The implications of antibiotic resistance for patients’ recovery from common infections in the community: a systematic review and meta-analysis

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Main summary:
This study addresses the clinical relevance of antibiotic resistance in primary or ambulatory care. It shows that antibiotic resistance significantly impacts on patients’ illness burden in the community, and may also impact on primary care workload.

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Abstract

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 which reported patient-level data on laboratory-confirmed infections (respiratory, urinary tract, skin or soft tissue), antibiotic resistance, and clinical outcomes. Our primary outcome was clinical response failure. Secondary outcomes were re-consultation, 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 (5,659 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, 2,432 participants), *Streptococcus pneumoniae* otitis media (OR 2.51, 95% CI 1.29–4.88, 921 participants), and *Streptococcus pneumoniae* community-acquired pneumonia (OR 2.15, 95% CI 1.32–3.51, 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 which matter to patients should inform more meaningful discussions between health care professionals and patients about antibiotic treatment for common infections.
Introduction

Antibiotic resistance is recognised 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. This major evidence gap may influence expectations for antibiotics and antibiotic prescribing decisions in the community.

While the consequences of antibiotic-resistant infections in hospitalised patients are known (increased mortality, longer hospital stays and increased health care costs), antibiotic resistance may also have important consequences for patients with common infections managed in the community. The proportion of consultations in primary care for respiratory tract (10-20%), urinary tract (1-3%), and skin and soft tissue infections (1%) account for approximately 300 million in the UK and 490 million consultations in the US each year. Almost 75% of all antibiotics in the UK are prescribed in primary care, and at considerable cost.

Antibiotic use is also the most important risk factor for carriage of antibiotic-resistant bacteria 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, urinary tract and skin or soft tissue infections.

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 MeSH terms and validated search filters for “antibiotic resistance” and “primary care/community setting”, and keywords “antibiotic resistance”, “skin or soft tissue infections”, “respiratory tract infections”, “otitis media”, and “urinary tract infections” (Suppl. File 1 and 2). The review protocol was registered on the PROSPERO database (CRD42015032441).

Observational studies and randomised 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 (e.g. cystic fibrosis), were excluded.

We categorised respiratory tract infections (RTI) 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 more than one time point, we selected the time point closest to 7 to 14 days from baseline to reflect the duration of typical antibiotic regimens. Secondary outcomes were re-consultation, further antibiotic prescriptions (both within 30 days from baseline), symptom duration, and symptom severity.

Data extraction and risk of bias assessment

Two reviewers (OVH, J JL) independently extracted data on the characteristics of included studies (Table 1 and Suppl. 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 randomised, hence randomisation 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 2x2 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 two reviewers (OVH, JL) 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 randomised trials and CASP checklist for cohort studies (Suppl. File 3).

**Statistical analysis**

To compare the odds of clinical response failure between antibiotic-resistant and antibiotic-sensitive infections, we calculated odds ratios (OR) with 95% confidence intervals for infections where data were available from three or more studies for the same bacterial pathogen using random effects meta-analysis. Heterogeneity was assessed using the chi-squared test and $I^2$-squared statistic. ORs in relation to re-consultation 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 sensitive infections.

Subgroup analyses were performed according to study design (observational studies versus RCTs) and type of health care setting (general practice, hospital outpatient clinic or emergency
department). Results were summarised 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 (31/110) was that clinical outcomes were not reported separately for antibiotic-resistant versus antibiotic-sensitive infections.

Twenty-six studies were included (Fig. 1), of which 13 were observational studies, eight were RCTs and five were secondary analyses of pooled RCT data. Six studies were conducted in primary care/general practice, 12 in hospital outpatients, one in a mixed outpatient/primary care setting, two in a mixed outpatient/inpatient setting, one in an emergency department setting, and six 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 one or more study outcomes were available for 15,580 patients of whom 6,617 patients had a laboratory-confirmed potentially pathogenic bacterial infection. Data on whether the infection was antibiotic-resistant or antibiotic-sensitive were also available for 5,659 of these patients (antibiotic-resistant, n=1,268; antibiotic-sensitive, n=4,391; Table 2).

Clinical criteria for obtaining urine samples and diagnosing urinary tract infections varied between studies. Diagnostic thresholds used to define \( E. \ coli \) UTIs were reported as being \( >10^4 \) CFU in three studies (Suppl. File 4a). Urine samples were obtained from patients with urinary symptoms and positive urine dipstick test in four studies, in two studies with urinary symptoms only, one study obtained urine samples from patients with “clinically suspected” UTI, and two studies did not report selection criteria for obtaining urine samples. 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 between 57-95%. Clinical diagnosis of *S. pneumoniae* CAP was based on symptoms, radiographic evidence and blood tests in three studies,\textsuperscript{29,40,41} on symptoms and blood tests in one study,\textsuperscript{30} and one study\textsuperscript{31} did not report how a diagnosis was established (Suppl. File 4b). Diagnostic criteria for *S. pneumoniae* AOM (Suppl. File 4c) were more uniform (symptoms, examination, and tympanocentesis) except for one study where this was not reported.\textsuperscript{31}

Data relating to our primary outcome (clinical response failure) were available from 13 RCTs,\textsuperscript{27-31,37,38,40,42-46} and nine observational studies.\textsuperscript{8,32-34,36,39,41,47,48} Three observational studies reported data on re-consultations,\textsuperscript{8,32,35} four studies for further antibiotic prescriptions,\textsuperscript{8,34,49,50} four studies for symptom duration,\textsuperscript{8,32,49,50} and one for symptom severity.\textsuperscript{50} Data on these outcomes were not reported by any RCTs or secondary analyses of pooled RCT data.

The appendix (Suppl. File 3) summarises our risk of bias assessment of included studies. For 12 of 13 RCTs, there was low risk of reporting bias.\textsuperscript{27-29,31,37,38,40,42-46} Only one RCT reported assessing outcomes blinded from knowledge of whether the infection was antibiotic-resistant or antibiotic-sensitive.\textsuperscript{42} We were not able to assess whether RCTs considered confounding variables between antibiotic-resistant and antibiotic-sensitive infections except for one RCT\textsuperscript{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 one study\textsuperscript{34} and generally clearly defined. Antibiotic exposure was accurately measured (e.g. secure medical records) in ten studies.\textsuperscript{8,32-34,36,39,41,48-50} Only six observational studies attempted to address potential confounders, and measurement of outcome was only satisfactorily blinded in two studies.\textsuperscript{8,35}

Figures 2 to 4 summarise 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 = 2,432 participants, eight studies). 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; 916 participants, five studies; AOM: OR 2·51 [95%CI 1·29–4·88], P<.007; 921 participants, five studies). Clinical heterogeneity precluded meta-analysis for skin or soft tissue infections, since data were only available from two studies, of which one involved children with impetigo and the other involved adults and adolescents with a range of different infections, including cellulitis, simple abscesses and wound infections (Suppl. File 5). Likewise for sore throat, there was uncertainty regarding similarity of study population characteristics between the two studies, and for sinus infections, one study had only one patient with an antibiotic-resistant infection.

Re-consultation was significantly more likely in patients with antibiotic-resistant E. coli UTIs (Suppl. File 6a, OR 5·07 [95%CI 2·17–11·82]; n=1,283 participants; three studies). Data on patient re-consultations were not available for other infections. Two studies involving patients with M. pneumoniae CAP reported data on further antibiotic prescriptions (Suppl. File 6b). However, meta-analysis was not performed because one study did not report which antibiotic was used to treat participants, and there were no outcome events among patients with antibiotic-sensitive infections in the other study. Two studies involving patients with E. coli UTIs also reported data on further antibiotic prescriptions. However, treatment antibiotic was not reported in one study and the other study focused specifically on extended-spectrum beta-lactamases (ESBL) E. coli infections.

Antibiotic-resistant infections were associated with longer duration of symptoms in two of three E. coli UTI studies (Suppl. File 7), but not in the one M. pneumoniae CAP study. Only one 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 two to four (antibiotic-resistant 2.01, standard deviation (0.89) vs antibiotic-sensitive 1.47, SD (0.88); p<0.001, 264 participants; severity grading 0 = no symptoms, 6 = as bad as it could be; Suppl. 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 (5.42 [3.87–7.61]) and primary care settings (3.29 [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 which examined highly-specific antibiotic-resistant bacteria (e.g. 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]; 1,426 participants, four studies).8,32,37,38

For S. pneumoniae CAP, the findings were no longer statistically significant (95%CI 1.22 [0.25–5.91]; 91 participants, two 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]; 573 participants, four studies), 27,31,42,45 after excluding one study conducted in an inpatient/outpatient setting.47

Discussion

Main findings

Our findings demonstrate that patients who present in community health care settings with antibiotic-resistant urinary and respiratory tract infections 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 re-consult a health care professional and experience prolonged
and more severe symptoms than patients with antibiotic-sensitive 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 though did not determine the
specific contribution (or association) of antibiotic resistance to response failure.

We were only able to estimate re-consultation rates for *E. coli* UTIs which are comparable with other
studies 28% (357/1,283) vs 26-55%.\(^ {58,59}\)

The prevalence of resistant *E. coli* in the UTI studies we included for our primary outcome (10-4%,
357/3,428) falls within the lower end of the spectrum compared to most community-based
population estimates (5-53%) as this depends on the antibiotic susceptibility measured, the clinical
criteria used for obtaining urine samples and diagnosing UTIs,\(^ {60-63}\) 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%, 3/171) for example, is similar
to other studies (<2%).\(^ {61,63}\) Similarly, the prevalence of resistant *S. pneumoniae* in CAP and AOM in
our included studies are lower than population estimates (5-4%, 246/4,591) vs 8-33% for CAP;\(^ {64,65}\)
0-4% (353/3,407) vs 1-48% for AOM.\(^ {56,67}\)

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

We focussed on more practical, clinically relevant outcomes for patients and clinicians, moving beyond a laboratory-focused, microbiological outcome. Since most of our included studies specifically excluded patients with known 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 one explanation for clinical response failure, which could also be due to factors such as co-infection or re-infection. We cannot say what the relative contribution of antibiotic resistance was compared to other factors which 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 criticised because many patients probably had viral infections and would not have been expected to recover because of antibiotic treatment.68 All included patients in our review had laboratory-confirmed bacterial infections. That said, this may limit generalisability of findings to clinical practice, given that treatment decisions in the community are based on clinical findings without 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 where 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,69 and therefore earlier treatment initiation and improved outcome.70
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 no greater likelihood of failure in resistant *S. pneumoniae* CAP compared to 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 one of the two studies. Data were limited for some infections (e.g. skin or soft tissue) and secondary outcomes. It remains unclear if 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 and trials are underway for UTIs.

Given that at least 1 in 3 women will experience a UTI during their lifetime and that the incidence of UTI is around 0.5 to 0.7 per person-year, our findings show that antibiotic resistance significantly impacts on patients’ illness burden. We estimate that clinical response failure is almost three times more likely in patients with antibiotic-resistant *E. coli* UTIs and around two 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% to 32%]; *S. pneumoniae* CAP: relative risk 1.97, OR 2.15, median failure rate of 8% [4-50%]; and *S. pneumoniae* AOM: 8,32-34,36-39 29-31,40,41
relative risk 2·18, OR 2·51, median failure rate of 10% [4-16%]). 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, 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 e.g. in children with UTIs. 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% (17·9-30·3%). For more common illnesses like RTIs, the impact of antibiotic-resistant *S.pneumoniae* CAP in adults may be considerable, as estimates vary considerably across European countries where around 1 to 50% of *S.pneumoniae* isolates have been recorded as non-susceptible to penicillin or macrolides.

A better grasp of the implications of antibiotic resistance on tangible outcomes, may help curb patients’ expectations for antibiotics, facilitate shared decision-making, and inform more appropriate antibiotic prescribing behaviour, by informing guidelines, campaigns and interventions to help health care professionals explain the potential implications of antibiotic-resistant infections in relation to outcomes which matter to patients.

More research is needed on the socioeconomic burden associated with antibiotic-resistant infections in the community both in relation to direct health care resource utilisation and indirect costs (e.g. days off work). 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.
Contributors

All authors have read the approved manuscript and agree to be answerable to all aspects of the work.

The authors OVH, KW and CCB designed and led the research that contributed to the manuscript and were responsible for the main analysis. NW, OVH and KW designed and completed the literature search. OVH and J JL collected and extracted data. Authors (OVH, KW, J JL and CCB) were involved in appraising and interpreting the data and all authors subsequently contributed to successive drafts of the paper.

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no competing interests.

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_Ethics approval_

Not required.
| Country | Setting | Infection type | Study design | Participants | Total number recruited | Total number with potential pathogens being studied | Number of potential pathogens being studied with evidence of antibiotic resistance | Number of patients where resistance and outcome data available | Primary Outcome time point | Secondary outcomes | Treatment antibiotic/antibiotic class | Antibiotic to which resistance measured |
|---------|---------|----------------|--------------|--------------|-----------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-----------------------------|----------------|-----------------------------|-------------------------------|
| Brown et al. (2002) | USA | OP/PHC | UTI | Obs (R) | Wo | E | NR | 601 isolates | 44 | 104 | - | Rec | TMP-SMX | TMP-SMX |
| Butler et al. (2005) | United Kingdom | PHC | UTI | CC Obs (P) | Adu | E | 932 | 922 | 94 | 797 | 862 (Rec) | 816 (Fab) | 420 (Sdur) | within 30 days | Rec | Fab | Sdur | Not specified | To prescribed antibiotic | To at least one antibiotic | TMP-SMX |
| Gupta et al. (2007) | USA | PHC | UTI | RCT | Wo | E | 338 | 276 | 34 | 308 | ** | Day 3 | - | TMP-SMX | Nitrofurantoin |
| Little et al. (2006) | United Kingdom | PHC | UTI | Obs (P) | Wo | NR | 843 | NR | 264 | (Sdur) | 264 (Savo) | - | Sdur | Savo | Not specified | To one or more antibiotics |
| McNulty et al. (2006) | United Kingdom | PHC | UTI | Obs (P) | Wo | E | 497 | 298 | 44 | 207 | (Sdur) | ** | 317 (Rec) | Day 7 | ** | Rec | Sdur | Trimethoprim | Trimethoprim |
| Noskin et al. (2001) | USA | OP | UTI | Obs (P) | Wo | E | 156 | 89 | 42 | 71 | ** | NR | - | Not specified | To one or more antibiotics |
| Raz et al. (2002) | Israel | OP | UTI | Obs (P) | Wo | E | 618 | 425 | 30 | 484 | ** | Day 5-9 | - | TMP-SMX | TMP-SMX |
| Sarrazin et al. (2004) | Norway | Other | UTI | Obs (P) | Adu | ESBL | 343 | 343 | 343 | 81 (ESBL-E) | 343 | within 14 days | Fab | - | Mecillinam | Non-mecillinam | Mecillinam and ESBL status |
| Vallano et al. (2006) | Spain | PHC | UTI | Obs (P) | Wo | E | 220 | 88 | 15 | 108 | ** | within 14 days | - | Not specified | To one or more antibiotics |
| Van Merode et al. (2003) | Netherlands | PHC | UTI | RCT | Wo | E | 324 | 80 | 17 | 114 | ** | Day 6-8 | - | Trimethoprim | Trimethoprim |

**Community-acquired pneumonia (CAP)**

| Cao et al. (2006) | China | OP | RTI (CAP) | Obs (P) | Adu; Adol | MP | 356 | 67 | 46 | 59 | - | Fab | Sdur | Not specified | Erythromycin |
| Hagberg et al. (2003) | Multiple | OP/OP | RTI (CAP) | Pooled data from 6 phase III trials | Adu; Adol | MP | 1,373 | 174 | 23 | 14 | 174 | Day 5-9 | - | Telithromycin | Pencillin or erythromycin |
| Kawai et al. (2002) | Japan | OP | RTI (CAP) | Obs (P) | Ch; Adol | MP | 476 | 50 | 21 | 30 | - | Fab | - | Not specified | To one or more macrolide |
| O’Doherty et al. (1997) | United Kingdom; Ireland | OP | RTI (CAP) | RCT | Adu | MP | 264 | 30 | 6 | 30 | - | Day 3-5 | - | Grupafloxacin | Amoxicillin |
| Van Rensburg et al. (2005) | Multiple | OP | RTI (CAP) | Pooled RCT (8 phase III trials and 1 phase II study) | Adu | SP | 2339 | 418 | 61 | 327 | Day 17-24 | - | Telithromycin | To erythromycin and penicillin |
| Yamagihara et al. (2004) | Japan | OP | RTI (CAP) | Obs (R) | Adu | SP | 306 | 306 | 120 | 306 | - | NR | - | Not specified | Pencillin |
| Zhan et al. (2004) | Multiple | Other | RTI (AMS) | RTI (CAP) | RTI (ACM) | Pooled RCT (11 RCTs; 2 phase III trials) | Adu; Ch; | SP | 872 | ** | 309 | CAP | 79 | CAP | 27 | CAP | 79 | NR | - | Azithromycin | Azithromycin |
### Acute otitis media (AOM)

| Authors          | Country | Study Type | Comparator | Data Source | Chi | SP | SR | Days to Failure | B-lactams (combined) | Others |
|------------------|---------|------------|------------|-------------|-----|----|----|----------------|----------------------|---------|
| Barry et al.     | France  | RCT (AOM)  | Pooled data from 3 RCTs | Chi; SP | 1,092 | 236 | 54 | 219 | - | B-lactams; Penicillin; B-lactams |
| Dagan et al.     | Israel  | ER; RCT (AOM) | RCT | Chi; SP | 266 | 98 | 18 | 77 | - | Cefuroxime; Cefaclor; Cefuroxime; Cefaclor |
| Hoibermann et al. | Multiple | RCT (AOM) | Obs (P) | Chi; SP | 917 | 298 | 82 | 260 | - | Co-amoxiclav; Penicillin |
| Hoibermann et al. | Multiple | RCT (AOM) | RCT | Chi; SP | 730 | 229 | 158 | 188 | - | Co-amoxiclav; Aminothromycin; Penicillin; Aminothromycin |
| Zhanel et al.    | Multiple | Other | RCT (AMS) | Pooled RCT (11 RCTs; 2 phase III trials) | Adu; Chi; SP | 872 | AOM 402 | AOM 177 | AOM 41 | AOM 177 | - | Aminothromycin; Aminothromycin |

### Acute sore throat

| Authors          | Country | Study Type | Comparator | Data Source | Chi | SP | SR | Days to Failure | B-lactams (combined) | Others |
|------------------|---------|------------|------------|-------------|-----|----|----|----------------|----------------------|---------|
| Quinn et al.     | USA; Canada | RCT (sore throat) | RCT | Adu; Adol | 526 | 360 | 9 | 285 | - | Telithromycin; Clarithromycin; Erythromycin |
| Saggala et al.   | Finland | RCT (sore throat) | Obs (R) | NR; Spy | 529 | 76 | 273 | - | Erythromycin; Penicillin; Erythromycin |

### Acute maxillary sinusitis (AMS)

| Authors          | Country | Study Type | Comparator | Data Source | Chi | SP | SR | Days to Failure | B-lactams (combined) | Others |
|------------------|---------|------------|------------|-------------|-----|----|----|----------------|----------------------|---------|
| Buchanan et al.  | Sweden  | Other | RCT (AMS) | Pooled data from 3 RCTs | Adu; Adol; SP | 1,298 | 126 | 1 | 78 | - | Telithromycin; Telithromycin |
| Zhanel et al.    | Multiple | Other | RCT (AMS) | Pooled RCT (11 RCTs; 2 phase III trials) | Adu; Chi; SP | 872 | AMS 161 | AMS 57 | AMS 19 | AMS 57 | - | Aminothromycin; Aminothromycin |

### Skin and soft tissue infection

| Authors          | Country | Study Type | Comparator | Data Source | Chi | SP | SR | Days to Failure | B-lactams (combined) | Others |
|------------------|---------|------------|------------|-------------|-----|----|----|----------------|----------------------|---------|
| Dagan et al.     | Israel  | RCT (Skin) | RCT | Chi; SA | 102 | 90 | 27 | 89 | - | Erythromycin; Mupirocin; Erythromycin; Mupirocin |
| Giordano et al.  | USA     | Other | Skin (USSS) | RCT | Adu; Adol | 392 | 171 | 79 | 151 | - | Ceftriaxone; Cephalexin; Methicillin |

| Overall          |         |           |            |             |     |     |     | 15,580 | 5,659 | 1 |

1 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 (i.e. 1–proportion of patients with clinical cure). 2 Data on clinical cure, rather than clinical response failure, were reported by ten RCTs. 29,32,37,38,40,42,43. Overall, clinical response failure was assessed between 3–5 days from baseline in three studies, 8,30,44, between 6–10 days in six studies, 28,31,34,42,47, between 11–14 days in four studies, 29,32,34,42,47, between 20–30 days in five studies, 8,26,30,44,46 and not reported in four studies. 31,34,42,46 2 Secondary outcomes: re-consultation (Rec), further antibiotic prescriptions (Fab), symptom duration (Sdur) and symptom severity (Ssev). 3 we assumed one isolate per participant.

3 Multiple antibiotics prescribed in separate study arms

OP: Hospital outpatients. PHC: primary care clinic/general practice. UTI: Urinary tract infections. Obs (R): Retrospective observational. Wo: women. E: E. coli. NR: not reported. TMP-SMX: Trimethoprim-sulfamethoxazole. CC: case control. Obs (P): Prospective observational. Ado: Adolescents. RTI: Respiratory tract infection. CAP: community-acquired pneumonia. Adol: adolescents. MP: M. pneumoniae. IP: Hospital inpatients. SP: S. pneumoniae. Chi: Children. AMS: acute maxillary sinusitis. AOM: acute otitis media. ER: Emergency room. Spy: S. pyogenes. Imp: impetigo. SA: S. aureus. USSSI: uncomplicated skin and skin structure infections (e.g. cellulitis, erysipelas, impetigo, simple abscess, wound infection, furunculosis, folliculitis).
a: One child in the SpRP group did not complete the treatment course because of adverse events and was not evaluable for clinical response. b: Coliforms; 242 single isolates were sent to HPA Antibiotic Resistance Monitoring and Reference Laboratory (ARMRL) of which E.coli accounted for 90% (219/242). c: Penicillin or erythromycin-resistant (all S.pneumoniae isolates were susceptible to telithromycin). d: Specific organism not reported. e: Only 81 were evaluated microbiologically. f: positive screening for Group A ß-haemolytic streptococcus. g: ESBL-E. coli and non-ESBL-E. coli only. h: excluded acute exacerbations of chronic bronchitis. -: not applicable. 1: Resistance measured to prescribed antibiotic; 2: Resistance measures to at least one antibiotic; 3: where more than one outcome data available, the lowest number was taken
Table 2. Data related to one or more study outcomes according to infection type and bacterial pathogen

| Infection       | Bacteria                          | Number of studies | Number of antibiotic resistant infections | Number of antibiotic-sensitive infections |
|-----------------|-----------------------------------|-------------------|------------------------------------------|------------------------------------------|
| UTI 8,32,39,50  | *E. coli*                         | 10                | 523                                      | 2,277                                    |
| CAP 69,31,40,41 | *S. pneumoniae*                   | 5                 | 246                                      | 670                                      |
| CAP             | *M. pneumoniae*                   | 2                 | 63                                       | 24                                       |
| AOM 27,31,42,45,47 | *S. pneumoniae*            | 5                 | 225                                      | 696                                      |
| Sore throat 46,48 | Group A ß-haemolytic Streptococcus | 2                 | 85                                       | 473                                      |
| AMS 28,31       | *S. pneumoniae*                   | 2                 | 20                                       | 115                                      |
| Skin infection 43,44 | *S. aureus*                        | 2                 | 106                                      | 134                                      |

UTI: urinary tract infection; *E. coli*: Escherichia coli; CAP: community-acquired pneumonia; *S. pneumoniae*: Streptococcus pneumoniae; *M. pneumoniae*: Mycoplasma pneumoniae; AOM: acute otitis media; AMS: acute maxillary sinusitis; *S. aureus*: Staphylococcus aureus
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Figure Legends

Figure 1. Study selection

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

Figure 3. Comparison between antibiotic-resistant and antibiotic-sensitive (*S. pneumoniae*) community-acquired pneumonia in relation to response failure; Odd ratio (OR) more than 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.

Figure 4. Comparison between antibiotic-resistant and antibiotic-sensitive (*S. pneumoniae*) acute otitis media in relation to response failure; Odd ratio (OR) more than 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.