy labels compared to non-allergic counterparts. The search included PubMed, EMBASE, Cochrane CENTRAL, EBSCO, Cochrane Database of Abstracts of Reviews of Effects and Web of Science. Two reviewers independently screened studies for inclusion and abstracted data. Studies were graded using the Newcastle-Ottawa quality assessment scale. Study outcomes included antibiotic use, clinical outcomes, and economic outcomes.

Results: In total, 41 studies met our criteria for inclusion. These studies varied in medical specialty, patient population, healthcare delivery system, and design, but most were conducted among adults age >18 years (85%) in the inpatient setting (82.5%). Among 34 studies examining antibiotic exposure, 32 (94%) found that patients with antibiotic allergy labels received more broad-spectrum antibiotics. Moreover, 31 studies examined clinical outcomes such as length of hospitalization, ICU admission, hospital readmission, multidrug-resistant or opportunistic infection, or mortality, and 27 (87%) found that allergy-labeled patients had at least 1 negative outcome. Of 9 studies examining healthcare costs, 7 (78%) found that allergy-labeled patients incurred significantly higher drug or hospital-related costs.

Conclusions: Antibiotic allergy labels have negative effects on antibiotic use, clinical outcomes, and economic outcomes in a variety of clinical settings and populations.

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Antibiotic allergy labels (ie, medical record documentation of a drug hypersensitivity or drug intolerance) are common and frequently occur in the absence of a true drug allergy. Estimates for the prevalence of penicillin allergy alone, for example, are 12% or higher.^{1,2} However, formal allergy assessment studies suggest that <10% of patients with antibiotic allergy labels are truly allergic.^{3,4} Allergy labels are not without consequence; over the past decade, many studies have highlighted both the personal and public health consequences of allergy labels.^{5,6} Potential consequences for patients include suboptimal therapy with fewer efficacious antibiotic choices, exposure to broad-spectrum antibiotics, longer courses of treatment, parenteral administration, toxic side effects associated with broad-spectrum therapy, and higher risk of opportunistic infections. Public health concerns include contribution to the emergence of multidrug-resistant organisms, higher costs of alternative therapy, and potentially higher healthcare costs due to longer hospital stays. Given these burdens and the fact that antibiotic overuse is associated with substantial

harms, many hospitals have implemented formalized programs to assess and “de-label” antibiotic allergies through antibiotic stewardship programs.^{7–10} Strategies may include de-labeling based on history alone or formal testing including skin testing or oral challenge.

In recognition of the evidence regarding the harms associated with antibiotic allergy, a previous systematic review through 2015 identified 8 studies examining clinical outcomes and antibiotic utilization in patients with antibiotic allergy labels.¹¹ However, research focused on this topic has substantially increased since that time. Therefore, we performed a systematic review to analyze how antibiotic allergy labels influence 3 broad domains: (1) antibiotic exposure and prescribing patterns, (2) healthcare related outcomes, and (3) healthcare costs.

Methods

We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance.¹² The study protocol was published in the PROSPERO database prior to conducting the review (registration no. CRD42019127971).¹³ A literature search was developed to identify all studies that report outcomes in those with any antibiotic allergy labels compared to nonallergic controls in pediatric (<18) and adult (≥18) cohorts in any

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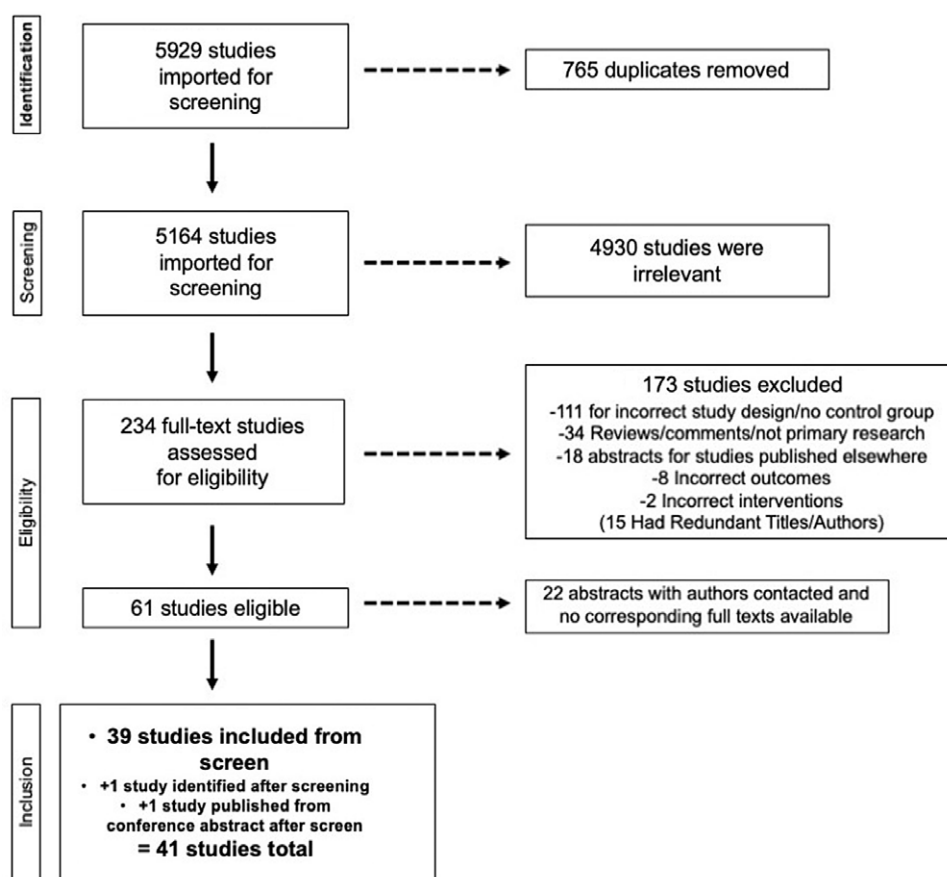


Fig. 1. Flow diagram for study selection on antibiotic allergy. Overall, 5,164 studies were eligible for screening after duplicates were removed. After irrelevant studies were removed, 234 full-text studies were assessed for eligibility; 173 studies were excluded for indicated reasons. Of 61 eligible studies, 39 were published in peer-reviewed journals and ultimately included. Also, 1 study was identified and included after the original screen and another study was advanced from conference abstract to peer-reviewed publication after our screen and was included.

healthcare setting. Studies that did not include a control population were excluded. The search was conducted in March and April 2019 without language or publication status restrictions in PubMed, EMBASE, Cochrane CENTRAL, EBSCO (CINAHL; EconLit), Cochrane Database of Abstracts of Reviews of Effects (Cochrane Library, Wiley), Web of Science (Core Collection: Science Citation Index Expanded, Emerging Sources Citation Index; KCI-Korean Journal Database; Russian Science Citation Index; ScIELO Citation Index) and the Infectious Diseases Society of America for conference abstracts (2015 forward). We searched reference lists of related reviews, clinical trial registries (ClinicalTrials.gov), and systematic review registries, and we tried to contact authors of reviews where data were missing or incomplete. Search strategies are included in the Supplementary Material (online). Search strategies consisted of controlled vocabulary, such as medical subject headings (ie, MeSH and Emtree terms), in combination with text words.

Records were screened in Covidence¹⁴ by at least 2 independent reviewers (initial title and/or abstract screening and full text screening) to identify studies that reported outcomes in those with antibiotic (any) allergy labels compared to nonallergic counterparts using the prespecified eligibility criteria and definitions described in the protocol.

To assess the risk of bias, studies were graded using the Newcastle-Ottawa quality assessment scale for cohort and case-control studies.¹⁵ Scores, which can range from 1 star (low quality) to 9 stars (high quality), were recorded by 2 authors independently and differences were resolved by informal consensus. Scores for

each domain and an overall summary score (maximum of 9 points) are shown in the Supplementary Material (online).

All data were extracted into an iteratively developed data extraction form. Included studies were thoroughly reviewed by 2 authors and verified by a third. Data pertaining to the following study characteristics were extracted: patient population (adult vs pediatrics), healthcare setting, number of patients, country of study, exposure, comparator or control group, study aim, inclusion criteria, and exclusion criteria. Categories for study outcomes were identified prior to data abstraction and included 3 broad domains: (1) antibiotic exposure or use; (2) clinical outcomes (eg, hospital length of stay (LOS), intensive care unit (ICU) admission, mortality, surgical site infection (SSI), or opportunistic/multidrug-resistant (MDR) infection), and (3) economic outcomes including cost of antibiotics or hospitalization. A narrative by text and tables was prepared to summarize all findings.

Results

Article inclusion and trends

After removing duplicates, 5,164 studies were identified; 234 (4.5%) met our criteria for full-text review, and 4,930 (95.5%) were excluded for reasons summarized in Fig. 1. Overall, 61 studies had pertinent findings and an appropriate control group to allow for data abstraction (Supplementary Material online). Of these 61 studies, 39 were published in peer-reviewed journals, and the remaining 22 were published as conference abstracts (Fig. 1). After contacting abstract authors, 1 abstract had been advanced

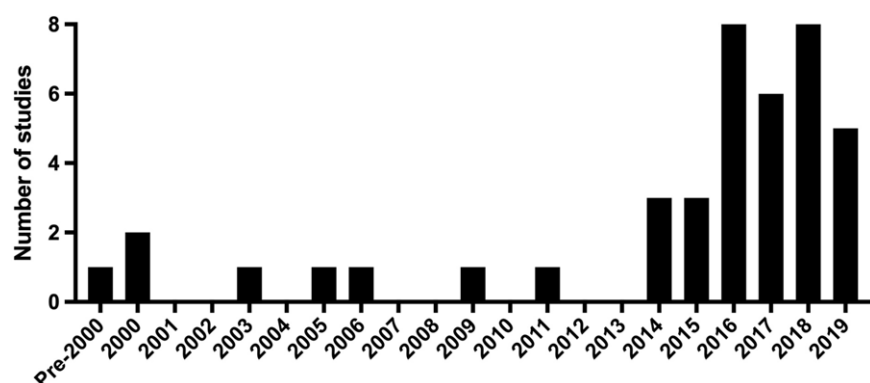


Fig. 2. Number of studies per year included in the final analysis.

to peer-reviewed publication and was included in the final analysis.¹⁶ There was not sufficient additional information for inclusion of the remaining 21 abstracts. Also, 1 study was published shortly after our search and was included in the final analysis.¹⁷ Ultimately, 41 articles met eligibility criteria and were included. Only 1 of these studies was published prior to 2000; 6 studies were published between 2000 and 2010; 7 studies were published between 2011 and 2015; and 27 of these studies were published between 2016 and 2019 (Fig. 2).

Population, setting, exposure, and study design

Of the 41 studies included for data abstraction, 35 (85%) focused exclusively on adult patients age >18 years; 4 (9.8%) focused solely on pediatrics; and 2 studies (5%) analyzed data from patients of all ages (Table 1). Most studies ($n = 34$, 83%) investigated inpatient cases, and 7 (17%) analyzed data from the outpatient setting (Table 1). Of the 41 studies, 20 (49%) were conducted in the United States, 8 (20%) were conducted in Australia, 5 (12%) were conducted in countries within the European Union, 3 (7%) were conducted in the United Kingdom, 2 (5%) were conducted in Canada, and 1 study (2%) was included from each of the following: China, Israel, or multinational. The number of study participants ranged from 72 to 301,339. Only 5 studies (12%) were prospective, and the remaining 36 (88%) were retrospective by design. More than half ($n = 21$, 51%) of studies focused exclusively on penicillin allergy, while 9 (22%) used β -lactam allergy labels as a primary exposure; the remaining 11 studies included either all “antibiotic” or “antimicrobial” allergy labels (Table 1). Broadly, antibiotic prescribing patterns and exposures were the most common domain reported, with 34 studies (83%) analyzing antibiotic exposure by drug class, number of doses administered, and/or total duration of treatment (Table 1 and Table 2). Clinical outcomes, such as LOS, ICU admission, readmission rates, opportunistic infection or MDR, and mortality were examined in 31 studies (76%) (Tables 1 and 3). Healthcare-related costs were the least examined outcome domain; 9 studies (~22%) reported these data (Tables 1 and 4). Also, 27 studies (66%) reported results from >1 domain (Table 1).

Antibiotic allergy labels and antibiotic exposure

Most studies reported at least 1 result suggesting that antibiotic allergy labels increased exposure to broad-spectrum therapy, the number of antibiotics administered, or duration of treatment (Fig. 3, first column). Of the studies examining antibiotic exposure, 32 of 34 (94%) found that allergy-labeled patients received more broad-spectrum antibiotics (eg, vancomycin, linezolid,

clindamycin, metronidazole, macrolides, fluoroquinolones and carbapenems) than non-allergy-labeled control patients (Table 2). Several studies that used penicillin or β -lactam allergy as the primary exposure confirmed that allergy-labeled patients received fewer, if any, drugs in these classes (Table 2). Notably, 1 study, which examined guideline adherence in penicillin allergic patients, found that there was increased adherence to guideline-recommended therapy when an allergy label was present.¹⁸

Additionally, 7 of 10 studies examining inpatients (70%) found that antibiotic allergy labels significantly increased the number of antibiotics administered.^{2,19–24} The other 3 studies reported equivocal results.^{17,25,26} The only 2 outpatient studies to examine number of antibiotics per patient found that allergy-labeled patients received significantly more antibiotic prescriptions over a defined time period.^{27,28} Also, 2 studies examined duration of treatment and both found that antibiotic allergy-labeled patients received longer treatment courses in the hospital and after hospital discharge.^{20,24} Of 3 studies examining adverse drug reactions (and had enough observations to draw meaningful comparisons), 2 found that allergy-labeled patients were more likely to have adverse reactions to alternative therapy.^{29,30} Furthermore, 2 studies demonstrated that patients with a penicillin allergy label were more likely to have other antibiotic allergies.^{31,32} Additionally, one study found that allergy-labeled patients were less likely to have antibiotics narrowed while in the hospital, and another study found that more allergy-labeled patients received parenteral therapy than controls.^{23,33}

Antibiotic allergy labels and clinical outcomes

Overall, 31 studies examined the effects of antibiotic allergy labels on clinical outcomes (Table 3). Moreover, 23 (74%) of these studies found that allergy labels negatively influenced at least 1 outcome while having no positive effects. Also, 4 studies (13%) reported equivocal results that did not reach statistical significance. Another 4 studies (13%) had at least 1 result suggesting that allergy labels negatively influenced an outcome, but another suggesting it positively influenced another (Fig. 3, column 2).^{17,19,24,31,32,34–36}

Of the 31 (71%) studies reporting clinical outcomes, 22 examined some aspect of hospitalization: LOS, ICU admission, or hospital readmission. Of the 20 studies examining LOS, 11 (55%) found that allergy-labeled patients had significantly longer LOS.^{2,19,20,25,29,30,36–40} Also, 8 studies found equivocal results and 1 found that allergy-labeled patients were hospitalized for shorter duration.^{17,21,23,24,31–33,41,42} Of 6 studies, 1 (17%) found that allergy-labeled patients were more likely to be admitted to the ICU, but all other studies reported no difference (Table 3).¹⁹ Furthermore, 13

Table 1. Characteristics of included studies. The study population and setting, number of patients, study design, primary exposure (allergy label type) and domains analyzed are indicated for each included study

Publication	Population and Setting	Patient No.	Study Design	Primary Exposure	Outcomes Examined Abx Exposure Clinical Cost		
Blumenthal et al, 2018 ³¹	Adult, Inpatient/Perioperative (USA)	8,385	Retrospective cohort	Penicillin allergy	X	X	
Blumenthal et al, 2018 ⁴³	Adult, outpatient – THIN database (UK)	301,339	Retrospective cohort	Penicillin allergy	X	X	
Blumenthal et al, 2016 ³²	Adult, Inpatient (USA)	456	Retrospective cohort	Penicillin allergy	X	X	
Butler et al, 2018 ⁵⁴	Pediatric, inpatient/perioperative (USA)	17,741	Retrospective cohort	Penicillin allergy	X		
Charneski et al, 2011 ¹⁹	Adult, inpatient (USA)	11,872	Retrospective cohort	Antimicrobial allergy	X	X	
Conway et al, 2017 ³³	Adult, Veterans' Affairs emergency dept (USA)	403	Retrospective cohort	Penicillin allergy	X	X	
Desai et al, 2017 ²⁹	Adult, Inpatient--labor and delivery (USA)	170,379	Retrospective cohort	Penicillin allergy	X	X	
Dewart et al, 2018 ⁵⁵	Adult, inpatient (USA)	6,361	Retrospective cohort	Penicillin allergy		X	
Fernandez-Rubio et al, 2014 ⁵⁶	Adult perioperative outpatient cataract surgery (Spain)	12,409	Retrospective cross-sectional	β -lactam allergy		X	
French et al, 2016 ⁵⁷	Adult, outpatient private practice dental implant procedures (Canada)	5,576	Retrospective cohort	Penicillin allergy	X	X	
Huang et al, 2018 ²⁰	Adult, inpatients with hematologic malignancy (USA)	4,671	Retrospective cohort	β -lactam allergy	X	X	X
Imlay et al, 2019 ¹⁷	Adult, inpatients with solid organ or hematopoietic cell transplant (USA)	2,153	Retrospective cohort	β -lactam allergy	X	X	
Irawati et al, 2006 ³⁷	Adult, inpatient (Australia)	155	Prospective cohort	Penicillin allergy	X	X	X
Khumra et al, 2017 ⁴¹	Adult, inpatient (Australia)	313	Retrospective cohort (matched)	Antibiotic allergy	X	X	
Knezevic et al, 2016 ⁴²	Adult, inpatient (Australia)	687	Retrospective cross-sectional	Antibiotic allergy	X	X	X
Kraemer et al, 1987 ²⁸	Pediatric, outpatient private practice (USA)	281	Retrospective cross-sectional	Penicillin allergy	X	X	X
Lam et al, 2019 ¹⁶	Adult, inpatient (USA)	1,343	Retrospective cohort	Antibiotic allergy		X	
Lee et al, 2000 ⁵⁸	Adult, inpatient (USA)	2,013	Retrospective cross-sectional	Antimicrobial allergy	X		
Lucas et al, 2019 ²⁵	Pediatric, inpatient (Australia)	1,672	Retrospective cohort	Antibiotic allergy	X	X	
MacFadden et al, 2016 ³⁰	Adult, inpatient (USA and Canada)	509	Prospective cohort	β -lactam allergy	X	X	
MacLaughlin et al, 2000 ⁴⁵	Adult and pediatric, outpatient family medicine (USA)	660	Retrospective cohort	β -lactam allergy	X		X
Macy et al, 2014 ²	Adult, inpatient (USA)	51,582	Retrospective cohort	Penicillin allergy	X	X	X
Philips et al, 2019 ¹⁸	Adult, inpatient (UK)	1,497	Prospective point prevalence and retrospective cohort	Penicillin allergy	X		
Ponce et al, 2014 ³⁴	Adult, inpatient/perioperative—Veterans' Affairs (USA)	18,830	Retrospective cohort	Penicillin allergy	X	X	
Powell et al, 2019 ⁵⁹	Adult and pediatrics, inpatient (UK)	24,715	Retrospective cohort	Penicillin allergy	X		
Sade et al, 2003 ²⁴	Adult, inpatient (Israel)	236	Retrospective cohort	Penicillin allergy	X	X	X
Saunders et al, 2017 ³⁸	Adult, inpatient/perioperative otolaryngology (USA)	72	Retrospective cohort	β -lactam allergy	X	X	

Schroek et al, 2015 ⁶⁰	Adult, outpatient—Veterans' Affairs (USA)	1,662	Retrospective chart review	Penicillin allergy	X	
Sousa-Pinto et al, 2018 ³⁹	Pediatric, inpatient (Portugal)	3,401	Retrospective cohort	Penicillin allergy	X	X
Sousa-Pinto et al, 2018 ³⁶	Adult, inpatient (Portugal)	102,872	Retrospective cohort	Penicillin allergy	X	X
Su et al, 2017 ²⁷	Adult, outpatient (The Netherlands)	5,010	Retrospective cohort	Penicillin allergy	X	X
Sun et al, 2017 ⁴⁴	Adult, inpatient/perioperative (China)	1,510	Retrospective cohort	Antimicrobial allergy	X	
Tan et al, 2016 ³⁵	Adult, inpatient/perioperative (USA)	10,391	Retrospective cohort	β -lactam allergy	X	
Trinh et al, 2009 ⁶¹	Adult, inpatient/postoperative (USA)	202	Retrospective case control	β -lactam allergy	X	X
Trubiano et al, 2016 ²²	Adult, inpatient—National Antimicrobial Prescribing Survey (Australia)	21,031	Retrospective cohort	Antimicrobial allergy	X	
Trubiano et al, 2015 ²¹	Adult, inpatient oncology patients (Australia)	198	Retrospective cohort	Antimicrobial allergy	X	X
Trubiano et al, 2015 ²⁶	Adult, Inpatient (Australia)	509	Point prevalence	Antimicrobial allergy	X	
Trubiano et al, 2016 ⁶²	Adult, Inpatient (Australia)	453	Multicenter cross-sectional	Antibiotic allergy	X	
Turnbull et al, 2005 ⁶³	Adult, inpatient/perioperative (Canada)	4,835	Prospective cohort	β -lactam allergy	X	
Turner et al, 2018 ⁴⁰	Adult, inpatients with MSSA (USA)	318	Retrospective cohort	Penicillin allergy	X	X
van Dijk et al, 2016 ²³	Adult, inpatient (The Netherlands)	17,959	Prospective cohort	Penicillin allergy	X	X

Table 2. Antibiotic Exposure and Use in Allergy-Labeled and Control Patients^a

Publication	Allergy Effect on Antimicrobial Exposure	Allergy Effect on No. of Antimicrobials, Duration of Treatment, or Additional Allergy Risk
Blumenthal et al, 2018 ³¹	Patients with a penicillin allergy label received less cefazolin (12% vs 92%; $P < .001$) but more clindamycin (49% vs 3%; $P < .001$), vancomycin (35% vs 3%; $P < .001$), gentamicin (24% vs 3%; $P < .001$), and fluoroquinolones (6.8% vs 1.3%; $P < .001$).	Patients with a penicillin allergy label were more likely to have allergy labels for cephalosporins, ($P < .001$), vancomycin ($P < .001$), or other therapeutics ($P < .001$).
Blumenthal et al, 2018 ⁴³	Patients with a penicillin allergy label received more macrolides, clindamycin, fluoroquinolones, and sulfonamide antibiotics. Adjusted IRRs were 4.15 (95% CI, 4.12–4.17), 3.89 (95% CI, 3.66–4.12), 2.10 (95% CI, 2.08–2.13) and 1.26 (95% CI, 1.25–1.27), respectively.	Not assessed
Blumenthal et al, 2016 ³²	Optimal therapy was less likely to be administered to patients with a penicillin allergy label (47% vs 80%; $P < .001$). After multivariate modeling patients with penicillin allergy labels were 36% less likely to be given a trial of optimal therapy (RR, 0.64; 95% CI, 0.49–0.83).	Patients with a penicillin allergy label were more likely to have allergies to cephalosporins (18% vs 2%; $P < .001$) and vancomycin (8% vs 3%; $P = .08$).
Butler et al, 2018 ⁵⁴	Penicillin allergy-labeled patients were more likely to receive clindamycin (58.4% vs 5.3%; $P < .001$) gentamicin (4% vs 0.1%; $P < .001$), vancomycin (2.8% vs 0.7%; $P < .001$), and less likely to receive cefazolin.	There was no difference in adverse drug reactions to cefazolin between patients allergic to penicillin and controls (1.04% vs 0.75%; $P = .485$). Allergy-labeled patients had adverse drug reactions to vancomycin (9.7%), noncefazolin cephalosporins (5.1%) and clindamycin (0.77%). Vancomycin was the antibiotic most associated with a perioperative adverse event, occurring in 3.3% of all cases.
Charneski et al, 2011 ¹⁹	Not assessed	Allergy-labeled patients were more likely to receive >1 antibiotic (OR, 1.61; 95% CI, 1.43–1.81; $P < .0001$).
Conway et al, 2017 ³³	Penicillin allergy-labeled patients received more carbapenem (5.3% vs 0.3%; $P < .0001$) and fluoroquinolones (61.4% vs 26.3%; $P < .0001$) but fewer cephalosporins (21.05% vs 36.42%) and penicillin (3.5% vs 32.3%).	Allergy-labeled patients were less likely to have antibiotics narrowed, (40.4% of allergic vs 58.7% of controls; $P = .01$).
Desai et al, 2017 ²⁹	Penicillin allergy-labeled patients received less penicillin (3.77% vs 83.68%; $P < .0001$) but more clindamycin (58.03% vs 3.25%; $P < .0001$), cefazolin (38.06% vs 27.23%; $P < .0001$), vancomycin (13.74% vs 0.16%; $P < .0001$), gentamicin (10.6% vs 5.99%; $P < .0001$), and azithromycin (2.54% vs 1.70%; $P = .0003$).	New antibiotic allergies were more prevalent in patients with penicillin allergy labels. Patients with an unverified penicillin allergy had significantly higher rates of adverse drug reactions associated with all antibiotic use.
French et al, 2016 ⁵⁷	All patients with a self-reported penicillin allergy label were given clindamycin instead of amoxicillin.	Not assessed
Huang et al, 2018 ²⁰	Patients with β -lactam allergy labels were less likely to receive cephalosporins (54.8% vs 86.4%; $P < .001$) and β -lactams (63.3% vs 89.3%; $P < .001$), but were more likely to receive vancomycin (62.2% vs 47.7%; $P < .001$), linezolid (5.5% vs 3.7%; $P = .034$), clindamycin (9.6 vs 2.7%; $P < .001$), fluoroquinolones (51.8% vs 15%; $P < .001$), aztreonam (3.2% vs 0.1%; $P < .001$), and aminoglycosides (35.9% vs 10.9%; $P < .001$).	Patients with β -lactam allergy labels received 3 (IQR, 2–4) classes of antimicrobials, vs 2 (IQR, 1–3) for non-labeled patients, ($P < .001$). The mean duration of antibiotic use was longer in allergy-labeled patients: 9 d (IQR, 3–23) vs 6 d (IQR, 2–14) in controls ($P < .001$).
Imlay et al, 2019 ¹⁷	β -Lactam allergy-labeled patients were exposed to significantly more antimicrobials, eg, vancomycin (IRR, 1.4; 95% CI, 1.2–1.7; $P < .001$), clindamycin (IRR, 7.6; 95% CI, 2.2–32.4; $P = .001$), aztreonam (IRR, 9.7; 95% CI, 3.3–35.0; $P < .001$), and fluoroquinolones (IRR, 2.9; 95% CI, 2.1–4.0; $P < .001$)	No difference; both groups received 2 different antimicrobials per hospital stay (IQR, 1–3).
Irawati et al, 2006 ³⁷	In mild or moderate community-acquired pneumonia, control patients received ampicillin and oral azithromycin, while patients with a penicillin allergy label received oral azithromycin and IV cephalothin.	Not assessed
Khumra et al, 2017 ⁴¹	Patients with an antibiotic allergy label received more cephalosporins ($P = .03$) and nitroimidazole ($P = .02$) and less penicillin V or G or aminopenicillin ($P = .14$) and β -lactam and β -lactamase inhibitors ($P = .31$).	Not assessed
Knezevic et al, 2016 ⁴²	Patients with β -lactam allergy labels received less penicillin (22% vs 58%; $P = .0002$), more aminoglycosides (7.3% vs 1.3%; $P = .043$) and metronidazole (17.1% vs 6.1%; $P = 0.021$).	Not assessed
Kraemer et al, 1987 ²⁸	Not assessed	The number of outpatient antibiotic prescriptions was higher in patients with allergy labels over the 2-year study period: 1.73 (range, 0–14) vs 0.80 (range, 0–9) ($P < .001$).

Lee et al, 2000 ⁵⁸	Patients with a penicillin allergy label received more vancomycin (39.7% vs 17.4%; $P < .001$) and levofloxacin (21.5% vs 8.0%; $P < .001$).	Minimal adverse drug reactions were reported in either group.
Lucas et al, 2019 ²⁵	Children with an antibiotic allergy label received less amoxicillin (6.52% vs 26.32%; $P = .002$) and more azithromycin (10.87% vs 3.98%; $P = .045$), ciprofloxacin (8.7% vs 1.28%; $P = .006$), ofloxacin (8.7% vs 1.42%; $P = .008$), clindamycin (15.22% vs 1.56%; $P < .001$), and metronidazole (13.04% vs 3.56%; $P = .009$).	No significant difference in number of antimicrobials received between allergy-labeled and non-labeled patients (OR, 1.5, 95% CI, 0.83–2.74; $P = .18$)
MacFadden et al, 2016 ³⁰	Patients with a penicillin allergy label were more likely to receive fluoroquinolones (22% vs 5%), glycopeptides (52% vs 12% of controls) and carbapenem (8% vs 4%).	After adjustment for confounders, patients who did not receive preferred therapy were at greater risk of adverse drug reactions (aOR, 3.1; 95% CI, 1.28–7.89) compared with control patients.
MacLaughlin et al, 2000 ⁴⁵	Patients with a reported β -lactam allergy were more likely to receive cephalosporins, macrolides, or other miscellaneous agents ($P = .001$).	Not assessed
Macy et al, 2014 ²	Patients with a penicillin allergy label received more vancomycin (21.2% vs 12.4%), ciprofloxacin (21.1% vs 13%), clindamycin (24.4% vs not reported), gentamicin (10.3% vs 5.6%) and moxifloxacin. Allergy-labeled patients were less likely to receive cefazolin and ceftriaxone.	Female patients with a penicillin allergy label were more likely to receive >1 antibiotic at the index hospitalization (56% vs 54.2% of controls, $P < .001$) or during any hospitalization (66.6% in allergic patients vs 63.8% in controls $P < .001$). Not statistically significant in male patients.
Philips et al, 2019 ¹⁸	Reported penicillin allergy increased overall adherence to antimicrobial guidelines (OR, 0.61; 95% CI, 0.46–0.82; $P < .001$), even after adjustment (OR, 0.52; 95% CI, 0.37–0.73; $P < .001$).	There was no difference in adverse drug reaction between groups.
Ponce et al, 2014 ³⁴	Preoperative prophylaxis with antibiotics other than cefazolin was more common in patients with a penicillin allergy label.	Not assessed
Powell et al, 2019 ⁵⁹	A penicillin allergy label was correlated with increased meropenem prescribing (OR, 6.70; 95% CI, 5.53–8.12; $P < .0001$). 1.06% of control patients received meropenem, while 6.97% of allergy-labeled patients received this drug. Amoxicillin was prescribed to 35.3% of control patients, but just 3.7% of patients with an allergy label.	Not assessed
Sade et al, 2003 ²⁴	Patients with a penicillin allergy label were more likely to receive a cephalosporin, macrolide, vancomycin or another agent ($P < .001$).	Allergy-labeled patients received 1.67 (SD, 0.71) antibiotics vs 1.43 (SD, 0.65) for nonallergic patients ($P = .40$). Duration of antibiotic treatment during the hospital stay was 3.99 (SD, 2.17) d for allergy-labeled patients vs 4.44 (SD, 2.51) for control patients ($P = .057$). At discharge, allergy-labeled patients were recommended to continue antibiotic treatment for 7.98 (SD, 2.57) d vs 6.16 (SD, 2.11) d, ($P < .001$).
Saunders et al, 2017 ³⁸	Patients with a penicillin allergy label received clindamycin instead of cefazolin.	No adverse drug reactions in either group.
Schroek et al, 2015 ⁶⁰	Multivariate regression analysis demonstrated that penicillin allergy label was a significant predictor for inappropriate treatment (OR, 2.9; 95% CI, 1.7–4.7; $P < .0001$).	Not assessed
Su et al, 2017 ²⁷	Patients with a penicillin allergy label were more likely to receive tetracyclines (OR, 2.24; 95% CI, 1.29–3.89), macrolides/lincosamides/streptogramins (OR, 8.69; 95% CI, 4.26–17.73) and quinolones (OR, 2.59; 95% CI, 1.22–5.48).	Allergy-labeled patients were more likely to receive >1 prescription per patient year (OR, 2.56, 95% CI, 2.046–3.197) and >1 second choice antibiotic prescription per year (OR, 2.21; 95% CI, 1.11–4.40)
Trinh et al, 2009 ⁶¹	Patients with a β -lactam allergy label were less likely to have adequate antimicrobial prophylaxis (48.6% vs 68% of control patients; $P = .19$) and less likely to receive appropriate antimicrobial agents (65.7% vs 80%; $P = .26$). More patients with a β -lactam allergy label received vancomycin (52.2% vs 35.7%; $P = .49$).	Not assessed
Trubiano et al, 2016 ²²	Inappropriate antimicrobial use was significantly higher in patients with an allergy label (OR, 1.12; 95% CI, 1.05–1.22; $P = .0002$). Allergy-labeled patients received fewer β -lactams (OR, 0.47; 95% CI, 0.43–0.50; $P = .001$) and more quinolones (OR, 2.07; 95% CI, 1.83–2.34; $P = .0001$), glycopeptides (OR, 1.59; 95% CI, 1.38–1.83; $P = .0001$) and carbapenem (OR, 1.74; 95% CI, 1.43–2.13; $P = .0001$).	The median number of antibiotics prescribed per patient was higher in patients with an allergy label (1.47 vs 1.44; $P = .024$).

(Continued)

Table 2. (Continued)

Publication	Allergy Effect on Antimicrobial Exposure	Allergy Effect on No. of Antimicrobials, Duration of Treatment, or Additional Allergy Risk
Trubiano et al, 2015 ²¹	Patients with an allergy label received more cephalosporins (17% vs 8%; $P < .05$), fluoroquinolones (11% vs 6%; $P < .05$), aminoglycosides (3% vs 1%; $P < .05$), carbapenem (13% vs 9%; $P < .05$), lincosamides (6% vs 1%; $P < .05$) and fewer β -lactams (29% vs 9%; $P < .05$).	The number of antibiotics used per admission was significantly higher in patients with an allergy label (3 vs 2; $P = .01$).
Trubiano et al, 2015 ²⁶	Oral antimicrobial administration was lower in patients with an allergy label (46% vs 60%, $P = .0001$). Fewer patients with a penicillin allergy label received β -lactams or cephalosporins: 60% vs 79% ($P = .0001$) and 24% vs 43% ($P = .05$) respectively. The proportion of inappropriate antimicrobial prescribing was higher, but not statistically significant in the allergy-labeled patient group vs control patient group (29% vs 23%; $P = .22$).	297 prescriptions for 128 patients with allergy labels vs 773 prescriptions for 381 control patients.
Trubiano et al, 2016 ⁶²	Fewer β -lactams were used in patients with a penicillin allergy label (16% vs 35%; $P = .02$); more third-/fourth-generation cephalosporins (33% vs 22%; $P = .05$) and more fluoroquinolones (6% vs 2%; $P = .04$) were used in penicillin allergic patients.	Not assessed
Turnbull et al, 2005 ⁶³	Factors negative for an effective first prophylactic dose were β -lactam allergy (OR, 0.49; 95% CI, 0.4–0.61; $P < .001$)	Not assessed
Turner et al, 2018 ⁴⁰	Patients with a penicillin allergy label were more likely to receive vancomycin (38% vs 11%; $P < .01$) and were less likely to receive nafcillin (5% vs 45%; $P < .01$). Allergy-labeled patients were more likely to have an infectious disease consult (74% vs 58%; $P = .02$).	Adverse drug events were too infrequent for analysis.
van Dijk et al, 2016 ²³	Patients with a penicillin allergy label were more likely to receive antibiotics (no antibiotic use in 54.5% of allergy patients vs 59.5% of nonallergic patients, $P < .01$). Allergy-labeled patients were less likely to receive β -lactams (6.6% of allergic patients vs 13.3 of nonallergic patients, $P < .01$). Allergic patients were more likely to receive tetracycline (1.8% vs 0.8%; $P < .01$), nonpenicillin β -lactams (28.4% vs 25.2%; $P = .03$), macrolides, lincosamides and streptogramins (12.5% vs 4.9%; $P < .01$), quinolones (7.9% vs 4.3%; $P < .01$), and other antibacterial agents (10.1% vs 7.8%; $P < .01$). Allergy label patients had a higher risk of receiving reserve antibiotics (RR, 1.38; 95% CI, 1.22–1.56).	21.7% of allergy label patients received >2 antibiotics while only 16.9% of nonallergic patients received >2 antibiotics ($P < .01$). 35.1% of allergy patients received IV antibiotics while only 32.2% of control patients did ($P = .06$).

Note. CI, confidence interval; IQR, interquartile range; IRR, incidence rate ratio; OR, odd ratio; RR, relative risk; SD, standard deviation.

^aFor each study analyzing antibiotic exposure, effect of allergy labels on antimicrobial administration (column 2) and effect on number of antimicrobials or duration of treatment (column 3) is indicated.

Table 3. Health Outcomes in Allergy-Labeled and Control Patients^a

Publication	Hospitalization Characteristics Length of stay ICU Admission Readmission			MDR or opportunistic infection	Mortality	Other
Blumenthal et al, 2018 ³¹	LOS was similar, although statistically shorter, for patients with an allergy label 3.3 (95% CI, 2.3–5.2) vs control patients 3.3 (95% CI, 2.4–5.6).	Not assessed	Not assessed	Patients with a penicillin allergy label had a higher frequency of VRE colonization or infection history (1.7% vs 0.9%; $P = .02$).	Not assessed	Patients with an allergy label were more likely to have a SSI (adjusted OR, 1.51; 95% CI, 1.02–2.22; $P = .04$).
Blumenthal et al, 2018 ⁴³	N/A – outpatient study	N/A – outpatient study	N/A – outpatient study	Patients with an allergy label were more likely to be infected with MRSA (HR, 1.69; 95% CI, 1.51–1.90) and <i>C. difficile</i> (HR, 1.26; 95% CI, 1.12–1.40).	Not assessed	None
Blumenthal et al, 2016 ³²	No difference: LOS was 10 d (IQR, 7–19) for patients with a penicillin allergy label and 11 d (IQR, 7–17) for control patients ($P = .63$).	Not assessed	Not assessed	Not assessed	Patients with an allergy label had 10% mortality vs 9% mortality in control patients ($P = .81$).	Allergy-labeled patients were equally likely to get an infectious disease consult (73% vs 71% for controls; $P = .99$) but were more likely to have an allergy/immunology consult (26% vs 14%; $P = .02$).
Charneski et al, 2011 ¹⁹	LOS was 1.2 d longer for patients with an allergy label (1.16 after adjustment for covariates).	17.5% of allergy-labeled patients were admitted to the ICU; only 12.0% of control patients were admitted to the ICU (OR, 1.42; 95% CI, 1.21–1.67; $P < .0001$).	There was a reduced risk of readmission in patients with allergy labels compared to control patients, (OR, 0.71; 95% CI, 0.63–0.80; $P < .0001$).	Not assessed	There was a higher risk of mortality in patients with an allergy label compared to control patients (5.14% vs 3.35%; OR, 1.56; 95% CI, 1.29–2.04; $P = .0009$).	None
Conway et al, 2017 ³³	No difference: LOS was 8.0 d for control patients and 8.3 d for patients with an allergy label ($P = .6$).	28.1% of patients with an allergy label vs 24.6% of nonallergic patients were admitted to the ICU ($P = .80$).	No difference; 16.1% of control patients vs 16.4% of allergy-labeled patients were readmitted ($P = .97$).	Not assessed	Not assessed	Time to initial treatment: 186.6 minutes (SD, 13.3) for control patients vs 236 minutes (SD, 22.9) for allergy-labeled patients ($P = .03$).
Desai et al, 2017 ²⁹	There were significantly more hospital d after delivery for patients with allergy labels: 3.55 (SD, 1.79) vs 3.45 (SD, 2.04) for control patients ($P < .0001$). The same result was obtained in the subgroup examining vaginal births.	Not assessed	Not assessed	No difference in <i>C. difficile</i> rates: 0.04% in allergy-labeled patients vs 0.05% in control patients ($P = .8928$).	Not assessed	There were more cesarean deliveries in mothers with a penicillin allergy label (32.32% of allergy-labeled patients vs 30.28% in control patients; $P < .0001$).
Dewart et al, 2018 ⁵⁵	Not assessed	Not assessed	Not assessed	Patients with a penicillin allergy label were more likely to have a ciprofloxacin-resistant UTI (aRR, 1.13; 95% CI, 1.06–1.19)	Not assessed	None

(Continued)

Table 3. (Continued)

Publication		Hospitalization Characteristics Length of stay ICU Admission Readmission		MDR or opportunistic infection	Mortality	Other
Fernandez-Rubio et al, 2014 ⁵⁶	Not assessed	Not assessed	Not assessed	Prevalence of pathogenic bacteria was higher in β -lactam allergy-labeled patients (OR, 2.09 for <i>Bacillus</i> and 1.76 for nonfermenting gram negative bacilli [NFGNR]). <i>Bacillus</i> prevalence was 1.28% vs 0.61% in control patients ($P = .036$), and 2.09% vs 1.20% for NFGNR (<i>Pseudomonas</i>) ($P = .035$). Prevalence of <i>Corynebacterium</i> (38.98% vs 50%) was higher in allergy-labeled patients ($P = .001$).	Not assessed	None
French et al, 2016 ⁵⁷	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Dental implants were more likely to become infected in allergy-labeled patients: 3.4% vs 0.6% of control patients ($P < .05$). Additionally, dental implants failed 2.1% of the time in allergy-labeled patients (10 of 470) vs 0.8% in control patients (39 of 5,106) (OR, 3.1; 95% CI, 1.5–6.4).
Huang et al, 2018 ²⁰	Patients with an allergy label had longer LOS: 11.3 d (95% CI, 4.7–25.8) vs 7.6 d (95% CI, 3.5–17.2) for control patients ($P < .001$). β -lactam allergy label was a risk factor for increased LOS after multivariable modeling ($P = .026$).	No difference; 26.5% of allergy-labeled patients vs 27.9% control patients required ICU admission ($P = .467$).	30-d readmission was 19.2% for patients with allergy labels vs 15.1% for control patients ($P = .008$).	Allergy-labeled patients were more likely to have a <i>C. difficile</i> infection than control patients (17.7% of allergy-labeled patients vs 11.6% of control patients; $P < .001$).	There was a higher risk of 30-d mortality in patients with allergy labels (7.6% vs 5.3%; $P = .017$) and 180-d mortality (15.8% vs 12.2%; $P = .013$). Multivariable logistic regression model of association between β -lactam allergy and 30-d Mortality showed an OR of 1.41 (95% CI, 1.00–2.00; $P = .050$).	None
Imlay et al, 2019 ¹⁷	No difference in LOS (adjusted IRR, 1.03; 95% CI, 0.96–1.12; $P = .40$)	Not assessed	Not assessed	8% of allergy-labeled patients contracted <i>C. difficile</i> , while 7% of control patients did (no significant difference (adjusted HR, 1.10; 95% CI, 0.73–1.66; $P = .66$))	Mortality was significantly higher in patients with reported β -lactam allergy in univariate analysis (HR, 1.66; 95% CI, 1.06–2.60; $P = .035$) but was no longer significant in multivariable analysis, although the trend remained (HR, 1.52; 95% CI, 0.97–2.39; $P = .08$).	None

Irawati et al, 2006 ³⁷	In the group with mild to moderate CAP, LOS was increased for patients with a penicillin allergy label (7.22 vs 5.98 d). This trend held in the subgroup with severe CAP (12.3 vs 8.1 d; $P = .054$).	Not assessed	Not assessed	Not assessed	Not assessed	None
Khumra et al, 2017 ⁴¹	Among liver transplant patients, there was no difference in LOS between allergy-labeled and control patients: 12 (IQR, 6–22) for allergy patients vs 13 (IQR, 8–30) for controls ($P = .20$).	There was no difference in ICU admission: 5 (8%) for both groups ($P = .99$)	There was no difference in readmission, 3 (IQR, 2–9) for allergy-labeled patients vs 2 (IQR, 2–5) for controls ($P = .36$).	MDR gram-negative organism isolation revealed no difference between groups: 4 of 51 allergic patients (8%) vs 1 of 52 nonallergic patients (2%) ($P = .20$). Rate of <i>C. difficile</i> infection trended toward significance for allergy patients: 9 allergic patients (18%) vs 3 control patients (6%) ($P = .07$).	Incidence of mortality between groups: 6 (18%) in the allergy-labeled group vs 4 (8%) in the nonallergic group ($P = .52$).	The total number of infective diagnoses in the 12-mo posttransplant period was increased in the allergy-labeled group (130 for allergy-labeled patients vs 103 for controls; $P = .01$).
Knezevic et al, 2016 ⁴²	There was no significant difference between groups. Allergy-labeled patients had a LOS of 10 d (IQR, 5–21) vs nonallergic patients 13 d (IQR, 6–27).	Not assessed	Allergy-labeled patients were more likely to be readmitted at 4 weeks (29% vs 17% for controls; $P = .001$) and at 6 mo (20% of allergy-labeled patients vs 18% of controls; $P = .025$)	Not assessed	No significant difference; 1 (1%) for allergy-labeled patients vs 23 (4%) of control patients	None
Kraemer et al, 1987 ²⁸	N/A – outpatient study	N/A – outpatient study	The total number of physician visits was significantly increased for patients with penicillin allergy labels (5.49; range, 0–39) compared to controls (3.27; range, 0–19; $P < .001$).	Not assessed	Not assessed	None
Lam et al, 2019 ¹⁶	Not directly assessed	Not assessed	Not assessed	The prevalence of MRSA colonization was significantly higher in patients with antibiotic allergies compared to control patients (8.3% vs 4.7%; $P = .025$). VRE colonization was not significantly different between groups (36.2% vs 46.9%; $P = .10$).	Not assessed	None
Lucas et al, 2019 ²⁵	Patients with any antibiotic allergy label had longer hospital courses (OR, 1.71; 95% CI, 1.16–2.53; $P = .007$). Similar results were obtained in multivariate analysis and in the subgroup of β -lactam allergic patients.	There was no difference between patients with any antibiotic allergy label and controls (OR, 1.83; 95% CI, 0.55–6.11; $P = .33$). Similar results were obtained in multivariate analyses and in the subgroup of β -lactam allergic patients.	Patients with antibiotic allergy labels were more likely to be readmitted at 4W (OR, 1.70; 95% CI, 1.01–2.85; $P = .045$) and 6W post infection (OR, 1.6; 95% CI, 1.02–2.50; $P = .04$). However, multivariate and β -lactam subgroup analyses were not statistically significant.	Not assessed	Not assessed	None

(Continued)

Table 3. (Continued)

Publication	Hospitalization Characteristics			MDR or opportunistic infection	Mortality	Other
	Length of stay	ICU Admission	Readmission			
MacFadden et al, 2016 ³⁰	Allergy-labeled patients were hospitalized for 14 d while controls had a LOS of 10 d (no statistics reported).	Not assessed	Allergy-labeled patients were more likely to be readmitted; there was an increase in readmissions when the preferred therapy was β -lactams, but they were not given (24% vs 4%; $P < .05$).	There was no difference in <i>C. difficile</i> infection (4% in both controls and allergy-labeled patients).	Inpatient mortality was 13% in control patients while it was 4% in allergy-labeled patients.	Combined readmission for <i>C. difficile</i> infection, drug reaction or AKI was not increased in allergic patients (OR, 1.43; 95% CI, 0.51–3.99) but was increased when β -lactam therapy was indicated but not administered (OR, 3.43; 95% CI, 1.48–7.96; $P < .05$).
Macy et al, 2014 ²	Both male and female patients had longer LOS: 7.1 ± 13.4 vs 6.8 ± 12.2 ($P = .007$) and 6.3 ± 12.4 vs 5.6 ± 10.1 ($P < .001$) for male and female patients with a penicillin allergy label vs controls).	Not assessed	Male and female patients with allergy labels were more likely to be admitted over the study period. Female allergy patients (1.8 ± 1.8) vs control 1.7 ± 1.6 ; $P < .0001$ and male allergy-labeled patients (1.9 ± 1.9) vs control (1.9 ± 1.8 ; $P = .0082$)	Female patients with a penicillin allergy label were more likely to develop <i>C. difficile</i> , MRSA, and VRE (2.9 vs 2.3%, 2.6 vs 2.2%, and 0.6 vs 0.5% respectively; $P < .0001$ for all data points). Penicillin allergy-labeled males were not more likely have these infections: <i>C. difficile</i> (2.9 vs 2.5%; $P = .0561$), MRSA (3.8 vs 3.5%; $P = .1574$), and VRE (0.5 vs 0.4%; $P = .6855$).	There was no difference in mortality between the allergy-labeled and control groups during hospitalization: 2.9% vs 3% for females and 4.6% vs 4.6% for males ($P = .9799$ for females and $P = .8233$ for males, respectively).	None
Ponce et al, 2014 ³⁴	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Multivariate models failed to show penicillin allergy label as a predictor for SSI (adjusted OR, 0.94; 95% CI, 0.59–1.49). For patients without penicillin allergy, the SSI rate was 2.6% with vancomycin only compared with 1.6% with vancomycin plus cefazolin ($P = .17$) and 1.3% with cefazolin only ($P < .01$).
Sade et al, 2003 ²⁴	No difference in hospital stay; allergy-labeled patients had a LOS of 5.2 ± 2.8 d while control patients stayed 5.5 ± 3.1 d ($P = .41$).	Not assessed	Not assessed	Not assessed	There was no difference in mortality between allergy-labeled patients and controls: 2 deaths in allergic group vs 3 in control group	None
Saunders et al, 2017 ³⁸	Patients who received clindamycin only (patients with an allergy label) had significantly longer LOS: 18 d (SD, 8.2) vs patients that received cefazolin and metronidazole 10.9 d (SD, 3.2) or other antimicrobials 11.8 d (SD, 6.5) ($P = .02$). This was also significant in a univariate analysis by perioperative antibiotic when comparing clindamycin to cefazolin/metronidazole as the control (OR, 7.1; 95% CI, 3.86–10.75; $P = .005$).	Not assessed	Not assessed	No difference in <i>C. difficile</i> between groups. Patients on clindamycin (allergy-labeled patients) had more surgical infections (55.5% vs 13.9 or 7.7%; $P = .005$) but there was no difference in medical infections (48% vs 26 or 23%; $P = .48$). Allergy-labeled patients had “any” type of infection with 100% frequency while controls had any infection type with 38.9% or 23.3% frequency ($P = .005$).	Not assessed	None

Sousa-Pinto et al, 2018 ³⁹	Allergy-labeled patients had longer LOS (4.5 d; median 2; 95% CI, 1–13) vs control patients (4.0 d; median, 2; 95% CI, 1–13; $P = .03$).	Not assessed	Not assessed	Not assessed	Not assessed	Allergy-labeled patients had a higher Charlson comorbidity index compared to control patients (mean, 0.11 vs 0.09; $P < .001$).
Sousa-Pinto et al, 2018 ³⁶	Allergy-labeled patients had longer hospital stays compared to control patients: 7.8 d (SD, 10.9) vs 7.2 d (SD, 12; $P < .001$). Total hospital days for allergy-labeled patients vs matched controls was 805,429 vs 741,045.	Not assessed	Not assessed	Patients with allergy labels had more infections with <i>Staphylococcus</i> , 923 (0.9%) vs 689 (0.7%) ($P < .001$); MRSA, 323 (0.3%) vs 211 (0.2%) ($P < .001$); <i>E. coli</i> , 2,056 (2.0%) vs 1,552 (1.5%) ($P < .001$); <i>Klebsiella</i> , 637 (0.6%) vs 506 (0.5%) ($P < .001$); <i>Enterococcus</i> , 460 (0.4%) vs 274 (0.3%) ($P < .001$); <i>Strep pneumoniae</i> , 376 (0.4%) vs 309 (0.3%) ($P = .010$); <i>Pseudomonas</i> , 571 (0.6%) vs 509 (0.5%) ($P = .059$); MDR organisms, 117 (0.11%) vs 84 (0.08%) ($P = .02$). No difference in <i>C. difficile</i> infection, 121 (0.1%) vs 111 (0.1%) ($P = .511$) or septicemia, 1,160 (1.1%) vs 1,147 (1.1%) ($P = .785$).	Allergy-labeled patients had lower mortality: 3,065 (3.0%) vs 4,691 (4.6%) in control patients; $P < .001$ by χ^2 test.	Allergy-labeled patients had a higher Charlson comorbidity index compared to controls: mean, 0.91 (95% CI, 0.90–0.92) vs 0.76 (95% CI, 0.75–0.76) ($P < .001$).
Su et al, 2017 ²⁷	Not assessed	Not assessed	Patients with a penicillin allergy label were more likely to have ≥ 4 general practitioner contacts per patient year (adjusted OR, 1.71; 95% CI, 1.460–1.999). The average number of general practitioner contacts per patient year was significantly higher for penicillin allergy labeled patients (16 vs 3, adjusted OR=3.052, 95% CI 2.316 to 3.788).	Not assessed	Not assessed	Not assessed
Sun et al, 2017 ⁴⁴	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	Incidence of SSI during hospitalization after open reduction, internal fixation of ankle fracture was 4.37%, and history of antimicrobial allergy label was an independent risk factor. Multivariate analysis showed OR, 3.00 (95% CI, 1.26–7.12; $P = .013$).

(Continued)

Table 3. (Continued)

Publication	Hospitalization Characteristics			MDR or opportunistic infection	Mortality	Other
	Length of stay	ICU Admission	Readmission			
Tan et al, 2016 ³⁵	Not assessed	Not assessed	Not assessed	The odds of deep SSI development were not different between patients with β -Lactam allergy label and controls (adjusted OR, 0.98; 95% CI, 0.67–1.43; $P = .907$). Patients with a history of β -Lactam allergy label received vancomycin and had more Gram negative infections (20.8% vs 9.9%; OR, 2.41; $P = .05$) but fewer gram positive infections (60.4% vs 81.6%; OR, 0.34; $P = .003$) and fewer resistant infections (adjusted OR, 0.10; 95% CI, 0.01–0.88; $P = .038$). There was no difference in culture negative infections ($P = .14$).	Not assessed	None
Trinh et al, 2009 ⁶¹	Not assessed	Not assessed	Not assessed	For gram-negative SSI, the risk factor of antibiotic allergy label had an OR of 1.39 (95% CI, 0.71–2.73).	Not assessed	None
Trubiano et al, 2015 ²¹	Among cancer patients, allergy label had no effect on LOS: 19 d (range, 2–151) for control patients vs 23 d (range, 3–157) for allergy-labeled patients ($P = .4618$).	No difference: 26% of control patients and 27% of allergy-labeled patients were admitted to the ICU ($P = .87$).	Patients with allergy labels were more likely to be readmitted. For controls median readmission was 2 (range, 0–11) vs median for allergy-labeled patients was 3.5 (range, 1–17; $P = .02$). Allergy-labeled patients were more likely to be readmitted with an infectious cause.	Not assessed	30-d mortality was 3.9% in control patients and 2.2% in allergy-labeled patients ($P = .59$). 60-d mortality was 6.5% in controls, and 4.5% in allergy labeled patients, $P = .89$.	None
Turner et al, 2018 ⁴⁰	Time to clear infection was significantly longer in allergy-labeled patients compared to control patients (6.2 d vs 4.1 d; $P < .01$).	Not assessed	90-d recurrence of infection was higher in allergy-labeled patients compared to controls (7.0% vs 1.5%; $P = .02$).	Not assessed	No difference between allergy-labeled and control patients in 30-d mortality (10.6 vs 11.9; $P = .99$) or 90-d mortality (13.6 vs 18.3; $P = .47$).	In multivariable analysis, β -lactam receipt was most strongly associated with survival (OR, 0.26; 95% CI, 0.12–0.54).
van Dijk et al, 2016 ²³	No difference in LOS between penicillin allergy-labeled patients and controls ($P = .80$)	ICU patients were excluded from the study.	Allergy-labeled patients were more likely to be rehospitalized within 12 weeks (RR, 1.28; 95% CI, 1.10–1.49). There was no significant difference in the risk of readmission within 4 weeks after discharge.	Not assessed	Mortality during hospitalization was not significantly different between patients with (1.2%) and without (1.0%) Penicillin allergy registration (RR, 1.49; 95% CI, 0.58–3.85).	None

Note. CAP, community-acquired pneumonia; ICU, intensive care unit; LOS, length of hospital stay; MDR, multidrug resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; SSI, surgical site infection; UTI, urinary tract infection; VRE, vancomycin resistant *Enterococcus*.

^aFor each study analyzing clinical outcomes, results on hospitalization characteristics including length of stay (LOS), ICU admission, and hospital readmission are indicated in columns 2–4. Multi-drug resistant or opportunistic infection, if analyzed, is indicated in column 5 and patient mortality in column 6. Other less commonly reported outcomes, such as surgical site infections, are reported in column 7.

Table 4. Healthcare-Related Costs in Allergy-Labeled and Control Patients^a

Publication Examining Cost	Inpatient Antimicrobial Costs	Outpatient Antimicrobial Costs	Overall Cost of Admission
Huang et al, 2018 ²⁰	Not addressed	Not addressed	Median total initial hospitalization charge was higher for patients with a β -Lactam allergy label: USD \$223,046 (IQR: \$93,013–417,487) for allergic patients vs \$173,256 (IQR \$73,832–310,206) for control patients ($P < .001$).
Irawati et al, 2006 ³⁷	Cost of antibiotics were increased for patients with a labeled penicillin allergy with mild to moderate CAP (AU \$222 vs \$176) and severe CAP (AU \$1,101 vs \$584)	Not addressed – inpatient study	Increased costs for allergy-labeled patients with mild/moderate and severe CAP (AU\$5,636 vs \$4,663), as well as for severe CAP (AU \$10,289 vs \$6,678; $P = .05$).
Knezevic et al, 2016 ⁴²	Cost of antibiotic per day was not significantly different between groups: Patients with an allergy label cost AU \$5 (\$1–\$32) per day vs \$10 (\$1–\$28) for nonallergic patients.	Not addressed – inpatient study	Not addressed
Kraemer et al, 1987 ²⁸	Not addressed – outpatient study	Average antibiotic costs per patient were significantly higher in allergy-labeled patients (USD \$4.60 vs \$1.75, $P < .001$). There was a higher cost per patient per month of observation in allergy-labeled patients: \$0.36 vs \$0.12 ($P < .001$).	Not addressed – outpatient study
MacLaughlin et al, 2000 ⁴⁵	Not addressed	The mean antimicrobial cost was significantly higher for patients with β -lactam allergy (USD \$26.81 for allergy-labeled patients vs \$16.28 for controls; $P = .004$).	Not addressed
Macy et al, 2014 ²	Not addressed	Not addressed	Patients with penicillin allergy labels required 30,433 extra hospital days, which cost an extra USD \$64,626,630.48 over the 3-year study period. The calculated cost of allergy testing the 51,582 cases of penicillin allergy was \$6,776,327.34 (\$131.37 each).
Sade et al, 2003 ²⁴	Antibiotics were more costly for allergy-labeled patients while in the hospital (cost per dose in USD \$33.90 $\pm$ 42.7 vs \$19.90 $\pm$ 20.20, $P = .0001$) and total cost per treatment (USD \$328.10 $\pm$ 389.50 vs \$232.50 $\pm$ 235.70, $P = .0085$). Allergy-labeled patients also had higher costs of total antibiotic treatment per day (\$136.70 vs \$75.40, $P = .0015$).	On discharge, allergy-labeled patients were prescribed more expensive antibiotics: price of each antibiotic dose was USD \$11.33 $\pm$ 12.80 vs \$6.16 $\pm$ 2.11, $P = .0048$. Total price per recommended outpatient antibiotic was \$379.60 $\pm$ 253.40 vs \$222.50 $\pm$ 148.70, $P < .001$. Total price per antibiotic treatment per day was increased for allergy-labeled patients (\$47.60 vs \$36.10).	Not addressed
Sousa-Pinto et al, 2018 ³⁹	Not addressed	Not addressed	The mean indirect hospitalization costs were higher in allergy-labeled patients – EUR \$2,071 (median, \$1,250.6; 95% CI, 530–5,711) vs EU \$1,798.7 (median, \$1,250.6; 95% CI, 530.5–4,107.7; $P = .12$).
Sousa-Pinto et al, 2018 ³⁶	Not addressed	Not addressed	Allergy-labeled patients had higher hospital charges: mean for allergy patients was USD \$3,809.0 (SD, 4,432.2) vs \$3,490.0 (SD, 4,079.5) for controls. Median values were \$2,418.3 for allergic patients vs \$2,285.3 for controls. Total amount spent was \$391,835,492.5 for allergic patients vs \$359,020,533 for controls ($P < .001$).

Note. AU, Australian dollars; CAP, community-acquired pneumonia; EUR, Euros; USD, United States dollars.

^aResults from studies that reported cost analyses, including inpatient and outpatient antibiotic cost, as well as total cost of hospitalization (cost of admission) are reported in columns 2–4.

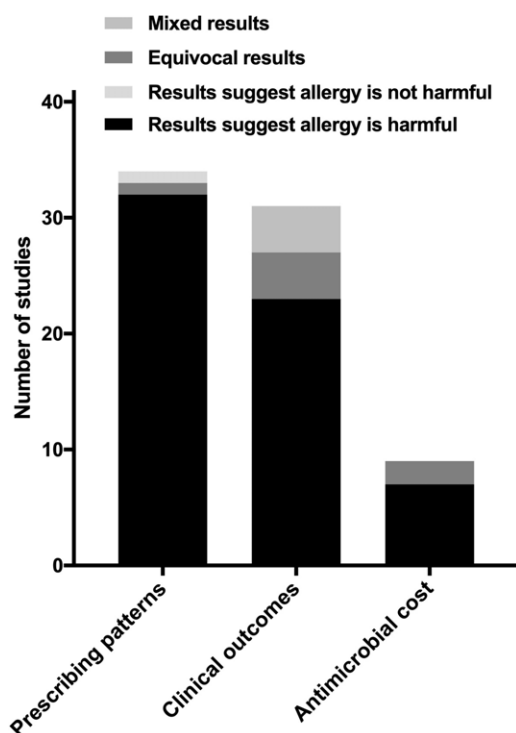


Fig. 3. Studies grouped by broad results in each of 3 domains: antibiotic exposure and prescribing patterns (34 studies), clinical outcomes (31 studies) and healthcare related costs (9 studies).

studies examined healthcare contact, and 10 of these studies (77%) found that allergy-labeled patients were more likely to be readmitted, to have infection recurrence, and to have more primary-care visits (Table 3).^{2,20,21,23,25,27,28,30,40,42} Also, 1 study found that allergy-labeled patients were readmitted less than control patients, and the remaining 2 studies had equivocal results (Table 3).^{19,33,41}

Of the studies examining MDR or opportunistic infections, 10 of 15 (67%) found that allergy-labeled patients were more likely to have an MDR infection or to be colonized with an MDR organism. Of the 9 studies that addressed *C. difficile* infection specifically, 4 (44%) found that allergy-labeled patients were more likely to experience infection.^{2,20,41,43} Most studies that analyzed methicillin-resistant *Staphylococcus aureus* (MRSA) (4 of 4, 100%) and vancomycin-resistant *Enterococcus* (VRE) infections (2 of 3, 67%), respectively, found that allergy-labeled patients were more likely to develop infection or to be colonized with a resistant organism than control patients (Table 3).^{2,16,31,36,43}

Overall, 13 studies analyzed hospital mortality. Furthermore, 3 studies (23%) found that allergy-labeled patients were more likely to die in the hospital, and 1 study (8%) found that allergy-labels conferred a mortality benefit.^{19,20,30,36} All other studies (n = 8, 69%) reported equivocal results that did not reach statistical significance (Table 3).^{2,21,23,24,32,40–42}

Furthermore, 2 studies found that antibiotic allergy labels were associated with an increased risk of surgical site infection.^{31,44} Also, 1 study that focused on obstetric patients found that there were more cesarean deliveries in a large cohort of mothers with a penicillin allergy label than among control patients (Table 3).²⁹ Other less frequently reported outcomes are included in the “other” column of Table 3.

Antibiotic allergy labels and healthcare costs

Only 9 studies examined the impact of antibiotic allergy labels on healthcare-related costs, and 7 (77.7%) found that allergy labels increased at least 1 cost component (Fig. 3, column 3).^{2,20,24,28,36,37,45} Cost data included multiple currencies from various countries. No studies found that allergy labels were associated with cost savings (Fig. 3, column 3). For example, 2 of 3 studies examining the cost of inpatient antibiotics found that allergy-labeled patients had a significantly higher cost of treatment than nonallergic control patients (Table 4).^{24,37} Similarly, 3 of 3 studies that examined the costs of outpatient antibiotic treatment found that patients with an allergy label were prescribed more expensive drugs (Table 4).^{24,28,45} Of 5 studies examining the total cost of hospitalization, 4 found that allergy-labeled patients incurred higher costs than nonallergic control patients, and the fifth study showed a trend toward significance (Table 4).^{2,20,36,37,39}

Evidence grading

The quality of studies ranged from 3 to 9 stars. Only 9 of 41 studies (22%) scored a maximum quality score of 9 stars, but 20 studies (49%) received scores of 7 or 8 stars (Supplementary Material online). Also, 5 studies (12%) had scores of 6, and 7 studies (17%) had scores ≤5. The mean value of stars achieved by all studies was 7.05, and the quality of studies did not differ by domain: 7.24 for antibiotic exposure, 7.28 for clinical outcomes, and 7.55 for healthcare cost. Studies that failed to achieve a high-quality score typically had concerns over comparability of allergy-labeled and control cohorts, as well as poorly defined follow-up for outcomes of interest.

Discussion

We identified 41 studies that directly compared patients with an antibiotic allergy label to non-allergy-labeled patients in at least 1 of 3 domains: antibiotic exposure and prescribing patterns, clinical outcomes, and healthcare-related costs. Most of these studies were published since 2016, underscoring the recent recognition of potential complications associated with antibiotic allergy labels. Indeed, we found that most studies published on this topic concluded that antibiotic allergy labels are detrimental across these domains of analysis. Perhaps most notably, nearly all studies examining antibiotic exposure found that allergy-labeled patients receive more broad-spectrum and inappropriate therapy, indicating that allergy labels do influence treatment decisions. The consequences of these differences in treatment manifest as longer hospital stays, higher rates of readmission, colonization or infection with MDR organisms, and higher costs for allergy-labeled patients. These findings build upon a previous systematic review that included 8 studies published before January 2016; this review concluded that allergy labels are associated with suboptimal drug selection and negative clinical outcomes.¹¹

A strength of the present review is the breadth of patient populations and settings of the included studies. For example, studies included inpatients, outpatients, patients with immunocompromised states (cancer and transplant patients), patients undergoing general surgery and subspecialty procedures, outpatient dentistry, pediatrics, and family medicine clinics. Notably, the included studies were performed in a variety of healthcare systems, including the United States (both private practice and academic centers), the United Kingdom, Australia, Canada, the European Union, and

Israel. Regardless of setting or healthcare system, these studies arrived at similar conclusions.

Despite the breadth of these studies, most studies included in this systematic review examined adult patients in the inpatient setting, which suggests that the strongest conclusions are generalizable to this group of patients, but not necessarily to other demographics. For example, only 6 studies included patients <18 years of age. This factor is important because many antibiotic allergies are acquired during childhood and their impact on pediatric patients remains a relatively understudied area. Similarly, only 7 studies included patients (of any age) in the outpatient setting. The growth of allergy de-labeling programs in hospitals suggests that the problem of allergy overdiagnosis is receiving recognition in this setting.^{6-8,46} However, most antibiotic prescriptions originate in the outpatient setting.^{47,48} Therefore, this is an important population for future investigation and education to ensure that outpatient-based clinicians, especially those practicing in offices, urgent care clinics, and emergency departments, are well informed about the harms associated with antibiotic allergy labels.

The difference in antibiotic exposure between those with and without allergies is not surprising. This is especially true for β -lactam antibiotics because this is the most common antibiotic allergy reported and the most commonly prescribed class of antibiotics in hospitalized patients.⁴⁹ However, the antibiotics to which allergic patients are frequently exposed include agents like vancomycin or clindamycin among others with broad-spectrum activity. The differences in antibiotic exposure likely contribute to the differences observed across numerous studies in terms of both clinical and economic outcomes. Exposure to broader-spectrum antibiotics has the potential to increase risk of *Clostridium difficile* infection or MDR colonization, and in many cases, the alternative agents used for allergic patients may be considered second-line therapies.^{2,43,50-52} The differences in economic costs may be attributable not only to receipt of suboptimal therapy but also to higher costs associated with alternative agents unto themselves.^{48,53}

We used the Newcastle-Ottawa evidence grading tool for this review. These studies were observational, and most were rated relatively highly, in part because our inclusion criteria required a control group. In general, high-quality and lower-quality studies reached similar outcomes; thus, there does not appear to be evidence that the conclusions of this review were biased by lower-quality studies. Many of these studies used epidemiologic methods to mitigate the consequences of confounding variables, which may differ between those with and without allergies and may affect matching and multivariable modeling. Although most of these studies are retrospective and cannot eliminate the possibility of residual confounding, many of the studies received high quality scores, which adds confidence to the conclusion that the differences observed between groups are due to the allergy label rather than other unmeasured confounding. Importantly, the studies included in each domain had similar NOS scores indicating that our conclusions about each domain are supported by similar-quality evidence.

Certain patient groups, such as immunocompromised patients, may be at higher risk of receiving broad-spectrum antibiotics regardless of allergy status. Moreover, 4 studies specifically examined antibiotic prescribing patterns and clinical outcomes in cancer and transplant patients.^{17,20,21,41} All 4 studies showed that allergy-labeled patients received more broad-spectrum therapy (Table 2). All 4 studies also demonstrated at least 1 negative clinical outcome, and 2 studies demonstrated an increased mortality in allergy-labeled patients with bone marrow transplant, solid-organ transplant, or hematological malignancy.^{17,20} These findings suggest

that allergy labels further exacerbate the treatment of already-complex medical conditions.

Our study has several limitations. This was a systematic review and not a meta-analysis, which is largely due to the variability with which results were reported between studies. Despite the consistency of findings between studies, study designs did vary, and our ability to control for confounding was limited. Outside broad categories, such as penicillin allergy, most studies did not provide detail about the types of antimicrobial allergies or severity of reactions. Although we used a comprehensive search strategy without language or publication restrictions to minimize the potential for biases, we may have missed some studies, including conference abstracts.

Collectively, our systematic review suggests that antibiotic allergy labels are consequential for patients across multiple domains. Allergy-labeled patients are prescribed broader-spectrum antibiotics and longer durations of therapy, and they may be unnecessarily exposed to multiple drugs for a single infection. Allergy-labeled patients also have worse clinical outcomes and increased health-care-related costs than comparable control patients. Given that only a small proportion of patients with allergy labels are truly allergic, implementation of safe and efficient interventions, including de-labeling based on history along with skin testing and oral challenge, are needed to de-label allergies. Furthermore, enhanced education about the harms of allergy overdiagnosis may aid in preventing unnecessary allergy labels in the first place.

Supplementary material. To view supplementary material for this article, please visit <https://doi.org/10.1017/ice.2020.1229>

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Conflicts of interest. All authors report no conflicts of interest relevant to this article.

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Supplemental Table 1: Quality Assessment of Included Studies. Comprehensive quality-assessment scoring using the Newcastle-Ottawa Scale for each study included in this systematic review.

Publication	Representativeness of cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Comparability of cohorts	Assessment of outcome	Adequate duration of follow-up	Adequate follow-up of cohort	Total score
Blumenthal et al., 2018 ³²	B (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	D (0*)	8
Blumenthal et al. 2018 ⁴³	B (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	B (1*)	9
Blumenthal et al. 2016 ³⁰	B (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	A (1*)	9
Butler et al. 2018 ⁵⁴	A (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	A (1*)	9
Charneski et al. 2011 ¹⁹	B (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	A (1*)	9
Conway et al. 2017 ²⁹	A (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	A (1*)	9
Desai et al., 2017 ³⁵	A (1*)	A (1*)	A (1*)	A (1*)	None (0*)	B (1*)	A (1*)	B (1*)	7
Dewart et al., 2018 ⁵⁵	B (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	A (1*)	9
Fernandez-Rubio et al. 2014 ⁵⁶	D (0*)	A (1*)	A (1*)	D (0*)	None (0*)	B (1*)	A (1*)	D (0*)	4
French et al. 2016 ⁵⁷	D (0*)	A (1*)	C (0*)	A (1*)	A+B (2*)	B (1*)	A (1*)	D (0*)	6
Huang et al., 2018 ²⁰	B (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	D (0*)	8
Imlay et al., 2019 ¹⁷	A (1*)	C (0*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	A (1*)	8
Irawati et al., 2006 ³⁶	B (1*)	A (1*)	A (1*)	A (1*)	None (0*)	B (1*)	A (1*)	D (0*)	7
Khumra et al., 2017 ⁴¹	B (1*)	A (1*)	A (1*)	A (1*)	None (0*)	B (1*)	A (1*)	D (0*)	6
Knezevic et al., 2016 ⁴²	B (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	C (0*)	8
Kraemer et al., 1987 ²⁸	B (1*)	A (1*)	B (1*)	B (0*)	None (0*)	B (1*)	B (0*)	D (0*)	4
Lam et al., 2019 ¹⁶	D (0*)	C (0*)	A (1*)	B (0*)	None (0*)	B (1*)	A (1*)	D (0*)	3
Lee et al., 2000 ⁵⁸	B (1*)	C (0*)	A (1*)	A (1*)	None (0*)	B (1*)	B (0*)	C (0*)	4
Lucas et al., 2019 ²⁵	B (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	D (0*)	8
MacFadden et al., 2016 ³⁷	C (0*)	A (1*)	B (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	D (0*)	7
MacLaughlin et al. 2000 ⁴⁵	A (1*)	A (1*)	A (1*)	A (1*)	None (0*)	B (1*)	A (1*)	B (1*)	7
Macy et al., 2014 ²	A (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	B (1*)	9
Phillips et al., 2019 ¹⁸	B (1*)	C (0*)	A (1*)	A (1*)	B (1*)	B (1*)	A (1*)	D (0*)	6
Ponce et al., 2014 ³¹	A (1*)	C (0*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	D (0*)	7
Powell et al., 2019 ⁵⁹	A (1*)	B (0*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	A (1*)	8
Sade et al., 2003 ²⁴	B (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	A (1*)	9
Saunders et al., 2017 ³⁸	B (1*)	C (0*)	C (0*)	A (1*)	None (0*)	B (1*)	A (1*)	D (0*)	4
Schroek et al., 2015 ⁶⁰	A (1*)	C (0*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	D (0*)	7
Sousa-Pinto et al., 2018 ³⁹	A (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	D (0*)	8
Sousa-Pinto et al., 2018 ³⁴	A (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	D (0*)	8
Su et al., 2017 ²⁷	A (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	D (0*)	8
Sun et al., 2017 ⁴⁴	A (1*)	B (0*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	D (0*)	7
Tan et al., 2016 ³³	D (0*)	D (0*)	C (0*)	A (1*)	A+B (2*)	B (1*)	B (0*)	D (0*)	4
Trinh et al., 2009 ⁶¹	B (1*)	A (1*)	A (1*)	B (0*)	A+B (2*)	B (1*)	A (1*)	D (0*)	7
Trubiano et al., 2016 ²²	A (1*)	D (0*)	A (1*)	A (1*)	None (0*)	B (1*)	A (1*)	D (0*)	5
Trubiano et al., 2015 ²¹	B (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	D (0*)	8
Trubiano et al., 2015 ²⁶	B (1*)	A (1*)	A (1*)	A (1*)	None (0*)	B (1*)	A (1*)	D (0*)	6
Trubiano et al., 2016 ⁶²	B (1*)	A (1*)	B (1*)	A (1*)	None (0*)	B (1*)	A (1*)	D (0*)	6
Turnbull et al., 2005 ⁶³	B (1*)	D (0*)	C (0*)	A (1*)	A+B (2*)	B (1*)	A (1*)	A (1*)	7
Turner et al., 2018 ⁴⁰	B (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	A (1*)	9
van Dijk et al., 2016 ²³	B (1*)	A (1*)	A (1*)	A (1*)	None (0*)	B (1*)	A (1*)	A (1*)	7

Supplemental Table 1: Quality Assessment of Included Studies. Comprehensive quality-assessment scoring using the Newcastle-Ottawa Scale for each study included in this systematic review.

Publication	Representativeness of cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Comparability of cohorts	Assessment of outcome	Adequate duration of follow-up	Adequate follow-up of cohort	Total score
Blumenthal et al., 2018 ³²	B (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	D (0*)	8
Blumenthal et al. 2018 ⁴³	B (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	B (1*)	9
Blumenthal et al. 2016 ³⁰	B (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	A (1*)	9
Butler et al. 2018 ⁵⁴	A (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	A (1*)	9
Charneski et al. 2011 ¹⁹	B (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	A (1*)	9
Conway et al. 2017 ²⁹	A (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	A (1*)	9
Desai et al., 2017 ³⁵	A (1*)	A (1*)	A (1*)	A (1*)	None (0*)	B (1*)	A (1*)	B (1*)	7
Dewart et al., 2018 ⁵⁵	B (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	A (1*)	9
Fernandez-Rubio et al. 2014 ⁵⁶	D (0*)	A (1*)	A (1*)	D (0*)	None (0*)	B (1*)	A (1*)	D (0*)	4
French et al. 2016 ⁵⁷	D (0*)	A (1*)	C (0*)	A (1*)	A+B (2*)	B (1*)	A (1*)	D (0*)	6
Huang et al., 2018 ²⁰	B (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	D (0*)	8
Imlay et al., 2019 ¹⁷	A (1*)	C (0*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	A (1*)	8
Irawati et al., 2006 ³⁶	B (1*)	A (1*)	A (1*)	A (1*)	None (0*)	B (1*)	A (1*)	D (0*)	7
Khumra et al., 2017 ⁴¹	B (1*)	A (1*)	A (1*)	A (1*)	None (0*)	B (1*)	A (1*)	D (0*)	6
Knezevic et al., 2016 ⁴²	B (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	C (0*)	8
Kraemer et al., 1987 ²⁸	B (1*)	A (1*)	B (1*)	B (0*)	None (0*)	B (1*)	B (0*)	D (0*)	4
Lam et al., 2019 ¹⁶	D (0*)	C (0*)	A (1*)	B (0*)	None (0*)	B (1*)	A (1*)	D (0*)	3
Lee et al., 2000 ⁵⁸	B (1*)	C (0*)	A (1*)	A (1*)	None (0*)	B (1*)	B (0*)	C (0*)	4
Lucas et al., 2019 ²⁵	B (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	D (0*)	8
MacFadden et al., 2016 ³⁷	C (0*)	A (1*)	B (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	D (0*)	7
MacLaughlin et al. 2000 ⁴⁵	A (1*)	A (1*)	A (1*)	A (1*)	None (0*)	B (1*)	A (1*)	B (1*)	7
Macy et al., 2014 ²	A (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	B (1*)	9
Phillips et al., 2019 ¹⁸	B (1*)	C (0*)	A (1*)	A (1*)	B (1*)	B (1*)	A (1*)	D (0*)	6
Ponce et al., 2014 ³¹	A (1*)	C (0*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	D (0*)	7
Powell et al., 2019 ⁵⁹	A (1*)	B (0*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	A (1*)	8
Sade et al., 2003 ²⁴	B (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	A (1*)	9
Saunders et al., 2017 ³⁸	B (1*)	C (0*)	C (0*)	A (1*)	None (0*)	B (1*)	A (1*)	D (0*)	4
Schroek et al., 2015 ⁶⁰	A (1*)	C (0*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	D (0*)	7
Sousa-Pinto et al., 2018 ³⁹	A (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	D (0*)	8
Sousa-Pinto et al., 2018 ³⁴	A (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	D (0*)	8
Su et al., 2017 ²⁷	A (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	D (0*)	8
Sun et al., 2017 ⁴⁴	A (1*)	B (0*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	D (0*)	7
Tan et al., 2016 ³³	D (0*)	D (0*)	C (0*)	A (1*)	A+B (2*)	B (1*)	B (0*)	D (0*)	4
Trinh et al., 2009 ⁶¹	B (1*)	A (1*)	A (1*)	B (0*)	A+B (2*)	B (1*)	A (1*)	D (0*)	7
Trubiano et al., 2016 ²²	A (1*)	D (0*)	A (1*)	A (1*)	None (0*)	B (1*)	A (1*)	D (0*)	5
Trubiano et al., 2015 ²¹	B (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	D (0*)	8
Trubiano et al., 2015 ²⁶	B (1*)	A (1*)	A (1*)	A (1*)	None (0*)	B (1*)	A (1*)	D (0*)	6
Trubiano et al., 2016 ⁶²	B (1*)	A (1*)	B (1*)	A (1*)	None (0*)	B (1*)	A (1*)	D (0*)	6
Turnbull et al., 2005 ⁶³	B (1*)	D (0*)	C (0*)	A (1*)	A+B (2*)	B (1*)	A (1*)	A (1*)	7
Turner et al., 2018 ⁴⁰	B (1*)	A (1*)	A (1*)	A (1*)	A+B (2*)	B (1*)	A (1*)	A (1*)	9
van Dijk et al., 2016 ²³	B (1*)	A (1*)	A (1*)	A (1*)	None (0*)	B (1*)	A (1*)	A (1*)	7

List of Excluded Studies from Full-text assessment

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SEARCH STRATEGY

Databases searched for studies	Results added to Covidence for screening	Comments (upload initial minus duplicates)
Pubmed	1956	1948 +10 – 2 duplicates removed=1956
Embase	2567	2933 - 366 duplicates = 2567
Cochrane CENTRAL in Cochrane Library	21	29-8=21
EBSCO (CINAHL; EconLit)	439	748-309 duplicates=439
Web of Science (as per protocol)	181	231 from Core Collection: Uploaded to Covidence - 154 studies added to Title and abstract screening; 77 duplicates removed; SCIELO: 27 studies added to Title and abstract screening 3 duplicates removed (154+27=181) o Web of Science Core Collection (1900-present; edition(s): Science Citation Index Expanded (1900-present), Emerging Sources Citation Index (2015-present) 231 o KCI-Korean Journal Database (1980-present) - no relevant o Russian Science Citation Index (2005-present) - no relevant o SciELO Citation Index (1997-present) - 30

PubMed

Date Search conducted: March 7th 2019

((((((((((((((((((("Aminoglycosides"[Mesh]) OR "Lactams"[Mesh]) OR "Vancomycin"[Mesh]) OR "Tetracycline"[Mesh]) OR "Anti-Bacterial Agents"[Mesh]) OR "Lincosamides"[Mesh]) OR "Daptomycin"[Mesh]) OR "Lipoglycopeptides"[Mesh]) OR "Macrolides"[Mesh]) OR "Linezolid"[Mesh]) OR "Cycloserine"[Mesh]) OR "tedizolid"[Supplementary Concept]) OR "Fluoroquinolones"[Mesh]) OR "Nalidixic Acid"[Mesh]) OR "Oxolinic Acid"[Mesh]) OR "Sulfamethoxazole"[Mesh]) OR (antimicrobial* AND anti-microbial*[Title/Abstract] OR antibacterial* AND anti-bacterial*[Title/Abstract] OR antibiotic* AND anti-biotic*[Title/Abstract] OR "ss-lactam*" [Title/Abstract] OR b-Lactam*[Title/Abstract] OR beta-lactam*[Title/Abstract] OR amdinocillin[Title/Abstract] OR amoxicillin*[Title/Abstract] OR ampicillin[Title/Abstract] OR aztreonam[Title/Abstract] OR pivampicillin[Title/Abstract] OR penicillin* AND carbenicillin[Title/Abstract] OR cloxacillin[Title/Abstract] OR dicloxacillin[Title/Abstract] OR oxacillin[Title/Abstract] OR piperacillin*[Title/Abstract] OR pivmecillinam[Title/Abstract] OR ticarcillin*[Title/Abstract] OR bacampicillin[Title/Abstract] OR carampicillin[Title/Abstract] OR floxacillin[Title/Abstract] OR flucloxacillin[Title/Abstract] OR cyclacillin[Title/Abstract] OR carbapenem*[Title/Abstract] OR doripenem[Title/Abstract] OR ertapenem[Title/Abstract] OR

imipenem* AND thienamycin*[Title/Abstract] OR meropenem*[Title/Abstract] OR cephalosporin*[Title/Abstract] OR cefadroxil[Title/Abstract] OR cefazolin[Title/Abstract] OR cephalixin[Title/Abstract] OR cefaclor[Title/Abstract] OR cepharin[Title/Abstract] OR cephradine[Title/Abstract] OR cefotetan[Title/Abstract] OR cefoxitin[Title/Abstract] OR cefprozil[Title/Abstract] OR cefuroxime[Title/Abstract] OR cefotiam[Title/Abstract] OR cefdinir[Title/Abstract] OR cefditoren[Title/Abstract] OR cefixime[Title/Abstract] OR cefmetazole[Title/Abstract] OR cefonicid[Title/Abstract] OR cefotaxime[Title/Abstract] OR cefpodoxime[Title/Abstract] OR ceftazidime[Title/Abstract] OR ceftibuten[Title/Abstract] OR ceftriaxone[Title/Abstract] OR cefmenoxime[Title/Abstract] OR cefoperazone[Title/Abstract] OR ceftizoxime[Title/Abstract] OR lincosamide*[Title/Abstract] OR clindamycin[Title/Abstract] OR lincomycin[Title/Abstract] OR macrolide*[Title/Abstract] OR azithromycin[Title/Abstract] OR clarithromycin[Title/Abstract] OR erythromycin[Title/Abstract] OR tetracycline*[Title/Abstract] OR chlortetracycline[Title/Abstract] OR oxytetracycline[Title/Abstract] OR demeclocycline[Title/Abstract] OR doxycycline[Title/Abstract] OR minocycline[Title/Abstract] OR tigecycline[Title/Abstract] OR sulphamethoxazole*[Title/Abstract] OR trimethoprim*[Title/Abstract] OR fluoroquinolones[Title/Abstract] OR ciprofloxacin[Title/Abstract] OR delafloxacin[Title/Abstract] OR gemifloxacin[Title/Abstract] OR levofloxacin[Title/Abstract] OR moxifloxacin[Title/Abstract] OR norfloxacin[Title/Abstract] OR ofloxacin[Title/Abstract] OR enoxacin[Title/Abstract] OR pefloxacin[Title/Abstract] OR lomefloxacin[Title/Abstract] OR aminoglycoside*[Title/Abstract] OR amikacin[Title/Abstract] OR gentamicin[Title/Abstract] OR kanamycin[Title/Abstract] OR neomycin, netilmicin[Title/Abstract] OR netrocin[Title/Abstract] OR plazomycin[Title/Abstract] OR streptomycin[Title/Abstract] OR tobramycin[Title/Abstract] OR nebramycin[Title/Abstract] OR lipoglycopeptide*[Title/Abstract] OR teicoplanin[Title/Abstract] OR daptomycin[Title/Abstract] OR vancomycin[Title/Abstract] OR linezolid[Title/Abstract] OR cycloserine[Title/Abstract] OR tedizolid[Title/Abstract] OR rifamycin[Title/Abstract] OR bacitracin[Title/Abstract] OR capreomycin[Title/Abstract] OR chloramphenicol[Title/Abstract] OR clofazimine[Title/Abstract] OR colistimethate[Title/Abstract] OR colistin[Title/Abstract] OR dapsone[Title/Abstract] OR fosfomycin[Title/Abstract] OR "fusidic acid"[Title/Abstract] OR methenamine[Title/Abstract] OR metronidazole[Title/Abstract] OR nitrofurantoin[Title/Abstract] OR polymyxin*[Title/Abstract] OR rifampin*[Title/Abstract] OR secnidazole[Title/Abstract] OR tinidazole[Title/Abstract] OR carfecillin[Title/Abstract] OR cefamandole[Title/Abstract] OR cefatrizine[Title/Abstract] OR cefsulodin[Title/Abstract] OR cephacetrile[Title/Abstract] OR cephaloglycin[Title/Abstract] OR cephaloridine[Title/Abstract] OR cephalothin[Title/Abstract] OR cephamycins[Title/Abstract] OR dibekacin[Title/Abstract] OR dihydrostreptomycin[Title/Abstract] OR enviomycin[Title/Abstract] OR framycetin[Title/Abstract] OR josamycin[Title/Abstract] OR kitasamycin[Title/Abstract] OR lymecycline[Title/Abstract] OR mepartricin[Title/Abstract] OR methacycline[Title/Abstract] OR methicillin[Title/Abstract] OR mezlocillin[Title/Abstract] OR moxalactam[Title/Abstract] OR nafcillin[Title/Abstract] OR "nalidixic acid"[Title/Abstract] OR novobiocin[Title/Abstract] OR oleandomycin AND "oxolinic acid"[Title/Abstract] OR "pipemidic acid"[Title/Abstract] OR ribostamycin[Title/Abstract] OR rifabutin[Title/Abstract] OR rolitetracycline[Title/Abstract] OR roxithromycin[Title/Abstract] OR sisomicin[Title/Abstract] OR spectinomycin[Title/Abstract] OR spiramycin[Title/Abstract] OR streptogramin*[Title/Abstract] OR quinupristin*[Title/Abstract] OR dalfopristin*[Title/Abstract] OR sulbactam[Title/Abstract] OR sulbenicillin[Title/Abstract] OR sulfamerazine[Title/Abstract] OR sulfamethoxypyridazine[Title/Abstract] OR talampicillin[Title/Abstract] OR thiamphenicol[Title/Abstract] OR troleandomycin[Title/Abstract])) AND (((("Hypersensitivity"[Mesh]) OR "Allergy and Immunology"[Mesh]) OR "Drug

Hypersensitivity"[Mesh]) OR (allerg*[Title/Abstract] OR hypersensitivit*[Title/Abstract])) AND (((("Medical Records"[Mesh]) OR "Nursing Records"[Mesh]) OR "Self Report"[Mesh]) OR "Medical History Taking"[Mesh]) OR (label*[Title/Abstract] OR document*[Title/Abstract] OR report*[Title/Abstract] OR record*[Title/Abstract] OR chart*[Title/Abstract] OR EHR[Title/Abstract] OR EMR[Title/Abstract] OR regist*[Title/Abstract] OR history[Title/Abstract])) AND ((prescrib*[Title/Abstract] OR prescript*[Title/Abstract] OR select*[Title/Abstract] OR stay*[Title/Abstract] OR "length of stay"[Title/Abstract] OR hospitali*[Title/Abstract] OR death[Title/Abstract] OR mortality[Title/Abstract] OR morbidity[Title/Abstract] OR readmi*[Title/Abstract] OR re-admi*[Title/Abstract] OR cost*[Title/Abstract] OR opportunistic[Title/Abstract] OR resist*[Title/Abstract] OR "C. difficile"[Title/Abstract] OR "C. diff*" [Title/Abstract] OR "Clostridium difficile"[Title/Abstract] OR "Clostridioides difficile"[Title/Abstract] OR CDI[Title/Abstract] OR C-diff[Title/Abstract] OR MRSA[Title/Abstract] OR VRE[Title/Abstract] OR duration[Title/Abstract] OR stewardship[Title/Abstract]) OR (((("Inappropriate Prescribing"[Mesh]) OR "Practice Patterns, Physicians"[Mesh]) OR "Drug Prescriptions"[Mesh]) OR "Medical Overuse"[Mesh]) OR (((("Costs and Cost Analysis"[Mesh]) OR "Economics, Pharmaceutical"[Mesh]) OR "Drug Utilization"[Mesh]) OR "Drug Utilization Review"[Mesh]) OR (((((((("Length of Stay"[Mesh]) OR "Patient Readmission"[Mesh]) OR "Mortality"[Mesh]) OR "mortality"[Subheading]) OR "Death"[Mesh]) OR "Morbidity"[Mesh]) OR "Epidemiology"[Mesh]) OR "epidemiology"[Subheading])) OR ("Patient Harm"[Mesh]) OR "Patient Reported Outcome Measures"[Mesh])))) NOT (animals[mh] NOT humans[mh]))

PubMed Inprocess

(antibiotic OR antibiotics) AND allergy AND (label OR labelling) AND (prescribing OR selection OR stay OR hospitalization OR hospitalization OR mortality OR morbidity OR death OR readmission OR re-admission OR cost OR opportunistic OR outcome OR outcomes OR side-effects OR side-effect OR adverse OR harms) AND inprocess[sb]

EMBASE

Date FINAL search conducted: April 17th 2019

Sources Embase, MEDLINE

Query('inappropriate prescribing'/exp OR 'drug use'/exp OR 'health care cost'/exp OR 'utilization review'/exp OR 'length of stay'/exp OR 'hospital readmission'/exp OR 'epidemiology'/exp OR 'death'/exp OR 'patient harm'/exp OR 'treatment outcome'/exp OR prescrib*:ti,ab,kw OR prescript*:ti,ab,kw OR ((drug:ti,ab,kw OR treatment:ti,ab,kw) AND select*:ti,ab,kw) OR stay*:ti,ab,kw OR 'length of stay':ti,ab,kw OR hospitali*:ti,ab,kw OR death:ti,ab,kw OR mortality:ti,ab,kw OR morbidity:ti,ab,kw OR readmi*:ti,ab,kw OR 're-admi*':ti,ab,kw OR cost*:ti,ab,kw OR opportunistic:ti,ab,kw OR resist*:ti,ab,kw OR 'c. difficile':ti,ab,kw OR 'c. diff*':ti,ab,kw OR 'clostridium difficile':ti,ab,kw OR 'clostridioides difficile':ti,ab,kw OR cdi:ti,ab,kw OR 'c diff':ti,ab,kw OR mrsa:ti,ab,kw OR vre:ti,ab,kw OR duration:ti,ab,kw OR stewardship:ti,ab,kw OR (adverse:ti AND outcome*:ti) OR (harmful:ti AND outcome*:ti) OR impact:ti OR burden:ti) AND (antimicrobial*:ti,ab,kw OR 'anti-microbial*':ti,ab,kw OR

antibacterial*:ti,ab,kw OR 'anti-bacterial*':ti,ab,kw OR antibiotic*:ti,ab,kw OR 'β-lactam*':ti,ab,kw OR 'b lactam*':ti,ab,kw OR 'beta-lactam*':ti,ab,kw OR 'beta lactam*' OR amdinocillin:ti,ab,kw OR amoxicillin*:ti,ab,kw OR ampicillin:ti,ab,kw OR aztreonam:ti,ab,kw OR pivampicillin:ti,ab,kw OR penicillin*:ti,ab,kw OR carbenicillin:ti,ab,kw OR cloxacillin:ti,ab,kw OR dicloxacillin:ti,ab,kw OR oxacillin:ti,ab,kw OR piperacillin*:ti,ab,kw OR pivmecillinam:ti,ab,kw OR ticarcillin*:ti,ab,kw OR bacampicillin:ti,ab,kw OR carampicillin:ti,ab,kw OR floxacillin:ti,ab,kw OR flucloxacillin:ti,ab,kw OR cyclacillin:ti,ab,kw OR carbapenem*:ti,ab,kw OR doripenem:ti,ab,kw OR ertapenem:ti,ab,kw OR imipenem*:ti,ab,kw OR thienamycin*:ti,ab,kw OR meropenem*:ti,ab,kw OR cephalosporin*:ti,ab,kw OR cefadroxil:ti,ab,kw OR cefazolin:ti,ab,kw OR cephalixin:ti,ab,kw OR cefaclor:ti,ab,kw OR cepharin:ti,ab,kw OR cephradine:ti,ab,kw OR cefotetan:ti,ab,kw OR cefoxitin:ti,ab,kw OR cefprozil:ti,ab,kw OR cefuroxime:ti,ab,kw OR cefotiam:ti,ab,kw OR cefdinir:ti,ab,kw OR cefditoren:ti,ab,kw OR cefixime:ti,ab,kw OR cefmetazole:ti,ab,kw OR cefonicid:ti,ab,kw OR cefotaxime:ti,ab,kw OR cefpodoxime:ti,ab,kw OR ceftazidime:ti,ab,kw OR ceftibuten:ti,ab,kw OR ceftriaxone:ti,ab,kw OR cefmenoxime:ti,ab,kw OR cefoperazone:ti,ab,kw OR ceftizoxime:ti,ab,kw OR lincosamide*:ti,ab,kw OR clindamycin:ti,ab,kw OR lincomycin:ti,ab,kw OR macrolide*:ti,ab,kw OR azithromycin:ti,ab,kw OR clarithromycin:ti,ab,kw OR erythromycin:ti,ab,kw OR tetracycline*:ti,ab,kw OR chlortetracycline:ti,ab,kw OR oxytetracycline:ti,ab,kw OR demeclocycline:ti,ab,kw OR doxycycline:ti,ab,kw OR minocycline:ti,ab,kw OR tigecycline:ti,ab,kw OR sulphamethoxazole*:ti,ab,kw OR trimethoprim*:ti,ab,kw OR fluoroquinolones:ti,ab,kw OR ciprofloxacin:ti,ab,kw OR delafloxacin:ti,ab,kw OR gemifloxacin:ti,ab,kw OR levofloxacin:ti,ab,kw OR moxifloxacin:ti,ab,kw OR norfloxacin:ti,ab,kw OR ofloxacin:ti,ab,kw OR enoxacin:ti,ab,kw OR pefloxacin:ti,ab,kw OR lomefloxacin:ti,ab,kw OR aminoglycoside*:ti,ab,kw OR amikacin:ti,ab,kw OR gentamicin:ti,ab,kw OR kanamycin:ti,ab,kw OR neomycin:ti,ab,kw OR netilmicin:ti,ab,kw OR netrocin:ti,ab,kw OR plazomycin:ti,ab,kw OR streptomycin:ti,ab,kw OR tobramycin:ti,ab,kw OR nebramycin:ti,ab,kw OR lipoglycopeptide*:ti,ab,kw OR teicoplanin:ti,ab,kw OR daptomycin:ti,ab,kw OR vancomycin:ti,ab,kw OR linezolid:ti,ab,kw OR cycloserine:ti,ab,kw OR tedizolid:ti,ab,kw OR rifamycin:ti,ab,kw OR bacitracin:ti,ab,kw OR capreomycin:ti,ab,kw OR chloramphenicol:ti,ab,kw OR clofazimine:ti,ab,kw OR colistimethate:ti,ab,kw OR colistin:ti,ab,kw OR dapson:ti,ab,kw OR fosfomycin:ti,ab,kw OR 'fusidic acid':ti,ab,kw OR methenamine:ti,ab,kw OR metronidazole:ti,ab,kw OR nitrofurantoin:ti,ab,kw OR polymyxin*:ti,ab,kw OR rifampin*:ti,ab,kw OR secnidazole:ti,ab,kw OR tinidazole:ti,ab,kw OR carfecillin:ti,ab,kw OR cefamandole:ti,ab,kw OR cefatrizine:ti,ab,kw OR cefsulodin:ti,ab,kw OR cephacetrile:ti,ab,kw OR cephaloglycin:ti,ab,kw OR cephaloridine:ti,ab,kw OR cephalothin:ti,ab,kw OR cephamycins:ti,ab,kw OR dibekacin:ti,ab,kw OR dihydrostreptomycin:ti,ab,kw OR enviomycin:ti,ab,kw OR framycetin:ti,ab,kw OR josamycin:ti,ab,kw OR kitasamycin:ti,ab,kw OR lymecycline:ti,ab,kw OR mepartricin:ti,ab,kw OR methacycline:ti,ab,kw OR methicillin:ti,ab,kw OR mezlocillin:ti,ab,kw OR moxalactam:ti,ab,kw OR nafcillin:ti,ab,kw OR 'nalidixic acid':ti,ab,kw OR novobiocin:ti,ab,kw OR oleandomycin:ti,ab,kw OR 'oxolinic acid':ti,ab,kw OR 'pipemidic acid':ti,ab,kw OR ribostamycin:ti,ab,kw OR rifabutin:ti,ab,kw OR rolitetracycline:ti,ab,kw OR roxithromycin:ti,ab,kw OR sisomicin:ti,ab,kw OR spectinomycin:ti,ab,kw OR spiramycin:ti,ab,kw OR streptogramin*:ti,ab,kw OR quinupristin*:ti,ab,kw OR dalbopristin*:ti,ab,kw OR sulbactam:ti,ab,kw OR sulbenicillin:ti,ab,kw OR sulfamerazine:ti,ab,kw OR sulfamethoxypyridazine:ti,ab,kw OR talampicillin:ti,ab,kw OR thiamphenicol:ti,ab,kw OR troleandomycin:ti,ab,kw OR 'antibiotic agent'/exp AND ('drug hypersensitivity'/exp OR allerg*:ti,ab,kw OR hypersensitivit*:ti,ab,kw) AND ('medical record'/exp OR 'self report'/exp OR

label*:ti,ab,kw OR report*:ti OR record*:ti OR hospital*:ti OR overreport*:ti OR 'over report*':ti
OR overdiagno*:ti OR document*:ti OR history:ti) NOT ([animals]/lim NOT [humans]/lim)

Mapped termsn/a

Cochrane CENTRAL in Cochrane Library

Date Search conducted: April 11th 2019

(antibiotic* or anti?bacterial* or penicillin*) AND allerg* AND label*

EBSCO (CINAHL; EconLit)

Date FINAL search conducted: April 17th 2019

#	Query	Limiters/Expanders	Last Run Via	Results
S33	S29 OR S32	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	748
S32	S5 AND S8 AND S31	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	301
S31	S9 OR S10 OR S30	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	471,008

#	Query	Limiters/Expanders	Last Run Via	Results
S30	AB (label*) OR TI (label* OR report* OR record* OR hospital* OR overreport* OR over-report* OR overdiagno* OR document* OR history)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	347,386
S29	S27 AND S28	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	625
S28	S5 AND S8 AND S12	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	1,051
S27	S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	1,791,693
S26	(MH "Patient-Reported Outcomes")	Expanders - Apply related words; Apply equivalent subjects	Interface - EBSCOhost Research Databases	1,361

#	Query	Limiters/Expanders	Last Run Via	Results
		Search modes - Boolean/Phrase	Search Screen - Advanced Search Database - CINAHL;EconLit	
S25	(MH "Outcomes (Health Care)+")	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	407,305
S24	(MH "Treatment Outcomes+")	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	306,179
S23	(MH "Opportunistic Infections+")	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	4,023
S22	(MH "Death+")	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	44,630
S21	(MH "Epidemiology+")	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search	598,442

#	Query	Limiters/Expanders	Last Run Via	Results
			Database - CINAHL;EconLit	
S20	(MH "Readmission")	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	10,900
S19	(MH "Length of Stay")	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	35,340
S18	(MH "Health Care Costs+")	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	49,588
S17	(MH "Health Resource Utilization")	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	15,705
S16	(MH "Utilization Review+")	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	9,076

#	Query	Limiters/Expanders	Last Run Via	Results
S15	(MH "Drug Utilization+")	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	7,263
S14	(MH "Inappropriate Prescribing")	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	1,919
S13	AB (prescrib* OR prescript* OR ((drug OR treatment) AND select*) OR stay* OR "length of stay" OR hospitali* OR death OR mortality OR morbidity OR readmi* OR re-admi* OR cost* OR opportunistic OR resist* OR "c. difficile" OR "c. diff*" OR "clostridium difficile" OR "clostridioides difficile" OR CDI OR "c diff" OR MRSA OR VRE OR duration OR stewardship) OR TI (prescrib* OR prescript* OR ((drug OR treatment) AND select*) OR stay* OR "length of stay" OR hospitali* OR death OR mortality OR morbidity OR readmi* OR re-admi* OR cost* OR opportunistic OR resist* OR "c. difficile" OR "c. diff*" OR "clostridium difficile" OR "clostridioides difficile" OR CDI OR "c diff" OR MRSA OR VRE OR duration OR stewardship OR (adverse AND outcome) OR (harmful AND outcome*) OR impact OR burden)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	1,033,359
S12	S9 OR S10 OR S11	Expanders - Apply related words; Apply equivalent subjects	Interface - EBSCOhost Research Databases	1,390,765

#	Query	Limiters/Expanders	Last Run Via	Results
		Search modes - Boolean/Phrase	Search Screen - Advanced Search Database - CINAHL;EconLit	
S11	AB (label* OR report* OR record* OR hospital* OR overreport* OR over-report* OR overdiagno* OR document* OR history) OR TI (label* OR report* OR record* OR hospital* OR overreport* OR over-report* OR overdiagno* OR document* OR history)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	1,325,719
S10	(MH "Self Report+")	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	62,048
S9	(MH "Medical Records+")	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	90,111
S8	S6 OR S7	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	31,255
S7	TI (allerg* OR hypersensitivit*) OR AB (allerg* OR hypersensitivit*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases	27,472

#	Query	Limiters/Expanders	Last Run Via	Results
			Search Screen - Advanced Search Database - CINAHL;EconLit	
S6	(MH "Drug Hypersensitivity+")	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	5,565
S5	S1 OR S2 OR S3	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	106,012
S4	S1 OR S2	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	96,288

[illegible]

#	Query	Limiters/Expanders	Last Run Via	Results
	cycloserine OR tedizolid OR rifamycin OR bacitracin OR capreomycin OR chloramphenicol OR clofazimine OR colistimethate OR colistin OR dapsone OR fosfomycin OR “fusidic acid” OR methenamine OR metronidazole OR nitrofurantoin OR polymyxin* OR rifampin* OR secnidazole OR tinidazole OR carfecillin OR cefamandole OR cefatrizine OR cefsulodin OR cephacetrile OR cephaloglycin OR cephaloridine OR cephalothin OR cephamycins OR dibekacin OR dihydrostreptomycin OR enviomycin OR framycetin OR josamycin OR kitasamycin OR lymecycline OR mepartricin OR methacycline OR methicillin OR mezlocillin OR moxalactam OR nafcillin OR “nalidixic acid” OR novobiocin OR oleandomycin OR “oxolinic acid” OR “pipemidic acid” OR ribostamycin OR rifabutin OR rolitetracycline OR roxithromycin OR sisomicin OR spectinomycin OR spiramycin OR streptogramin* OR quinupristin* OR dalfopristin* OR sulbactam OR sulbenicillin OR sulfamerazine OR sulfamethoxypyridazine OR talampicillin OR thiamphenicol OR troleandomycin) OR AB (amdinocillin OR amoxicillin* OR ampicillin OR aztreonam OR pivampicillin OR penicillin* OR carbenicillin OR cloxacillin OR dicloxacillin OR oxacillin OR piperacillin* OR pivmecillinam OR ticarcillin* OR bacampicillin OR carampicillin OR floxacillin OR flucloxacillin OR cyclacillin OR carbapenem* OR doripenem OR ertapenem OR imipenem* OR thienamycin* OR meropenem* OR cephalosporin* OR cefadroxil OR cefazolin OR			

#	Query	Limiters/Expanders	Last Run Via	Results
	cephalixin OR cefaclor OR cepharin OR cephradine OR cefotetan OR cefoxitin OR cefprozil OR cefuroxime OR cefotiam OR cefdinir OR cefditoren OR cefixime OR cefmetazole OR cefonicid OR cefotaxime OR cefpodoxime OR ceftazidime OR ceftibuten OR ceftriaxone OR cefmenoxime OR cefoperazone OR ceftizoxime OR lincosamide* OR clindamycin OR lincomycin OR macrolide* OR azithromycin OR clarithromycin OR erythromycin OR tetracycline* OR chlortetracycline OR oxytetracycline OR demeclocycline OR doxycycline OR minocycline OR tigecycline OR sulphamethoxazole* OR trimethoprim* OR fluoroquinolones OR ciprofloxacin OR delafloxacin OR gemifloxacin OR levofloxacin OR moxifloxacin OR norfloxacin OR ofloxacin OR enoxacin OR pefloxacin OR lomefloxacin OR aminoglycoside* OR amikacin OR gentamicin OR kanamycin OR neomycin, OR netilmicin OR netrocin OR plazomycin OR streptomycin OR tobramycin OR nebramycin OR lipoglycopeptide* OR teicoplanin OR daptomycin OR vancomycin OR linezolid OR cycloserine OR tedizolid OR rifamycin OR bacitracin OR capreomycin OR chloramphenicol OR clofazimine OR colistimethate OR colistin OR dapsone OR fosfomycin OR “fusidic acid” OR methenamine OR metronidazole OR nitrofurantoin OR polymyxin* OR rifampin* OR secnidazole OR tinidazole OR carfecillin OR cefamandole OR cefatrizine OR cefsulodin OR cephacetrile OR cephaloglycin OR cephaloridine			

#	Query	Limiters/Expanders	Last Run Via	Results
	OR cephalothin OR cephamycins OR dibekacin OR dihydrostreptomycin OR enviomycin OR framycetin OR josamycin OR kitasamycin OR lymecycline OR mepartricin OR methacycline OR methicillin OR mezlocillin OR moxalactam OR nafcillin OR "nalidixic acid" OR novobiocin OR oleandomycin OR "oxolinic acid" OR "pipemidic acid" OR ribostamycin OR rifabutin OR rolitetracycline OR roxithromycin OR sisomicin OR spectinomycin OR spiramycin OR streptogramin* OR quinupristin* OR dalfopristin* OR sulbactam OR sulbenicillin OR sulfamerazine OR sulfamethoxypyridazine OR talampicillin OR thiamphenicol OR troleandomycin)			
S2	AB (antimicrobial* OR anti- microbial* OR antibacterial* OR anti-bacterial OR antibiotic* OR "β-lactam*" OR "b lactam*" OR "beta lactam*" OR "beta-lactam*" OR penicillin*) OR TI (antimicrobial* OR anti-microbial* OR antibacterial* OR anti- bacterial OR antibiotic* OR "β- lactam*" OR "b lactam*" OR "beta lactam*" OR "beta-lactam*" OR penicillin*)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	57,414
S1	(MH "Antibiotics+")	Expanders - Apply related words; Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL;EconLit	64,226

Web of Science

Date Search conducted: April 12th 2019

o **Web of Science Core Collection** (1900-present; edition(s): Science Citation Index Expanded (1900-present), Emerging Sources Citation Index (2015-present))

Results: 205

(from Web of Science Core Collection)

TS=((antibiotic* or anti-bacterial* or antibacterial* or penicillin*) AND (allerg* OR hypersensitivit*) AND label*)

Indexes=SCI-EXPANDED, ESCI Timespan=All years

Results: 34

(from Web of Science Core Collection)

TI=((antibiotic* or anti-bacterial* or antibacterial or penicillin*) AND (allerg* OR hypersensitivit*) AND (label* OR document* OR report* OR self-report OR record* OR chart* OR HER OR EMR OR regist*OR history) AND (prescrib* OR prescript* OR select* OR stay* OR "length of stay" OR hospitali* OR death OR mortality OR morbidity OR readmi* or re-admi* OR cost* OR opportunistic OR resist* OR C. difficile OR C. diff* OR "Clostridium difficile" OR "Clostridioides difficile" OR CDI OR C-diff OR MRSA OR VRE OR duration OR stewardship))

Indexes=SCI-EXPANDED, ESCI Timespan=All years

Combined 205 results or 34 results

o **KCI-Korean Journal Database** (1980-present) - no relevant results

Results: 30

(from KCI-Korean Journal Database)

You searched for: TOPIC: ((antibiotic* or anti-bacterial* or antibacterial or penicillin*) AND (allerg* OR hypersensitivit*) AND (label* OR document* OR report* OR self-report OR record* OR chart* OR HER OR EMR OR regist*OR history) AND (prescrib* OR prescript* OR select* OR stay* OR "length of stay" OR hospitali* OR death OR mortality OR morbidity OR readmi* or re-admi* OR cost* OR opportunistic OR resist* OR C. difficile OR C. diff* OR "Clostridium difficile" OR "Clostridioides difficile" OR CDI OR C-diff OR MRSA OR VRE OR duration OR stewardship))

Timespan: All years. Indexes: KJD.

Results: 1
(from KCI-Korean Journal Database)

You searched for: TOPIC: ((antibiotic* or anti-bacterial* or antibacterial* or penicillin*) AND (allerg* OR hypersensitivit*) AND label*)

Timespan: All years. Indexes: KJD.

Results: 30
(from KCI-Korean Journal Database)

You searched for: #3 OR #1

Timespan: All years. Indexes: KJD.

o **Russian Science Citation Index** (2005-present) - no relevant results

Results: 3
(from Russian Science Citation Index)

You searched for: TS=((antibiotic* or anti-bacterial* or antibacterial* or penicillin*) AND (allerg* OR hypersensitivit*) AND label*)

Timespan: All years. Indexes: RSCI.

Results: 3
(from Russian Science Citation Index)

You searched for: TS=((antibiotic* or anti-bacterial* or antibacterial or penicillin*) AND (allerg* OR hypersensitivit*) AND (label* OR document* OR report* OR self-report OR record* OR chart* OR HER OR EMR OR regist*OR history) AND (prescrib* OR prescript* OR select* OR stay* OR "length of stay" OR hospitali* OR death OR mortality OR morbidity OR readmi* or re-admi* OR cost* OR opportunistic OR resist* OR C. difficile OR C. diff* OR "Clostridium difficile" OR "Clostridioides difficile" OR CDI OR C-diff OR MRSA OR VRE OR duration OR stewardship))

Timespan: All years. Indexes: RSCI.

o **SciELO Citation Index** (1997-present) – 30

3 30 Results
#2 OR #1

Indexes=SCIELO Timespan=All years

2

1 Result

TS=((antibiotic* or anti-bacterial* or antibacterial* or penicillin*) AND (allerg* OR hypersensitivit*) AND label*)

Indexes=SCIELO Timespan=All years

1

30 Results

TS=((antibiotic* or anti-bacterial* or antibacterial or penicillin*) AND (allerg* OR hypersensitivit*) AND (label* OR document* OR report* OR self-report OR record* OR chart* OR HER OR EMR OR regist*OR history) AND (prescrib* OR prescript* OR select* OR stay* OR "length of stay" OR hospitali* OR death OR mortality OR morbidity OR readmi* or re-admi* OR cost* OR opportunistic OR resist* OR C. difficile OR C. diff* OR "Clostridium difficile" OR "Clostridioides difficile" OR CDI OR C-diff OR MRSA OR VRE OR duration OR stewardship))

Indexes=SCIELO Timespan=All years