

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

## **Authors:**

<sup>1\*</sup>Oliver van Hecke, general practitioner and clinical research fellow

<sup>1</sup>Kay Wang, academic clinical lecturer

<sup>1</sup>Joseph J. Lee, general practitioner

<sup>2</sup>Nia W. Roberts, specialist medical librarian

<sup>1</sup>Chris C. Butler, professor of primary care

## **Author affiliations:**

<sup>1</sup>Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

<sup>2</sup>Bodleian Health Care Libraries, Knowledge Centre, ORC Research Building, Old Road Campus, Oxford, UK

## **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.

**Keywords:** antibiotic resistance; primary care; clinical significance

Number of pages: 26

Number of figures: 4

Number of tables: 2

**\*Corresponding author:**

Dr Oliver van Hecke

Nuffield Department of Primary Care Health Sciences  
University of Oxford  
Radcliffe Observatory Quarter  
Woodstock Road  
Oxford  
OX2 6GG

Tel: +44 (0) 1865 617 839

Email: [oliver.vanhecke@phc.ox.ac.uk](mailto:oliver.vanhecke@phc.ox.ac.uk)

**Alternate corresponding author:**

Professor Chris Butler

Nuffield Department of Primary Care Health Sciences  
University of Oxford  
Radcliffe Observatory Quarter  
Woodstock Road  
Oxford  
OX2 6GG

Email: [christopher.butler@phc.ox.ac.uk](mailto:christopher.butler@phc.ox.ac.uk)

## **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.<sup>1-3</sup> This major evidence gap may influence expectations for antibiotics and antibiotic prescribing decisions in the community.<sup>4,5</sup>

While the consequences of antibiotic-resistant infections in hospitalised patients are known (increased mortality, longer hospital stays and increased health care costs),<sup>6,7</sup> antibiotic resistance may also have important consequences for patients with common infections managed in the community.<sup>8</sup> The proportion of consultations in primary care for respiratory tract (10-20%),<sup>9-11</sup> urinary tract (1-3%),<sup>12,13</sup> and skin and soft tissue infections (1%),<sup>14-16</sup> account for approximately 300 million in the UK and 490 million consultations in the US each year.<sup>14,17</sup> Almost 75% of all antibiotics in the UK are prescribed in primary care,<sup>18</sup> and at considerable cost.<sup>19-21</sup>

Antibiotic use is also the most important risk factor for carriage of antibiotic-resistant bacteria<sup>22,23</sup> 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”<sup>23</sup> and “primary care/community setting”,<sup>24</sup> 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, JJJ) 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).<sup>25,26</sup>

### *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.<sup>27-31</sup> 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).<sup>32-34</sup> Urine samples were obtained from patients with urinary symptoms and positive urine dipstick test in four studies,<sup>32,33,35,36</sup> in two studies with urinary symptoms only,<sup>37,38</sup> one study obtained urine samples from patients with “clinically suspected” UTI,<sup>8</sup> and two studies did not report selection criteria for obtaining urine samples.<sup>34,39</sup> 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<sup>29,40,41</sup>, on symptoms and blood tests in one study<sup>30</sup> and one study<sup>31</sup> 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.<sup>31</sup>

Data relating to our primary outcome (clinical response failure) were available from 13 RCTs,<sup>27-31,37,38,40,42-46</sup> and nine observational studies.<sup>8,32-34,36,39,41,47,48</sup> Three observational studies reported data on re-consultations<sup>8,32,35</sup>, four studies for further antibiotic prescriptions<sup>8,34,49,50</sup>, four studies for symptom duration<sup>8,32,49,50</sup> and one for symptom severity.<sup>50</sup> 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.<sup>27-29,31,37,38,40,42-46</sup> Only one RCT reported assessing outcomes blinded from knowledge of whether the infection was antibiotic-resistant or antibiotic-sensitive.<sup>42</sup> We were not able to assess whether RCTs considered confounding variables between antibiotic-resistant and antibiotic-sensitive infections except for one RCT<sup>42</sup> 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<sup>34</sup> and generally clearly defined. Antibiotic exposure was accurately measured (e.g. secure medical records) in ten studies.<sup>8,32-34,36,39,41,48-50</sup> Only six observational studies attempted to address potential confounders, and measurement of outcome was only satisfactorily blinded in two studies.<sup>8,35</sup>

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).<sup>8,32-34,36-39</sup> 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;<sup>29-31,40,41</sup> AOM: OR 2.51 [95%CI 1.29–4.88],  $P < .007$ ; 921 participants, five studies).<sup>27,31,42,45,47</sup>

Clinical heterogeneity precluded meta-analysis for skin or soft tissue infections, since data were only available from two studies,<sup>43,44</sup> 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,<sup>46,48</sup> and for sinus infections,<sup>28,31</sup> one study<sup>28</sup> 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).<sup>8,32,35</sup> 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).<sup>49,51</sup> However, meta-analysis was not performed because one study did not report which antibiotic was used to treat participants,<sup>49</sup> and there were no outcome events among patients with antibiotic-sensitive infections in the other study.<sup>51</sup> Two studies involving patients with *E. coli* UTIs also reported data on further antibiotic prescriptions.<sup>8,34</sup> However, treatment antibiotic was not reported in one study<sup>8</sup> and the other study focused specifically on extended-spectrum beta-lactamases (ESBL) *E. coli* infections.<sup>34</sup>

Antibiotic-resistant infections were associated with longer duration of symptoms in two<sup>32,50</sup> of three *E. coli* UTI studies (Suppl. File 7),<sup>8,32,50</sup> but not in the one *M. pneumoniae* CAP study.<sup>49</sup> 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).<sup>50</sup>

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,<sup>36</sup> studies which examined highly-specific antibiotic-resistant bacteria (e.g. ESBL-*E. coli*),<sup>34</sup> studies where the reported susceptibility did not match the treatment antibiotic class,<sup>29,30,40,41</sup> and studies where the treatment antibiotic was not specified.<sup>33,39</sup> This did not change the overall findings (OR 3.27 [95%CI 2.32–4.60]; 1,426 participants, four studies).<sup>8,32,37,38</sup>

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

## 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.<sup>22,23,52</sup> Our estimates are consistent with estimates of clinical response failure rates in community populations for UTIs (14-38%),<sup>53,54</sup> CAP (11-24%),<sup>55</sup> and AOM (7-24%).<sup>56,57</sup> 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%.<sup>58,59</sup>

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,<sup>60-63</sup> and study population characteristics.<sup>52</sup> 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%).<sup>61,63</sup> 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;<sup>64,65</sup> 0.4% (353/3,407) vs 1-48% for AOM).<sup>66,67</sup>

### *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,<sup>8,27,28,30,32-40,43-50</sup> 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.<sup>68</sup> 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,<sup>69</sup> and therefore earlier treatment initiation and improved outcome.<sup>70</sup>

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.<sup>31</sup> 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<sup>71</sup> and trials are underway for UTIs.<sup>72 73</sup>

Given that at least 1 in 3 women will experience a UTI during their lifetime<sup>4</sup> and that the incidence of UTI is around 0.5 to 0.7 per person-year,<sup>74</sup> 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%];<sup>8,32-34,36-39</sup> *S. pneumoniae* CAP: relative risk 1.97, OR 2.15, median failure rate of 8% [4-50%];<sup>29-31,40,41</sup> and *S. pneumoniae* AOM:

relative risk 2.18, OR 2.51, median failure rate of 10% [4-16%]).<sup>27,31,42,45,47</sup> 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,<sup>2</sup> 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.<sup>52</sup> 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%).<sup>52</sup> 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.<sup>75 76</sup>

A better grasp of the implications of antibiotic resistance on tangible outcomes, may help curb patients' expectations for antibiotics,<sup>77</sup> facilitate shared decision-making,<sup>78</sup> and inform more appropriate antibiotic prescribing behaviour,<sup>79</sup> 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).<sup>80</sup> 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 JIL collected and extracted data. Authors (OVH, KW, JIL and CCB) were involved in appraising and interpreting the data and all authors subsequently contributed to successive drafts of the paper.

### *Acknowledgements*

The authors are grateful to Associate Professor Ann Van den Bruel for her helpful suggestions and critical reading of the manuscript, and Constantinos Koshari for his statistical advice.

CCB is supported in part by the Oxford NIHR Health Protection Research Unit (HPRU) in Healthcare Associated Infections and Antimicrobial Resistance.

The ARCHIE research programme (The early use of Antibiotics for 'at Risk' CHILDren with Influenza) is funded by the National Institute for Health Research's (NIHR) Applied Research Programme. This publication summarises independent research funded by the NIHR under its Programme Grants for Applied Research Programme (Grant Reference RP-PG-1210-12012). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

### *Competing interests*

All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare no competing interests.

### *Funding*



The funding source was not involved in study design, data collection, analysis or interpretation, report writing, or submission for publication.

*Ethics approval*

Not required.

**Table 1.** Characteristics of 26 included studies (primary and/or secondary outcomes) according to infection

	Country	Setting	Infection type	Study design	Participants	Potential pathogen being studied	Total number recruited	Total number with potential pathogen 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 <sup>† §</sup>	Secondary outcomes <sup>‡</sup>	Treatment antibiotic/antibiotic class <sup>¶</sup>	Antibiotic to which resistance measured
<b>Urinary tract infection (UTI)</b>														
Brown et al. (2002) <sup>35</sup>	USA	OP/PHC	UTI	Obs (R)	Wo	<i>E</i>	NR	601 isolates <sup>§</sup>	44	104	-	Rec <sup>‡</sup>	TMP-SMX	TMP-SMX
Butler et al. (2006) <sup>8</sup>	United Kingdom	PHC	UTI	CC Obs (P)	Adu	<i>E</i>	932	922	94	797 <sup>1</sup> 862 (Rec) <sup>2</sup> 816 (Fab) <sup>2</sup> 420 (Sdur) <sup>2</sup>	within 30 days	Rec <sup>‡</sup> Fab <sup>‡</sup> Sdur <sup>‡</sup>	Not specified	To prescribed antibiotic <sup>1</sup> To at least one antibiotic <sup>2</sup>
Gupta et al. (2007) <sup>37</sup>	USA	PHC	UTI	RCT	Wo	<i>E</i>	338	276	34	308 **	Day 3 <sup>§</sup>	-	TMP-SMX Nitrofurantoin	TMP-SMX Nitrofurantoin
Little et al. (2010) <sup>50</sup>	United Kingdom	PHC	UTI	Obs (P)	Wo	NR <sup>d</sup>	843	NR	NR	264 (Sdur) 264 (Ssev)	-	Sdur <sup>‡</sup> Ssev <sup>‡</sup>	Not specified	To one or more antibiotics
McNulty et al. (2006) <sup>32</sup>	United Kingdom	PHC	UTI	Obs (P)	Wo	<i>E</i>	497	298 <sup>b</sup>	44	207 (Sdur)** 317 (Rec)	Day 7 <sup>§</sup>	Sdur <sup>‡</sup> Rec <sup>‡</sup>	Trimethoprim	Trimethoprim
Noskin et al. (2001) <sup>33</sup>	USA	OP	UTI	Obs (P)	Wo	<i>E</i>	156	89	42	71	NR <sup>§</sup>	-	Not specified	To one or more antibiotics
Raz et al. (2002) <sup>36</sup>	Israel	OP	UTI	Obs (P)	Wo	<i>E</i>	618	425	30	484 **	Day 5-9 <sup>§</sup>	-	TMP-SMX	TMP-SMX
Soraas et al. (2014) <sup>34</sup>	Norway	Other	UTI	Obs (P)	Adu	ESBL- <i>E</i>	343	343 <sup>e</sup>	81 (ESBL- <i>E</i> )	343	within 14 days <sup>§</sup>	Fab <sup>‡</sup>	Mecillinam Non-mecillinam	Mecillinam and ESBL status
Vallano et al. (2006) <sup>39</sup>	Spain	PHC	UTI	Obs (P)	Wo	<i>E</i>	220	88	15 **	108 **	within 14 days <sup>§</sup>	-	Not specified	To one or more antibiotics
Van Merode et al. (2005) <sup>38</sup>	Netherlands	PHC	UTI	RCT	Wo	<i>E</i>	324	80	17	114 **	Day 6-8 <sup>§</sup>	-	Trimethoprim	Trimethoprim
<b>Community-acquired pneumonia (CAP)</b>														
Cao et al. (2010) <sup>49</sup>	China	OP	RTI (CAP)	Obs (P)	Adu; Adol	<i>MP</i>	356	67	46	59	-	Fab <sup>‡</sup> Sdur <sup>‡</sup>	Not specified	Erythromycin
Hagberg et al. (2003) <sup>28</sup>	Multiple	IP/OP	RTI (CAP)	Pooled data from 6 phase III trials	Adu	<i>SP</i>	1,373	174	23 <sup>c</sup>	174	Day 3-5 <sup>§</sup>	-	Telithromycin	Penicillin or erythromycin
Kawai et al. (2012) <sup>51</sup>	Japan	OP	RTI (CAP)	Obs (P)	Chi; Adol	<i>MP</i>	476	50	21	30	-	Fab <sup>‡</sup>	Not specified	To one or more macrolide
O'Doherty et al. (1997) <sup>40</sup>	United Kingdom; Ireland	OP	RTI (CAP)	RCT	Adu	<i>SP</i>	264	30 <sup>e</sup>	6	30	Day 3-5 <sup>§</sup>	-	Grepafloxacin Amoxicillin	Amoxicillin
Van Rensburg et al. (2005) <sup>30</sup>	Multiple	OP	RTI (CAP)	Pooled RCT (8 phase III trials and 1 phase II study)	Adu	<i>SP</i>	2339	418	61	327	Day 17-24 <sup>§</sup>	-	Telithromycin	To erythromycin and penicillin
Yanagihara et al. (2004) <sup>41</sup>	Japan	OP	RTI (CAP)	Obs (R)	Adu	<i>SP</i>	306	306	129	306	NR <sup>§</sup>	-	Not specified	Penicillin
Zhan et al. (2014) <sup>31</sup>	Multiple	Other	RTI (AMS) RTI (CAP) RTI (AOM)	Pooled RCT (11 RCTs; 2 phase III trials)	Adu; Chi	<i>SP</i>	872 <sup>h</sup> CAP 309	CAP 79	CAP 27	CAP 79	NR <sup>§</sup>	-	Azithromycin	Azithromycin

Acute otitis media (AOM)														
Barry et al. (1994) <sup>27</sup>	France	OP	RTI (AOM)	Pooled data from 3 RCTs	Chi	SP	1,092	236	54 <sup>a</sup>	219	Day 10	-	B-lactams (combined)	Penicillin; B-lactams
Dagan et al. (1996) <sup>42</sup>	Israel	ER	RTI (AOM)	RCT	Chi	SP	266	98	18	77	Day 10	-	Cefuroxime Cefaclor	Cefuroxime Cefaclor
Hoberman et al. (1996) <sup>47</sup>	Multiple	IP/OP	RTI (AOM)	Obs (P)	Chi	SP	917	298	82	260	Day 12-14 <sup>§</sup>	-	Co-amoxiclav	Penicillin
Hoberman et al. (2005) <sup>45</sup>	Multiple	OP	RTI (AOM)	RCT	Chi	SP	730	229	158	188	Day 12-14 <sup>§</sup>	-	Co-amoxiclav Azithromycin	Penicillin Azithromycin
Zhanet et al. (2014) <sup>31</sup>	Multiple	Other	RTI (AMS) RTI (CAP) RTI (AOM)	Pooled RCT (11 RCTs; 2 phase III trials)	Adu; Chi	SP	872 <sup>h</sup> AOM 402	AOM 177	AOM 41	AOM 177	NR	-	Azithromycin	Azithromycin
Acute sore throat														
Quinn et al. (2003) <sup>46</sup>	USA; Canada	OP	RTI (sore throat)	RCT	Adu; Adol	Spy	526	360 <sup>†</sup>	9	285	Day 16-23 <sup>§</sup>	-	Telithromycin Clarithromycin	Erythromycin
Seppala et al. (2002) <sup>48</sup>	Finland	OP	RTI (sore throat)	Obs (R)	NR	Spy	NR	529	76	273	NR	-	Erythromycin Penicillin	Erythromycin
Acute maxillary sinusitis (AMS)														
Buchanan et al. (2005) <sup>28</sup>	Sweden	Other	RTI (AMS)	Pooled data from 3 RCTs	Adu; Adol	SP	1,298	126	1	78	Day 17-24 <sup>§</sup>	-	Telithromycin	Telithromycin
Zhanet et al. (2014) <sup>31</sup>	Multiple	Other	RTI (AMS) RTI (CAP) RTI (AOM)	Pooled RCT (11 RCTs; 2 phase III trials)	Adu; Chi	SP	872 <sup>h</sup> AMS 161	AMS 57	AMS 19	AMS 57	NR	-	Azithromycin	Azithromycin
Skin and soft tissue infection														
Dagan et al. (1992) <sup>43</sup>	Israel	OP	Skin (Imp)	RCT	Chi	SA	102	90	27	89	Day 3-8	-	Erythromycin Mupirocin	Erythromycin, Mupirocin
Giordano et al. (2006) <sup>44</sup>	USA	Other	Skin (USSSI)	RCT	Adu; Adol	SA	392	171	79	151	Day 17-24 <sup>§</sup>	-	Cefdinir Cephalixin	Methicillin
<b>Overall</b>							<b>15,580</b>			<b>5,659<sup>3</sup></b>				

<sup>†</sup> 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). <sup>§</sup> Data on clinical cure, rather than clinical response failure, were reported by ten RCTs<sup>28-31,37,38,40,44-46</sup>, and seven observational studies.<sup>32-34,36,39,41,47</sup> Overall, clinical response failure was assessed between 3-5 days from baseline in three studies,<sup>29,37,40</sup> between 6-10 days in six studies,<sup>27,32,36,38,42,43</sup> between 11-14 in four studies,<sup>34,39,45,47</sup> between 20-30 days in five studies,<sup>8,28,30,44,46</sup> and not reported in four studies.<sup>31,33,41,48</sup>

<sup>‡</sup> Secondary outcomes: re-consultation (Rec), further antibiotic prescriptions (Fab), symptom duration (Sdur) and symptom severity (Ssev). <sup>§</sup> we assumed one isolate per participant.

<sup>¶</sup> 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. coli*. NR: not reported. TMP-SMX: Trimethoprim-sulfamethoxazole. CC: case control. Obs (P): Prospective observational. Adu: Adults. RCT: Randomised controlled trial. Other: community setting (not specified). ESBL-*E. coli*. \*\* all combined pathogens. Other: Other community setting. 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  $\beta$ -haemolytic streptococcus. g: ESBL-*E. coli* and non-ESBL-*E. coli* only. h: excluded acute exacerbations of chronic bronchitis. -: not applicable. <sup>1</sup>: Resistance measured to prescribed antibiotic; <sup>2</sup>: Resistance measures to at least one antibiotic; <sup>3</sup>: 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 <sup>8,32-39,50</sup>	<i>E. coli</i>	10	523	2, 277
CAP <sup>29-31,40,41</sup>	<i>S. pneumoniae</i>	5	246	670
CAP <sup>49,51</sup>	<i>M. pneumoniae</i>	2	63	24
AOM <sup>27,31,42,45,47</sup>	<i>S. pneumoniae</i>	5	225	696
Sore throat <sup>46,48</sup>	Group A $\beta$ -haemolytic Streptococcus	2	85	473
AMS <sup>28,31</sup>	<i>S. pneumoniae</i>	2	20	115
Skin infection <sup>43,44</sup>	<i>S. aureus</i>	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

## References

1. Simpson SA, Wood F, Butler CC. General practitioners' perceptions of antimicrobial resistance: a qualitative study. *The Journal of antimicrobial chemotherapy* 2007; **59**(2): 292-6.
2. McCullough AR, Parekh S, Rathbone J, Del Mar CB, Hoffmann TC. A systematic review of the public's knowledge and beliefs about antibiotic resistance. *The Journal of antimicrobial chemotherapy* 2016; **71**(1): 27-33.
3. Brookes-Howell L, Elwyn G, Hood K, et al. 'The body gets used to them': patients' interpretations of antibiotic resistance and the implications for containment strategies. *Journal of general internal medicine* 2012; **27**(7): 766-72.
4. Butler CC, Hawking MK, Quigley A, McNulty CA. Incidence, severity, help seeking, and management of uncomplicated urinary tract infection: a population-based survey. *The British journal of general practice : the journal of the Royal College of General Practitioners* 2015; **65**(639): e702-7.
5. Wood F, Simpson S, Butler CC. Socially responsible antibiotic choices in primary care: a qualitative study of GPs' decisions to prescribe broad-spectrum and fluoroquinolone antibiotics. *Family practice* 2007; **24**(5): 427-34.
6. de Kraker ME, Davey PG, Grundmann H. Mortality and hospital stay associated with resistant *Staphylococcus aureus* and *Escherichia coli* bacteremia: estimating the burden of antibiotic resistance in Europe. *PLoS medicine* 2011; **8**(10): e1001104.
7. de Kraker ME, Wolkewitz M, Davey PG, et al. Burden of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay associated with bloodstream infections due to *Escherichia coli* resistant to third-generation cephalosporins. *The Journal of antimicrobial chemotherapy* 2011; **66**(2): 398-407.
8. Butler CC, Hillier S, Roberts Z, Dunstan F, Howard A, Palmer S. Antibiotic-resistant infections in primary care are symptomatic for longer and increase workload: outcomes for patients with *E. coli* UTIs. *The British journal of general practice : the journal of the Royal College of General Practitioners* 2006; **56**(530): 686-92.
9. Ashworth M, Latinovic R, Charlton J, Cox K, Rowlands G, Gulliford M. Why has antibiotic prescribing for respiratory illness declined in primary care? A longitudinal study using the General Practice Research Database. *Journal of public health (Oxford, England)* 2004; **26**(3): 268-74.
10. Grijalva CG, Nuorti JP, Griffin MR. Antibiotic prescription rates for acute respiratory tract infections in US ambulatory settings. *Jama* 2009; **302**(7): 758-66.
11. Shapiro DJ, Hicks LA, Pavia AT, Hersh AL. Antibiotic prescribing for adults in ambulatory care in the USA, 2007-09. *The Journal of antimicrobial chemotherapy* 2014; **69**(1): 234-40.
12. MeReC. Urinary tract infection. *MeReC Bulletin* 1995; **6**(8): 1-7.
13. Schappert SM, Rechtsteiner EA. Ambulatory medical care utilization estimates for 2007. *Vital and health statistics Series 13, Data from the National Health Survey* 2011; (169): 1-38.
14. Hippisley-Cox J, Vinogradova Y. Trends in consultation rates in General Practice 1995/1996 to 2008/2009: Analysis of the QResearch® database. Final report to the NHS Information Centre and Department of health. Leeds, UK: The NHS Information Centre for health and social care, 2009.
15. McCormick A, Fleming D, Charlton J. Morbidity statistics from general practice. Fourth National Study 1991-1992. London, 1995.
16. Pallin DJ, Espinola JA, Leung DY, Hooper DC, Camargo CA, Jr. Epidemiology of dermatitis and skin infections in United States physicians' offices, 1993-2005. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2009; **49**(6): 901-7.
17. National Center for Health Statistics (US). Health, United States, 2010: With Special Feature on Death and Dying. Hyattsville MD; 2011.
18. Public Health England. English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) Report 2014. London, 2014.
19. Cals JW, Ament AJ, Hood K, et al. C-reactive protein point of care testing and physician communication skills training for lower respiratory tract infections in general practice: economic

- evaluation of a cluster randomized trial. *Journal of evaluation in clinical practice* 2011; **17**(6): 1059-69.
20. Hollinghurst S, Gorst C, Fahey T, Hay AD. Measuring the financial burden of acute cough in pre-school children: a cost of illness study. *BMC family practice* 2008; **9**: 10.
  21. Rosenberg M. Pharmacoeconomics of treating uncomplicated urinary tract infections. *International journal of antimicrobial agents* 1999; **11**(3-4): 247-51; discussion 61-4.
  22. Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC infectious diseases* 2014; **14**: 13.
  23. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ (Clinical research ed)* 2010; **340**: c2096.
  24. Gill PJ, Roberts NW, Wang KY, Heneghan C. Development of a search filter for identifying studies completed in primary care. *Family practice* 2014; **31**(6): 739-45.
  25. Cochrane Collaboration. Cochrane Risk of Bias Assessment Tools for Randomised Controlled Trials In: Higgins JPT, Green S, eds. in Cochrane handbook for systematic reviews of interventions 2011.
  26. Critical Appraisals Skills Programme (CASP). CASP Checklists. 2013. <http://www.casp-uk.net/> (accessed 22/12/2015).
  27. Barry B, Gehanno P, Blumen M, Boucot I. Clinical outcome of acute otitis media caused by pneumococci with decreased susceptibility to penicillin. *Scandinavian journal of infectious diseases* 1994; **26**(4): 446-52.
  28. Buchanan P, Roos K, Tellier G, Rangaraju M, Leroy B. Bacteriological efficacy of 5-day therapy with telithromycin in acute maxillary sinusitis. *International journal of antimicrobial agents* 2005; **25**(3): 237-46.
  29. Hagberg L, Carbon C, van Rensburg DJ, Fogarty C, Dunbar L, Pullman J. Telithromycin in the treatment of community-acquired pneumonia: a pooled analysis. *Respiratory medicine* 2003; **97**(6): 625-33.
  30. van Rensburg DJ, Fogarty C, Kohno S, Dunbar L, Rangaraju M, Nusrat R. Efficacy of telithromycin in community-acquired pneumonia caused by pneumococci with reduced susceptibility to penicillin and/or erythromycin. *Chemotherapy* 2005; **51**(4): 186-92.
  31. Zhanel GG, Wolter KD, Calciu C, et al. Clinical cure rates in subjects treated with azithromycin for community-acquired respiratory tract infections caused by azithromycin-susceptible or azithromycin-resistant *Streptococcus pneumoniae*: analysis of Phase 3 clinical trial data. *The Journal of antimicrobial chemotherapy* 2014; **69**(10): 2835-40.
  32. McNulty CA, Richards J, Livermore DM, et al. Clinical relevance of laboratory-reported antibiotic resistance in acute uncomplicated urinary tract infection in primary care. *The Journal of antimicrobial chemotherapy* 2006; **58**(5): 1000-8.
  33. Noskin GA, Zembower T, Chmielewski J, Tang P, La Rosa M, Peterson LR. Disappearance of the 'uncomplicated' urinary tract infection - The impact of emerging resistance. *Clinical Drug Investigation* 2001; **21**: 13-20.
  34. Soraas A, Sundsfjord A, Jorgensen SB, Liestol K, Jenum PA. High rate of per oral mecillinam treatment failure in community-acquired urinary tract infections caused by ESBL-producing *Escherichia coli*. *PloS one* 2014; **9**(1): e85889.
  35. Brown PD, Freeman A, Foxman B. Prevalence and predictors of trimethoprim-sulfamethoxazole resistance among uropathogenic *Escherichia coli* isolates in Michigan. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2002; **34**(8): 1061-6.
  36. Raz R, Chazan B, Kennes Y, et al. Empiric use of trimethoprim-sulfamethoxazole (TMP-SMX) in the treatment of women with uncomplicated urinary tract infections, in a geographical area with a

- high prevalence of TMP-SMX-resistant uropathogens. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2002; **34**(9): 1165-9.
37. Gupta K, Hooton TM, Roberts PL, Stamm WE. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. *Archives of internal medicine* 2007; **167**(20): 2207-12.
  38. van Merode T, Nys S, Raets I, Stobberingh E. Acute uncomplicated lower urinary tract infections in general practice: clinical and microbiological cure rates after three- versus five-day treatment with trimethoprim. *The European journal of general practice* 2005; **11**(2): 55-8.
  39. Vallano A, Rodriguez D, Barcelo ME, et al. [Antimicrobial susceptibility of uropathogens and outcome following antibiotic treatment for urinary tract infections in primary health care]. *Enfermedades infecciosas y microbiologia clinica* 2006; **24**(7): 418-25.
  40. O'Doherty B, Dutchman DA, Pettit R, Maroli A. Randomized, double-blind, comparative study of grepafloxacin and amoxycillin in the treatment of patients with community-acquired pneumonia. *The Journal of antimicrobial chemotherapy* 1997; **40 Suppl A**: 73-81.
  41. Yanagihara K, Otsu Y, Ohno H, et al. Clinical characteristics of pneumonia caused by penicillin resistant and sensitive *Streptococcus pneumoniae* in Japan. *Internal medicine (Tokyo, Japan)* 2004; **43**(11): 1029-33.
  42. Dagan R, Abramson O, Leibovitz E, et al. Impaired bacteriologic response to oral cephalosporins in acute otitis media caused by pneumococci with intermediate resistance to penicillin. *The Pediatric infectious disease journal* 1996; **15**(11): 980-5.
  43. Dagan R, Bar-David Y. Double-blind study comparing erythromycin and mupirocin for treatment of impetigo in children: implications of a high prevalence of erythromycin-resistant *Staphylococcus aureus* strains. *Antimicrobial agents and chemotherapy* 1992; **36**(2): 287-90.
  44. Giordano PA, Elston D, Akinlade BK, et al. Cefdinir vs. cephalexin for mild to moderate uncomplicated skin and skin structure infections in adolescents and adults. *Current medical research and opinion* 2006; **22**(12): 2419-28.
  45. Hoberman A, Dagan R, Leibovitz E, et al. Large dosage amoxicillin/clavulanate, compared with azithromycin, for the treatment of bacterial acute otitis media in children. *The Pediatric infectious disease journal* 2005; **24**(6): 525-32.
  46. Quinn J, Ruoff GE, Ziter PS. Efficacy and tolerability of 5-day, once-daily telithromycin compared with 10-day, twice-daily clarithromycin for the treatment of group A beta-hemolytic streptococcal tonsillitis/pharyngitis: a multicenter, randomized, double-blind, parallel-group study. *Clinical therapeutics* 2003; **25**(2): 422-43.
  47. Hoberman A, Paradise JL, Block S, Burch DJ, Jacobs MR, Balanescu MI. Efficacy of amoxicillin/clavulanate for acute otitis media: relation to *Streptococcus pneumoniae* susceptibility. *The Pediatric infectious disease journal* 1996; **15**(10): 955-62.
  48. Seppala H, Nissinen A, Jarvinen H, et al. Resistance to erythromycin in group A streptococci. *The New England journal of medicine* 1992; **326**(5): 292-7.
  49. Cao B, Zhao CJ, Yin YD, et al. High prevalence of macrolide resistance in *Mycoplasma pneumoniae* isolates from adult and adolescent patients with respiratory tract infection in China. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2010; **51**(2): 189-94.
  50. Little P, Merriman R, Turner S, et al. Presentation, pattern, and natural course of severe symptoms, and role of antibiotics and antibiotic resistance among patients presenting with suspected uncomplicated urinary tract infection in primary care: observational study. *BMJ (Clinical research ed)* 2010; **340**: b5633.
  51. Kawai Y, Miyashita N, Yamaguchi T, et al. Clinical efficacy of macrolide antibiotics against genetically determined macrolide-resistant *Mycoplasma pneumoniae* pneumonia in paediatric patients. *Respirology (Carlton, Vic)* 2012; **17**(2): 354-62.
  52. Bryce A, Hay AD, Lane IF, Thornton HV, Wootton M, Costelloe C. Global prevalence of antibiotic resistance in paediatric urinary tract infections caused by *Escherichia coli* and association



with routine use of antibiotics in primary care: systematic review and meta-analysis. *BMJ (Clinical research ed)* 2016; **352**: i939.

53. Gagyor I, Bleidorn J, Kochen MM, Schmiemann G, Wegscheider K, Hummers-Pradier E. Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: randomised controlled trial. *BMJ (Clinical research ed)* 2015; **351**: h6544.

54. Ferry SA, Holm SE, Stenlund H, Lundholm R, Monsen TJ. Clinical and bacteriological outcome of different doses and duration of pivmecillinam compared with placebo therapy of uncomplicated lower urinary tract infection in women: the LUTIW project. *Scandinavian journal of primary health care* 2007; **25**(1): 49-57.

55. Pakhale S, Mulpuru S, Verheij TJ, Kochen MM, Rohde GG, Bjerre LM. Antibiotics for community-acquired pneumonia in adult outpatients. *The Cochrane database of systematic reviews* 2014; **10**: Cd002109.

56. Tahtinen PA, Laine MK, Huovinen P, Jalava J, Ruuskanen O, Ruohola A. A placebo-controlled trial of antimicrobial treatment for acute otitis media. *The New England journal of medicine* 2011; **364**(2): 116-26.

57. Venekamp RP, Sanders SL, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2015; (6).

58. Fahey T, Webb E, Montgomery AA, Heyderman RS. Clinical management of urinary tract infection in women: a prospective cohort study. *Family practice* 2003; **20**(1): 1-6.

59. Little P, Turner S, Rumsby K, Warner G, Moore M. Dipsticks and diagnostic algorithms in urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort, and qualitative study. *Health Technology Assessment* 2009; **13**(19): 96.

60. Farrell DJ, Morrissey I, De Rubeis D, Robbins M, Felmingham D. A UK multicentre study of the antimicrobial susceptibility of bacterial pathogens causing urinary tract infection. *The Journal of infection* 2003; **46**(2): 94-100.

## 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.