Clinical Infectious Diseases

MAJOR ARTICLE

Implications of Antibiotic Resistance for Patients' Recovery From Common Infections in the Community: A Systematic Review and Meta-analysis

Oliver van Hecke,[1] Kay Wang,[1] Joseph J. Lee,[1] Nia W. Roberts,[2] and Chris C. Butler[1]

[1]Nuffield Department of Primary Care Health Sciences, University of Oxford, and [2]Bodleian Health Care Libraries, Knowledge Centre, Oxford, United Kingdom

Background. Antibiotic use is the main driver for carriage of antibiotic-resistant bacteria. The perception exists that failure of antibiotic treatment due to antibiotic resistance has little clinical impact in the community.

Methods. We searched MEDLINE, EMBASE, PubMed, Cochrane Central Register of Controlled Trials, and Web of Science from inception to 15 April 2016 without language restriction. We included studies conducted in community settings that reported patient-level data on laboratory-confirmed infections (respiratory tract, urinary tract, skin or soft tissue), antibiotic resistance, and clinical outcomes. Our primary outcome was clinical response failure. Secondary outcomes were reconsultation, further antibiotic prescriptions, symptom duration, and symptom severity. Where possible, we calculated odds ratios with 95% confidence intervals by performing meta-analysis using random effects models.

Results. We included 26 studies (5659 participants). Clinical response failure was significantly more likely in participants with antibiotic-resistant *Escherichia coli* urinary tract infections (odds ratio [OR] = 4.19; 95% confidence interval [CI] = 3.27–5.37; n = 2432 participants), *Streptococcus pneumoniae* otitis media (OR = 2.51; 95% CI = 1.29–4.88; n = 921 participants), and *S. pneumoniae* community-acquired pneumonia (OR = 2.15; 95% CI = 1.32–3.51; n = 916 participants). Clinical heterogeneity precluded primary outcome meta-analysis for *Staphylococcus aureus* skin or soft-tissue infections.

Conclusions. Antibiotic resistance significantly impacts on patients' illness burden in the community. Patients with laboratory-confirmed antibiotic-resistant urinary and respiratory-tract infections are more likely to experience delays in clinical recovery after treatment with antibiotics. A better grasp of the risk of antibiotic resistance on outcomes that matter to patients should inform more meaningful discussions between healthcare professionals and patients about antibiotic treatment for common infections.

Keywords. antibiotic resistance; primary care; clinical significance.

Antibiotic resistance is recognized as an important societal health issue. Yet members of the public consider the risk of antibiotic resistance to apply to society at large and in the distant future, rather than constituting a risk to their own health, and primary-care clinicians report that they rarely encounter treatment failure because of antibiotic resistance, leading to the perception that antibiotic resistance is remote from prescribing decisions [1–3]. This major evidence gap may influence expectations for antibiotics and antibiotic-prescribing decisions in the community [4, 5].

Although the consequences of antibiotic-resistant infections in hospitalized patients are known (increased mortality, longer hospital stays, and increased healthcare costs) [6, 7], antibiotic resistance may also have important consequences for patients with common infections managed in the community [8]. Approximately 300 million primary-care consultations in the United Kingdom and 490 million consultations in the United States each year [14, 17] are for respiratory-tract (10%–20%) [9–11], urinary-tract (1%–3%) [12, 13], and skin and soft-tissue infections (1%) [14–16]. Almost 75% of all antibiotics in the United Kingdom are prescribed in primary care [18] and at considerable cost [19–21].

Antibiotic use is also the most important risk factor for carriage of antibiotic-resistant bacteria [22, 23] and the development of subsequent antibiotic-resistant infections. However, the clinical relevance of antibiotic resistance for patients with common infections in the community is less well understood. This systematic review aims to compare clinical outcomes between antibiotic-resistant and antibiotic-sensitive infections in the community for patients with respiratory-tract, urinary-tract, and skin or soft-tissue infections.

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Correspondence: O. van Hecke, Nuffield Department of Primary Care Health Sciences, University of Oxford, Radcliffe Observatory Quarter, Woodstock Rd, Oxford OX2 6GG, UK (oliver.vanhecke@phc.ox.ac.uk).

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METHODS

Search Strategy and Inclusion Criteria

We systematically searched electronic databases (MEDLINE, EMBASE, PubMed, Cochrane Central Register of Controlled Trials, and Web of Science) from inception to 15 April 2016 with no language restrictions. We used the Medical Subject Headings (MeSH) terms and validated search filters for "antibiotic resistance" [23] and "primary care/community setting" [24] and keywords "antibiotic resistance," "skin or soft tissue infections," "respiratory tract infections," "otitis media," and "urinary tract infections" (Supplementary Data Files 1 and 2).The review protocol was registered on the PROSPERO database (CRD42015032441).

Observational studies and randomized controlled trials (RCTs) were eligible for inclusion if the study was conducted in a community setting (general practice, hospital outpatient clinic, or emergency department) and reported patient-level data on laboratory-confirmed potentially pathogenic infections, antibiotic resistance, and clinical outcomes. Studies solely conducted in hospital inpatient settings, involving patients with hospital-acquired infections and highly specific patient groups in whom specialised antibiotic treatment strategies are recommended (eg, cystic fibrosis), were excluded.

We categorized respiratory-tract infections (RTIs) into community-acquired pneumonia (CAP), sore throat/pharyngitis, acute otitis media (AOM), and acute maxillary sinusitis (AMS).

Our primary outcome was clinical response failure, which we defined as the persistence of symptoms after completion of antibiotic treatment. Where studies reported outcomes at >1 time point, we selected the time point closest to 7–14 days from baseline to reflect the duration of typical antibiotic regimens. Secondary outcomes were reconsultation, further antibiotic prescriptions (both within 30 days from baseline), symptom duration, and symptom severity.

Data Extraction and Risk of Bias Assessment

Two reviewers (O. V. H., J. J. L.) independently extracted data on the characteristics of included studies (Table 1 and Supplementary Data File 2). For RCTs, outcome data for antibiotic-resistant and antibiotic-sensitive infections were extracted separately for each treatment arm because RCT studies only determined whether infections were antibiotic-resistant or antibiotic-sensitive after patients had already been randomized, hence randomization was not stratified according to antibiotic resistance.

Data had to be reported in sufficient detail to assess relevant outcomes between patients with antibiotic-resistant and antibiotic-sensitive infections in order to construct a 2 × 2 contingency table. Where possible, we extracted outcomes for antibiotic-resistant and antibiotic-sensitive infections whereby resistance and sensitivity were defined in relation to the same antibiotic or class of antibiotic as the antibiotic being prescribed. If studies reported intermediate levels of antibiotic resistance for certain infections, these were classified as antibiotic-resistant infections in our analysis. If there was no agreement between susceptibility and treatment antibiotic, or the study did not report the type of antibiotic prescribed, studies were still included but specifically highlighted.

The quality of the included studies was assessed independently by 2 reviewers (O. V. H., J. L.) for RCTs and observational studies based on their respective risk-of-bias tool, namely the Cochrane Collaboration's tool for assessing risk of bias in randomized trials and critical appraisal skills programme (CASP) checklist for cohort studies (Supplementary Data File 3) [25, 26].

Statistical Analysis

To compare the odds of clinical response failure between antibiotic-resistant and antibiotic-sensitive infections, we calculated odds ratios (ORs) with 95% confidence intervals (Cis) for infections where data were available from ≥3 studies for the same bacterial pathogen using random effects meta-analysis. Heterogeneity was assessed using the χ^2 test and I^2 statistic. Odds ratios in relation to reconsultation and further antibiotic prescriptions were calculated using similar methods. For continuous data, we planned to plot survival curves where possible for duration and severity of symptoms in antibiotic-resistant versus antibiotic-sensitive infections.

Subgroup analyses were performed according to study design (observational studies vs RCTs) and type of healthcare setting (general practice, hospital outpatient clinic, or emergency department). Results were summarized narratively where data were not sufficient to perform meta-analysis or plot survival curves. Analysis was conducted using StataSE version 13.

RESULTS

We identified 10 681 records, of which 136 full-text articles were assessed. The most common reason for exclusion (n = 31/110) was that clinical outcomes were not reported separately for antibiotic-resistant versus antibiotic-sensitive infections.

Twenty-six studies were included (Figure 1), of which 13 were observational studies, 8 were RCTs, and 5 were secondary analyses of pooled RCT data [27–31]. Six studies were conducted in primary care/general practice, 12 in hospital outpatients, 1 in a mixed outpatient/primary care setting, 2 in a mixed outpatient/inpatient setting, 1 in an emergency department setting, and 4 in another community setting which was not clearly defined (Table 1). Our included RCTs and secondary analyses of pooled RCTs did not report any duplicate data.

Data relating to ≥1 study outcomes were available for 15 580 patients, of whom 6617 patients had a laboratory-confirmed potentially pathogenic bacterial infection. Data on whether the infection was antibiotic-resistant or antibiotic-sensitive were

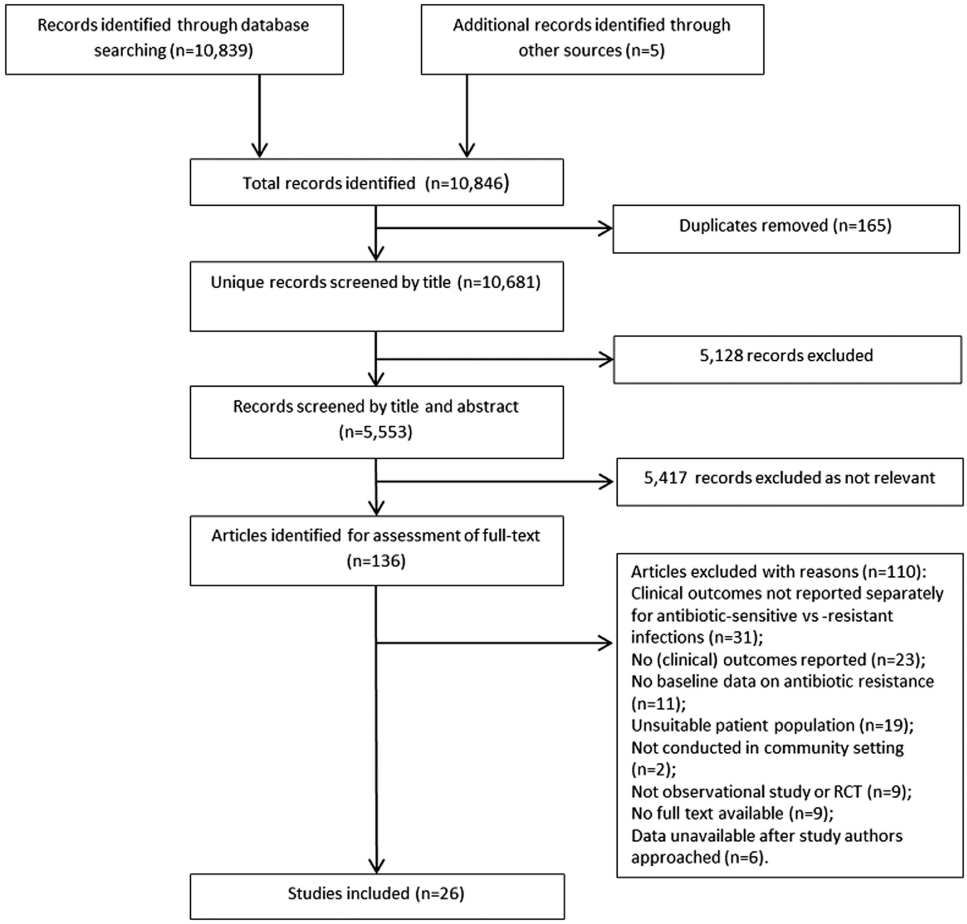

Figure 1. Study selection. Abbreviation: RCT, randomized controlled trial.

also available for 5659 of these patients (antibiotic-resistant: n = 1268; antibiotic-sensitive: n = 4391) (Table 2).

Clinical criteria for obtaining urine samples and diagnosing urinary-tract infections (UTIs) varied between studies. Diagnostic thresholds used to define *Escherichia coli* UTIs were reported as being $>10^4$ colony-forming units (CFU) in 3 studies (Supplemetary Data File 4*A*) [32–34]. Four studies obtained urine samples from patients with urinary symptoms and positive urine dipstick test [32, 33, 35, 36], 2 studies obtained urine samples from patients with urinary symptoms only [37, 38], 1 study obtained urine samples from patients with "clinically suspected" UTI [8], and 2 studies did not report selection criteria for obtaining urine samples [34, 39]. Most UTI studies counted infections of mixed uropathogens as indicating an infection; however, the dominant bacterium (>65%) was *E. coli* in all UTI studies. Where calculations were possible, the proportion of clinically suspected UTIs that had a laboratory-confirmed infection was 57%–95%. Three studies based clinical diagnosis of *S. pneumoniae* CAP on symptoms, radiographic evidence, and blood tests [29, 40, 41], 1 study based diagnosis on symptoms and blood tests [30], and 1 study [31] did not report how a diagnosis was established (Supplementary Data File 4*B*). Diagnostic criteria for *S. pneumoniae* AOM (Supplementary Data File 4*C*) were more uniform (symptoms, examination, and tympanocentesis) except for 1 study for which this was not reported [31].

Data relating to our primary outcome (clinical response failure) were available from 13 RCTs [27–31, 37, 38, 40, 42–46] and 9 observational studies [8, 32–34, 36, 39, 41, 47, 48]. Three observational studies reported data on reconsultations [8, 32, 35]; 4 studies reported data on further antibiotic prescriptions [8, 34, 49, 50]; 4 studies reported data on symptom duration [8, 32, 49, 50]; and 1 study reported data on symptom severity [50]. Data on these outcomes were not reported by any RCTs or secondary analyses of pooled RCT data.

The appendix (Supplementary Data File 3) summarizes our risk of bias assessment of included studies. For 12 of 13 RCTs, there was low risk of reporting bias [27–29, 31, 37, 38, 40, 42–46]. Only 1 RCT reported assessing outcomes blinded from knowledge of whether the infection was antibiotic-resistant or antibiotic-sensitive [42]. We were not able to assess whether RCTs considered confounding variables between

Table 1. Characteristics of 26 Included Studies (Primary and/or Secondary Outcomes) According to Infection

Study	Country	Setting	Infection type	Study design	Participants	Potential pathogen being studied	Total no. recruited	Total no. with potential pathogen being studied	No. of potential pathogens being studied with evidence of antibiotic resistance	No. of patients where resistance and outcome data available	Primary outcome time point[a, b]	Secondary outcomes[c]	Treatment antibiotic/ antibiotic class[d]	Antibiotic to which resistance measured
Urinary-tract infection														
Brown et al (2002) [35]	United States	OP/ PHC	UTI	Obs (R)	Women	E	NR	601 isolates[e]	44	104	…	Rec[c]	TMP-SMX	TMP-SMX
Butler et al (2006) [8]	United Kingdom	PHC	UTI	CC Obs (P)	Aduluts	E	932	922	94	797 [1] 862 (Rec) [2] 816 (Fab) [2] 420 (Sdur) [2]	Within 30 days	Rec[c] Fab[c] Sdur[c]	Not specified	To prescribed antibiotic [1] To at least 1 antibiotic [2]
Gupta et al (2007) [37]	United States	PHC	UTI	RCT	Women	E	338	276	34	308[f]	Day 3[b]	…	TMP-SMX Nitrofurantoin	TMP-SMX Nitrofurantoin
Little et al (2010) [50]	United Kingdom	PHC	UTI	Obs (P)	Women	NR[g]	843	NR	NR	264 (Sdur) 264 (Ssev)	-	Sdur[c] Ssev[c]	Not specified	To >1 antibiotics
McNulty et al (2006) [32]	United Kingdom	PHC	UTI	Obs (P)	Women	E	497	298[h]	44	207 (Sdur)[f] 317 (Rec)	Day 7[b]	Sdur[c] Rec[c]	Trimethoprim	Trimethoprim
Noskin et al (2001) [33]	United States	OP	UTI	Obs (P)	Women	E	156	89	42	71	NR[b]	…	Not specified	To >1 antibiotics
Raz et al (2002) [36]	Israel	OP	UTI	Obs (P)	Women	E	618	425	30	484[f]	Days 5–9[b]	…	TMP-SMX	TMP-SMX
Soraas et al (2014) [34]	Norway	Other	UTI	Obs (P)	Adults	ESBL-E	343	343[i]	81 (ESBL-E)	343	Within 14 days[b]	Fab[c]	Mecillinam Nonmecillinam	Mecillinam and ESBL status
Vallano et al (2006) [39]	Spain	PHC	UTI	Obs (P)	Women	E	220	88	15[f]	108[f]	Within 14 days[b]	…	Not specified	To >1 antibiotics
Van Merode et al (2005) [38]	Netherlands	PHC	UTI	RCT	Women	E	324	80	17	114[f]	Days 6–8[b]	…	Trimethoprim	Trimethoprim
Community-acquired pneumonia														
Cao et al (2010) [49]	China	OP	RTI (CAP)	Obs (P)	Adults; adolescents	MP	356	67	46	59	…	Fab[c] Sdur[c]	Not specified	Erythromycin
Hagberg et al (2003) [29]	Multiple	IP/OP	RTI (CAP)	Pooled data from 6 phase III trials	Adults	SP	1373	174	23[j]	174	Days 3–5[b]	…	Telithromycin	Penicillin or erythromycin
Kawai et al (2012) [51]	Japan	OP	RTI (CAP)	Obs (P)	Children; adolescents	MP	476	50	21	30	…	Fab[c]	Not specified	To >1 macrolide
O'Doherty et al (1997) [40]	United Kingdom; Ireland	OP	RTI (CAP)	RCT	Adults	SP	264	30[k]	6	30	Days 3–5[b]	…	Grepafloxacin Amoxicillin	Amoxicillin
Van Rensburg et al (2005) [30]	Multiple	OP	RTI (CAP)	Pooled RCT (8 phase III trials and 1 phase II study)	Adults	SP	2339	418	61	327	Days 17–24[b]	…	Telithromycin	To erythromycin and penicillin
Yanagihara et al (2004) [41]	Japan	OP	RTI (CAP)	Obs (R)	Adults	SP	306	306	129	306	NR[b]	…	Not specified	Penicillin
Zhanel et al (2014) [31]	Multiple	Other	RTI (AMS) RTI (CAP) RTI (AOM)	Pooled RCT (11 RCTs; 2 phase III trials)	Adults; children	SP	872[l] 309 CAP	CAP 79	CAP 27	CAP 79	NR[b]	…	Azithromycin	Azithromycin

Study	Country	Setting	Infection type	Study design	Participants	Potential pathogen being studied	Total no. recruited	Total no. with potential pathogen being studied	No. of potential pathogens being studied with evidence of antibiotic resistance	No. of patients where resistance and outcome data available	Primary outcome time point[a, b]	Secondary outcomes[c]	Treatment antibiotic/ antibiotic class[d]	Antibiotic to which resistance measured
Acute otitis media														
Barry et al (1994) [27]	France	OP	RTI (AOM)	Pooled data from 3 RCTs	Children	SP	1092	236	54[m]	219	Day 10	…	B-lactams (combined)	Penicillin; B-lactams
Dagan et al (1996) [42]	Israel	ER	RTI (AOM)	RCT	Children	SP	266	98	18	77	Day 10	…	Cefuroxime Cefaclor	Cefuroxime Cefaclor
Hoberman et al (1996) [47]	Multiple	IP/OP	RTI (AOM)	Obs (P)	Children	SP	917	298	82	260	Days 12–14[b]	…	Co-amoxiclav	Penicillin
Hoberman et al (2005) [45]	Multiple	OP	RTI (AOM)	RCT	Children	SP	730	229	158	188	Days 12–14[b]	…	Co-amoxiclav Azithromycin	Penicillin Azithromycin
Zhanel et al (2014) [31]	Multiple	Other	RTI (AMS) RTI (CAP) RTI (AOM)	Pooled RCT (11 RCTs; 2 phase III trials)	Adults; children	SP	872[l] AOM 402	AOM 177	AOM 41	AOM 177	NR	…	Azithromycin	Azithromycin
Acute sore throat														
Quinn et al (2003) [46]	United States; Canada	OP	RTI (sore throat)	RCT	Adults; adolescents	Spy	526	360[n]	9	285	Days 16–23[b]	…	Telithromycin Clarithromycin	Erythromycin
Seppala et al (2002) [48]	Finland	OP	RTI (sore throat)	Obs (R)	NR	Spy	NR	529	76	273	NR	…	Erythromycin Penicillin	Erythromycin
Acute maxillary sinusitis														
Buchanan et al (2005) [28]	Sweden	Other	RTI (AMS)	Pooled data from 3 RCTs	Adults; adolescents	SP	1298	126	1	78	Days 17–24[b]	…	Telithromycin	Telithromycin
Zhanel et al (2014) [31]	Multiple	Other	RTI (AMS) RTI (CAP) RTI (AOM)	Pooled RCT (11 RCTs; 2 phase III trials)	Adults; children	SP	872[l] AMS 161	AMS 57	AMS 19	AMS 57	NR	…	Azithromycin	Azithromycin
Skin and soft-tissue infection														
Dagan et al (1992) [43]	Israel	OP	Skin (Imp)	RCT	Children	SA	102	90	27	89	Days 3–8	…	Erythromycin Mupirocin	Erythromycin, Mupirocin
Giordano et al (2006) [44]	United States	Other	Skin (USSSI)	RCT	Adults; adolescents	SA	392	171	79	151	Days 17–24[b]	…	Cefdinir Cephalexin	Methicillin
Overall							15 580			5659 [3]				

Abbreviations: AMS, acute maxillary sinusitis; AOM, acute otitis media; CAP, community-acquired pneumonia; CC, case control; E, *Escherichia coli*; ER, Emergency room; ESBL-E, extended spectrum β-lactamase *Escherichia coli*; Imp, impetigo; IP, hospital inpatients; MP, *Mycoplasma pneumoniae*; NR, not reported; Obs (P), prospective observational; Obs (R), retrospective observational; OP, hospital outpatients; Other, community setting (not specified); PHC, primary care clinic/general practice; RCT, randomized controlled trial; RTI, respiratory-tract infection; SA, *Staphylococcus aureus*; SP, *Streptococcus pneumoniae*; Spy, *Streptococcus pyogenes*; TMP-SMX, trimethoprim-sulfamethoxazole; USSSI, uncomplicated skin and skin structure infections (eg, cellulitis, erysipelas, impetigo, simple abscess, wound infection, furunculosis, folliculitis); UTI, urinary-tract infection.

[a]Primary outcome: "response failure" defined as the persistence of symptoms after completion of antibiotic treatment. Where the outcome was reported as "clinical cure" in the study, we calculated the proportion of patients that had failed to respond to antibiotic treatment within the designated timescale (ie, 1 – proportion of patients with clinical cure).

[b]Data on clinical cure, rather than clinical response failure, were reported by 10 randomized controlled trials [28–31, 37, 38, 40, 44–46] and 7 observational studies [32–34, 36, 39, 41, 47]. Overall, clinical response failure was assessed 3–5 days from baseline in 3 studies [29, 37, 40], 6–10 days from baseline in 6 studies [27, 32, 36, 38, 42, 43], 11–14 days from baseline in 4 studies [34, 39, 45, 47], 20–30 days from baseline in 5 studies [8, 28, 30, 44, 46], and not reported in 4 studies [31, 33, 41, 48].

[c]Secondary outcomes: reconsultation (Rec), further antibiotic prescriptions (Fab), symptom duration (Sdur), and symptom severity (Ssev).

[d]Multiple antibiotics prescribed in separate study arms.

[e]We assumed 1 isolate per participant.

Table 1. Continued

[f]All combined pathogens.
[g]Specific organism not reported.
[h]Coliforms; 242 single isolates were sent to HPA Antibiotic Resistance Monitoring and Reference Laboratory (ARMRL) of which *Escherichia coli* accounted for 90% (n = 219/242).
[i]ESBL *E. coli* and non-ESBL *E. coli* only.
[j]Penicillin- or erythromycin-resistant (all *Streptococcus pneumoniae* isolates were susceptible to telithromycin).
[k]Only 81 were evaluated microbiologically.
[l]Excluded acute exacerbations of chronic bronchitis.
[m]One child in the SpRP group did not complete the treatment course because of adverse events and was not evaluable for clinical response.
[n]Positive screening for group A ß-haemolytic streptococcus.
. . .not applicable [1];: Resistance measured to prescribed antibiotic [2];: Resistance measured to at least one antibiotic [3];: where more than one outcome data available, the lowest number was taken.

antibiotic-resistant and antibiotic-sensitive infections except for 1 RCT [42] because baseline characteristics of the study population were not reported according to whether participants had an antibiotic-resistant or antibiotic-sensitive infection.

For the 13 observational studies, participants were representative of the defined population except for 1 study [34] and generally clearly defined. Antibiotic exposure was accurately measured (eg, secure medical records) in 10 studies [8, 32–34, 36, 39, 41, 48–50]. Only 6 observational studies attempted to address potential confounders, and measurement of outcome was only satisfactorily blinded in 2 studies [8, 35].

Figures 2–4 summarize odds ratios with 95% confidence intervals for participants with antibiotic-resistant *E. coli* UTIs (Figure 2), *S. pneumoniae* CAP (Figure 3), and *S. pneumoniae* AOM (Figure 4) in relation to clinical response failure. Clinical response failure was significantly more likely in antibiotic-resistant than antibiotic-sensitive *E. coli* UTIs (OR = 4.19; 95% CI = 3.27–5.37; $P < .001$; n = 2432 participants, 8 studies) [8, 32–34, 36–39]. Antibiotic-resistant *S. pneumoniae* CAP and AOM were also associated with significantly greater odds of clinical response failure (CAP: OR = 2.15, 95% CI = 1.32–3.51, $P < .002$, n = 916 participants, 5 studies [29–31, 40, 41]; AOM: OR = 2.51, 95% CI = 1.29–4.88, $P < .007$, n = 921 participants, 5 studies [27, 31, 42, 45, 47]).

Clinical heterogeneity precluded meta-analysis for skin or soft-tissue infections because data were only available from 2 studies [43, 44], of which 1 involved children with impetigo and the other involved adults and adolescents with a range of different infections, including cellulitis, simple abscesses, and wound infections (Supplementary Data File 5). Likewise for sore throat, there was uncertainty regarding similarity of study population characteristics between the 2 studies [46, 48], and for sinus infections [28, 31], 1 study [28] had only 1 patient with an antibiotic-resistant infection.

Reconsultation was significantly more likely in patients with antibiotic-resistant *E. coli* UTIs (Supplementary Data File 6*A*) (OR = 5.07; 95% CI = 2.17–11.82; n = 1283 participants, 3 studies) [8, 32, 35]. Data on patient reconsultations were not available for other infections. Two studies involving patients with *M. pneumoniae* CAP reported data on further antibiotic prescriptions (Supplementary File 6*B*) [49, 51]. However, meta-analysis was not performed because 1 study did not report which antibiotic was used to treat participants [49], and there were no outcome events among patients with antibiotic-sensitive infections in the other study [51]. Two studies involving patients with *E. coli* UTIs also reported data on further antibiotic prescriptions [8, 34]. However, treatment antibiotic was not reported in 1 study [8], and the other study focused specifically on extended-spectrum beta-lactamases (ESBL) *E. coli* infections [34].

Antibiotic-resistant infections were associated with longer duration of symptoms in 2 [32, 50] of 3 *E. coli* UTI studies

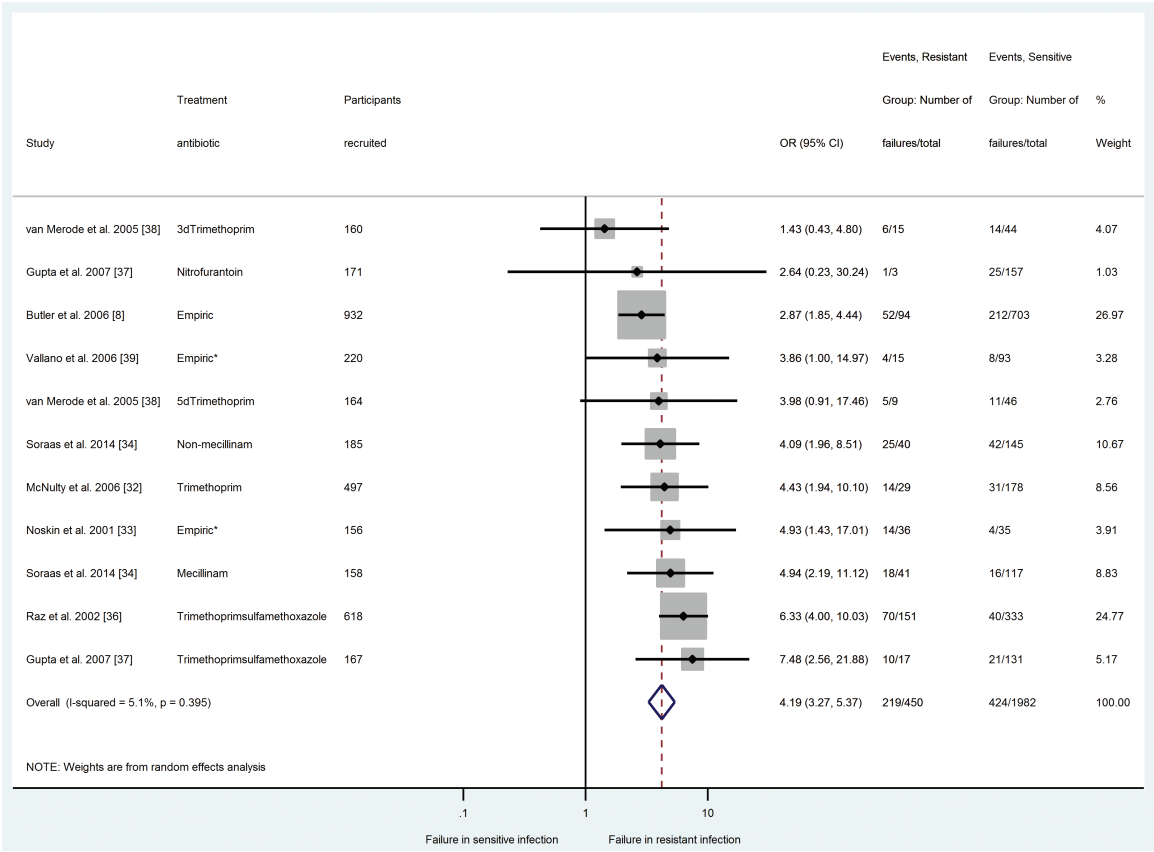

Figure 2. Comparison between antibiotic-resistant and antibiotic-sensitive (*Escherichia coli*) urinary tract infections in relation to response failure. Odds ratio > 1 indicated higher odds of response failure in the presence of antibiotic-resistant infection. *indicates there was no agreement between susceptibility and treatment antibiotic, or the study did not report the type of antibiotic prescribed. Abbreviations: 3d, 3-day regimen; 5d, 5-day regimen; CI, confidence interval; OR, odds ratio.

(Supplementary Data File 7) [8, 32, 50], but not in the 1 *M. pneumoniae* CAP study [49]. Only 1 study compared symptom severity between antibiotic-resistant and antibiotic-sensitive *E. coli* UTIs and found that patients with resistant infections had significantly greater symptom severity between days 2 and 4 (antibiotic-resistant: 2.01, standard deviation = 0.89 vs antibiotic-sensitive: 1.47, SD = 0.88; $P < .001$; n = 264 participants; severity grading 0 = no symptoms, 6 = as bad as it could be) (Supplementary Data File 8) [50].

Increased odds of clinical response failure in antibiotic-resistant *E. coli* UTIs were demonstrated in both observational studies (OR = 4.28; 95% CI = 3.31–5.54) and RCTs (OR = 3.49; 95% CI = 1.53–7.97).Odds of clinical response failure were also increased among participants recruited from both hospital outpatient (OR = 5.42; 95% CI = 3.87–7.61) and primary-care settings (OR = 3.29; 95% CI = 2.38–4.56).

For *E. coli* UTIs, post hoc sensitivity analysis was conducted excluding studies conducted in areas where the prevalence of antibiotic-resistant infections was reported to be high [36], studies that examined highlyspecific antibiotic-resistant bacteria (eg, ESBL *E. coli)* [34], studies where the reported susceptibility did not match the treatment antibiotic class [29, 30, 40, 41], and studies where the treatment antibiotic was not specified [33, 39]. This did not change the overall findings (OR = 3.27; 95% CI = 2.32–4.60; n = 1426 participants, 5 studies) [8, 32, 37, 38].

For *S. pneumoniae* CAP, the findings were no longer statistically significant (OR = 1.22; 95% CI = 0.25–5.91; n = 91 participants, 2 studies) [31, 40], after excluding studies where the reported susceptibility did not match the prescribed treatment antibiotic class [29, 30] or where the treatment antibiotic was not reported [41]. For *S. pneumoniae* AOM, the overall findings did not change (OR = 3.37; 95% CI = 2.04–5.56; n = 573 participants, 4 studies) [27, 31, 42, 45], after excluding 1 study conducted in an inpatient/outpatient setting [47].

DISCUSSION

Main Findings

Our findings demonstrate that patients who present in community healthcare settings with antibiotic-resistant UTIs and RTIs are more likely to experience clinical response failures than patients with antibiotic-sensitive infections. Patients with antibiotic-resistant *E. coli* UTIs are also more likely to reconsult a healthcare professional and experience prolonged and more severe symptoms than patients with antibiotic-sensitive

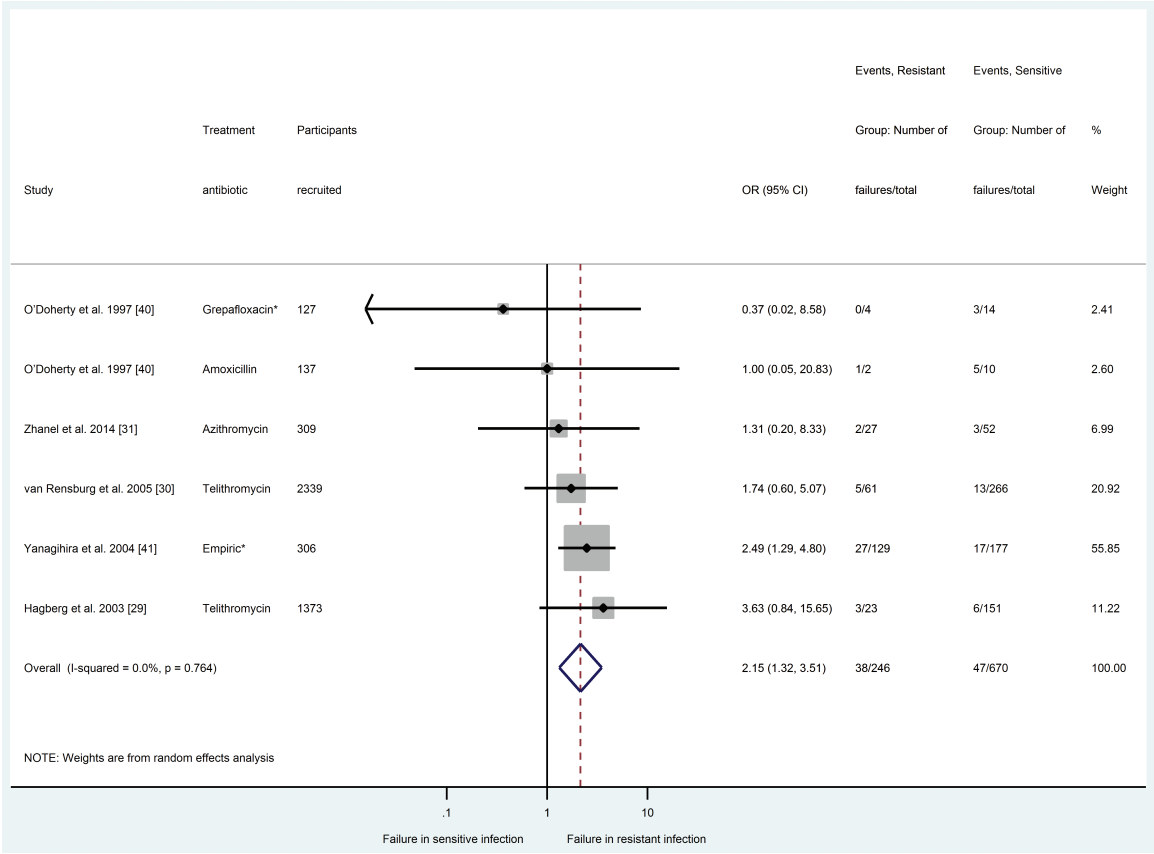

Figure 3. Comparison between antibiotic-resistant and antibiotic-sensitive (*Streptococcus pneumoniae)* community-acquired pneumonia in relation to response failure. Odds ratio > 1 indicated higher odds of response failure in the presence of antibiotic-resistant infection. *indicates there was no agreement between susceptibility and treatment antibiotic, or the study did not report the type of antibiotic prescribed. Abbreviations: CI, confidence interval; OR, odds ratio.

infections. This challenges the perception that patients in the community are at little additional personal risk from the impact of antibiotic resistance for common infections.

Comparison With Existing Literature

Previous systematic reviews have demonstrated a clear association between commonly prescribed antibiotics in the community and carriage of antibiotic-resistant bacteria [22, 23, 52]. Our estimates are consistent with estimates of clinical response failure rates in community populations for UTIs (14%–38%) [53, 54], CAP (11%–24%) [55], and AOM (7%–24%) [56, 57]. These earlier studies did not, however, determine the specific contribution (or association) of antibiotic resistance to response failure.

We were only able to estimate reconsultation rates for *E. coli* UTIs, with our results (28%; n = 357/1283) being comparable with those of other studies (26%–55%) [58, 59].

The prevalence of resistant *E. coli* in the UTI studies we included for our primary outcome (10.4%; n = 357/3428) falls within the lower end of the spectrum compared with most community-based population estimates (5%–53%) because this depends on the antibiotic susceptibility measured, the clinical criteria used for obtaining urine samples and diagnosing UTIs [60, S61–S63], and study population characteristics [52]. However, when examining resistance to the same antibiotic in community populations, our prevalence of *E. coli* resistant to nitrofurantoin (1.75%; n = 3/171), for example, is similar to that of other studies (<2%) [S61, S63]. Similarly, the prevalence of resistant *S. pneumoniae* in CAP and AOM in our included studies are lower than population estimates (5.4%, n = 246/4591 vs 8%–33% for CAP [S64, S65]; 0.4%, n = 353/3407 vs 1%–48% for AOM [S66, S67]).

Strengths and Limitations

Our search strategy used validated search filters, and we included both RCTs and observational studies conducted in community healthcare settings. We identified studies that may have collected but did not publish relevant data, and we contacted a sample of the authors to request unpublished and/or additional data (Supplementary Data File 2).

We focussed on more practical, clinically relevant outcomes for patients and clinicians, moving beyond a laboratory-focused, microbiological outcome. Because most of our included studies specifically excluded patients with known

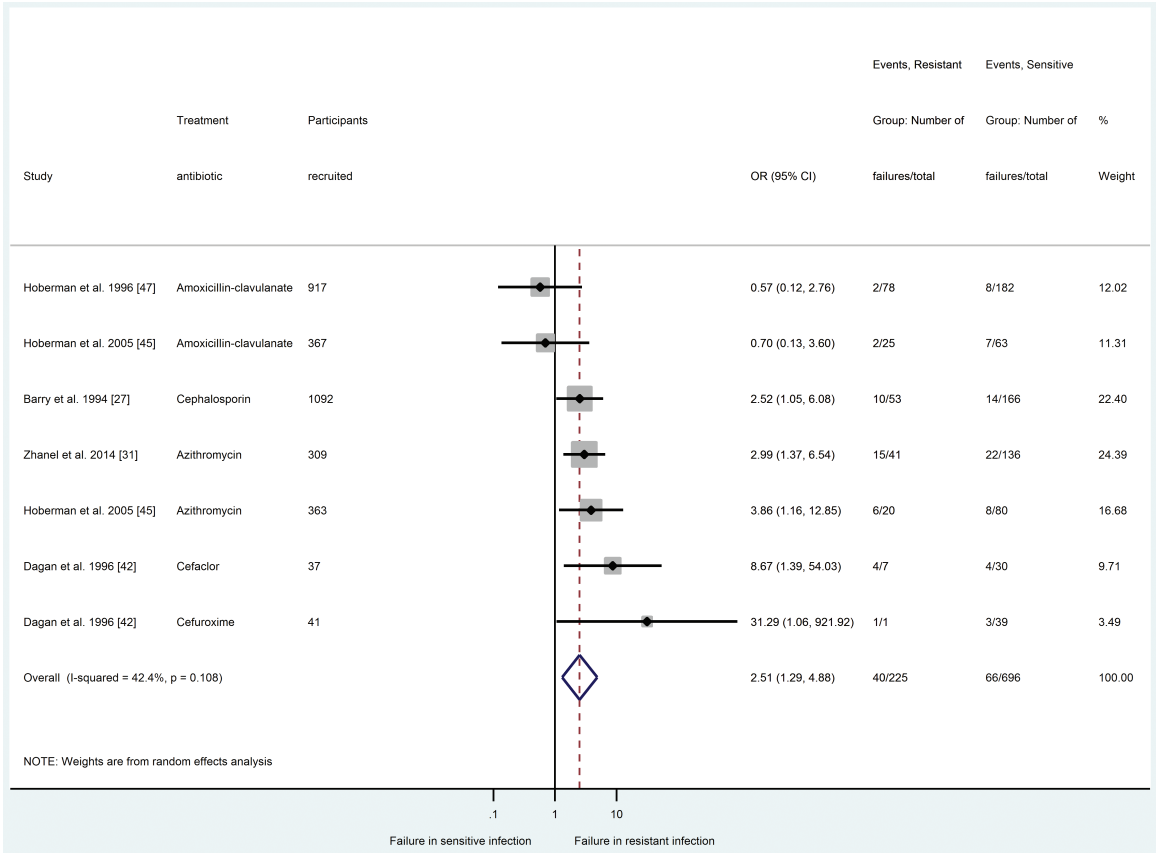

Figure 4. Comparison between antibiotic-resistant and antibiotic-sensitive (*Streptococcus pneumoniae)* acute otitis media in relation to response failure. Odds ratio > 1 indicated higher odds of response failure in the presence of antibiotic-resistant infection. *indicates there was no agreement between susceptibility and treatment antibiotic, or the study did not report the type of antibiotic prescribed. Abbreviations: CI, confidence interval; OR, odds ratio.

medical conditions [8, 27, 28, 30, 32–40, 43–50], we may be underestimating the impact of antibiotic-resistant infections in patients with multimorbidity. Individual patient data were not available to allow us to adjust for potential confounders.

An important limitation is that antibiotic resistance is just 1 explanation for clinical response failure, which could also be due to factors such as coinfection or reinfection. We cannot say what the relative contribution of antibiotic resistance was compared with other factors that could potentially influence the likelihood of clinical response failure. Such factors may also explain why a significant proportion of patients with sensitive infections failed to respond to antibiotics. Previous studies of failure from antibiotic treatment have been criticized because many patients probably had viral infections and would not have been expected to recover with antibiotic treatment [S68]. All included patients in our review had laboratory-confirmed bacterial infections. That said, this may limit generalizability of findings to clinical practice, given that treatment decisions in the community are based on clinical findings without

Table 2. Data Related to 1 or More Study Outcomes According to Infection Type and Bacterial Pathogen

Infection	Bacteria	No. of studies	No. of antibiotic-resistant infections	No. of antibiotic-sensitive infections
UTI [8, 32–39, 50]	*Escherichia coli*	10	523	2277
CAP [29–31, 40, 41]	*Streptococcus pneumoniae*	5	246	670
CAP [49, 51]	*Mycoplasma pneumoniae*	2	63	24
AOM [27, 31, 42, 45, 47]	*Streptococcus pneumoniae*	5	225	696
Sore throat [46, 48]	Group A ß-haemolytic Streptococcus	2	85	473
AMS [28, 31]	*Streptococcus pneumoniae*	2	20	115
Skin infection [43, 44]	*Staphylococcus aureus*	2	106	134

Abbreviations: AMS, acute maxillary sinusitis; AOM, acute otitis media; CAP, community-acquired pneumonia; UTI, urinary tract infection.

knowledge of the causative pathogen and where most respiratory infections, for example, are viral.

Clinical criteria for diagnosing infections varied between studies, which could impact on clinical outcome. This was particularly evident for *E. coli* UTIs, for which criteria for obtaining urine samples and diagnostic thresholds varied. Using a lower reference standard of $\geq 10^2$ CFU/mL and of $\geq 10^3$ CFU/mL and combining nitrite dipstick test results with clinical symptoms and signs improves diagnostic accuracy for UTI [S69] and, therefore, earlier treatment initiation and improved outcome [S70].

Although we applied a consistent approach associating resistance and sensitivity data to a specific antibiotic class, the class of treatment antibiotic was not always consistent with the class of antibiotic against which resistance was measured. This potentially overestimates clinical response failure associated with resistance to the specific antibiotic being used for treatment. Clinical response failures were more likely in both the main analysis and sensitivity analysis for *E. coli* UTIs and *S. pneumoniae* AOM but not sustained for the sensitivity analysis for *S. pneumoniae* CAP. We therefore cannot reach a robust conclusion that there was there was no greater likelihood of failure in resistant *S. pneumoniae* CAP compared with sensitive *S. pneumoniae.* Potential reasons for this may be the limited number of participants with CAP (n = 91), the low number of outcome events overall (n = 11), or that clinical criteria for CAP diagnosis were not reported in 1 of the 2 studies [31]. Data were limited for some infections (eg, skin or soft tissue) and secondary outcomes. It remains unclear whether other infections or bacteria have similar implications on patients' illness burden.

Implications for Practice, Policy, and Future Research

Clinically, our findings support the need to better identify patients who might need an antibiotic. By testing for antibiotic resistance through promoting and evaluating rapid diagnostics, we can avoid or reduce the risk of clinical response failure. Early evidence suggests that rapid diagnostics used in a community setting can guide antibiotic prescribing for CAP [S71], and trials are underway for UTIs [S72, S73].

Given that at least 1 in 3 women will experience a UTI during their lifetime [4] and that the incidence of UTI is approximately 0.5–0.7 per person-year [S74], our findings show that antibiotic resistance significantly impacts on patients' illness burden. We estimate that clinical response failure is almost 3 times more likely in patients with antibiotic-resistant *E. coli* UTIs and around 2 times more likely in patients with antibiotic-resistant *S. pneumoniae* CAP and AOM than in patients whose infections are antibiotic-sensitive based on our odds ratio estimate and median clinical response failure rate (*E. coli* UTI: relative risk = 2.96, OR = 4.19, median failure rate = 13%, range = 9%–32% [8, 32–34, 36–39]; *S.pneumoniae* CAP: relative risk = 1.97, OR = 2.15, median failure rate = 8%, range = 4%–50% [29–31, 40, 41]; and *S.pneumoniae* AOM: relative risk = 2.18, OR = 2.51, median failure rate = 10%, range = 4%–16% [27, 31, 42, 45, 47]). Expressing the consequences of antibiotic-resistant infections in terms that are more meaningful to patients, among whom the concept of antibiotic resistance has been shown to be misunderstood [2], is important, especially where decisions about whether to start antibiotics may not be clear cut.

This impact may be much greater where the prevalence of antibiotic-resistant *E. coli* is higher (eg, in children with UTIs) [52]. Recent evidence reports that the global pooled prevalence of trimethoprim resistance used as first-line antibiotic treatment for *E.coli* UTI in children is 23.6% (range = 17.9%–30.3%) [52]. For more common illnesses like RTIs, the impact of antibiotic-resistant *S.pneumoniae* CAP in adults may be considerable because estimates vary considerably across European countries where approximately 1%–50% of *S.pneumoniae* isolates have been recorded as nonsusceptible to penicillin or macrolides [S75, S76].

A better grasp of the implications of antibiotic resistance on tangible outcomes may help curb patients' expectations for antibiotics [S77], facilitate shared decision making [S78], and inform more appropriate antibiotic prescribing behavior [S79] by informing guidelines, campaigns, and interventions to help healthcare professionals explain the potential implications of antibiotic-resistant infections in relation to outcomes that matter to patients.

More research is needed on the socioeconomic burden associated with antibiotic-resistant infections in the community, both in relation to direct healthcare resource utilization and indirect costs (eg, days off work) [S80]. Future work needs to develop a better understanding of the relationship between antibiotic prescribing levels and development of clinically significant antibiotic resistance in the community.

CONCLUSIONS

Antibiotic resistance has worse implications for patients' illness burden in the community. These findings could usefully inform better dialogue between clinician and patient, guidelines and campaigns about the benefits and risks of antibiotic treatment.

Supplementary Data

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

Notes

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