Supplementary Appendix

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Supplementary File 1

A. Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R): 1946-16 April 2016

1	exp Drug Resistance, Bacterial/
2	((antibiotic or antimicrob* or anti-biot* or bact*) adj3 resistance).ti,ab.
3	1 or 2
4	(clinic? or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre? or center or office).ab,ti.
5	Emergency service*.ab,ti.
6	(emergenc* adj3 (hospital* or department* or dept* or unit*1 or ward*1)).ab,ti.
7	("accident and emergency" or "accident & emergency" or a&e).ab,ti.
8	4 or 5 or 6 or 7
9	cellulitis/ or exp skin diseases, bacterial/ or soft tissue infections/
10	exp Respiratory Tract Infections/ or exp Otitis Media/
11	exp Urinary Tract Infections/
12	9 or 10 or 11
13	3 and 8 and 12
14	exp animals/ not humans/
15	13 not 14

B. Embase: 1974 to 15 April 2016

1	antibiotic resistance/
2	drug resistance/ and exp antibiotic agent/
3	((antibiot* or antimicrob* or antibiot* or bact*) adj3 resistance).ab,ti.
4	1 or 2 or 3
5	general practice/ or general practitioner/
6	(clinic? or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre? or center or office).ab,ti.
7	emergency ward/
8	Emergency service*.ab,ti.
9	(emergenc* adj3 (hospital* or department* or dept* or unit*1 or ward*1)).ab,ti.
10	("accident and emergency" or "accident & emergency" or a&e).ab,ti.
11	5 or 6 or 7 or 8 or 9 or 10
12	exp bacterial skin disease/
13	soft tissue disease/ or cellulitis/
14	exp respiratory tract infection/ or exp respiratory tract inflammation/ or exp otitis media/
15	exp urinary tract infection/
16	12 or 13 or 14 or 15
17	4 and 11 and 16
18	(exp animals/ or nonhuman/) not human/
19	17 not 18

C. Cochrane Central Register of Controlled Trials: Issue 3 of 12, March 2016

1	MeSH descriptor: [Drug Resistance, Bacterial] explode all trees
2	((antibiot* or antimicrob* or anti-biot* or bact*) near resistance):ti,ab,kw (Word variations have been searched)
3	#1 or #2
4	clinic? or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre? or center or office:ti,ab,kw (Word variations have been searched)
5	Emergency service*:ti,ab,kw (Word variations have been searched)
6	(emergenc* near (hospital* or department* or dept or depts or unit or units or ward or wards)):ti,ab,kw (Word variations have been searched)
7	("accident and emergency" or "accident & emergency" or a&e):ti,ab,kw (Word variations have been searched)
8	#4 or #5 or #6 or #7
9	MeSH descriptor: [Cellulitis] explode all trees
10	MeSH descriptor: [Skin Diseases, Bacterial] explode all trees
11	MeSH descriptor: [Soft Tissue Infections] explode all trees
12	MeSH descriptor: [Respiratory Tract Infections] explode all trees
13	MeSH descriptor: [Urinary Tract Infections] explode all trees
14	(cellulitis or dermatitis or ((skin or cutaneous) near infect*)):ti,ab,kw (Word variations have been searched)
15	(((resp* or chest) near infect*) or "common cold" or sinusitis or rhinosinusitis or rhinitis or "sore throat*" or pharyngitis or nasopharyngitis or tonsillitis or laryngitis or bronchiolitis or bronchitis or pneumonia or "otitis media"):ti,ab,kw (Word variations have been searched)
16	((urin* near infect*) or cystitis):ti,ab,kw (Word variations have been searched)
17	#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
18	#3 and #8 and #17

D. Science Citation Index & Conference Proceedings Citation Index (Web of Science): 1945-15 April 2016

1	TOPIC: (((antibiotic* OR anti-biotic* OR antimicrobial* OR bacterial) NEAR/3 resistance)) OR TITLE: (((antibiotic* OR anti-biotic* OR antimicrobial* OR bacterial) AND resistance))
2	TOPIC: (clinic or clinics or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre OR centres or center or centers or office*) OR TOPIC: (emergency)
3	TOPIC: ((respiratory OR chest) NEAR/2 infection*) OR TOPIC: (URTI OR LRTI)
4	TOPIC: (cough* OR "common cold" OR "sore throat*" OR pharyngitis OR nasopharyngitis OR laryngitis OR tonsilitis OR sinusitis OR rhinosinusitis OR rhinitis) OR TOPIC: ("otitis media") OR TOPIC: (bronchiolitis OR bronchitis OR pneumonia)
5	TOPIC: (cellulitis OR dermatitis OR (skin NEAR/3 infect*))
6	TOPIC: (cystitis OR (urin* NEAR/3 infect*))
7	#6 OR #5 OR #4 OR #3
8	#7 AND #2 AND #1

E. Pubmed (http://www.pubmed.gov): inception to 15 April 2016

15	Search (((((clinic[tw] OR clinics[tw] OR practi*[tw] or primary[tw] or physician*[tw] or refer*[tw] or visit*[tw] or outpatient* or consult* or family[tw] or communit*[tw] or ambulatory[tw] or centre[tw] or centres[tw] or center[tw] or centers[tw] or office[tw] OR emergency[tw])) AND ((((cellulitis[tw] OR skin infection*[tw] OR dermatitis[tw])) OR (urine infection*[tw] OR urinary infection*[tw] OR urinary tract infection*[tw] OR cystitis[tw])) OR (respiratory infetion*[tw] OR chest infection*[tw] OR respiratory tract infection*[tw] OR "common cold"[tw] OR "sore throat"[tw] OR cough[tw] OR pharyngitis[tw] OR nasopharyngitis[tw] OR sinusitis[tw] OR rhinosinusitis[tw] OR rhinitis[tw] OR tonsillitis[tw] OR laryngitis[tw] OR bronchiolitis[tw] OR bronchitis[tw] OR pneumonia[tw]))) AND ((((antibiotic*[ti] OR anti-biotic*[ti] OR antimicrob*[ti] OR bacter*[ti]) AND resistance[ti])) OR ("antibiotic resistance"[tw] OR "anti-biotic resistance"[tw] OR "antimicrobial resistance"[tw] OR "bacterial resistance"[tw]))) AND (pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb])
14	Search pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb]
13	Search (((clinic[tw] OR clinics[tw] OR practi*[tw] or primary[tw] or physician*[tw] or refer*[tw] or visit*[tw] or outpatient* or consult* or family[tw] or communit*[tw] or ambulatory[tw] or centre[tw] or centres[tw] or center[tw] or centers[tw] or office[tw] OR emergency[tw])) AND ((((cellulitis[tw] OR skin infection*[tw] OR dermatitis[tw])) OR (urine infection*[tw] OR urinary infection*[tw] OR urinary tract infection*[tw] OR cystitis[tw])) OR (respiratory infetion*[tw] OR chest infection*[tw] OR respiratory tract infection*[tw] OR "common cold"[tw] OR "sore throat"[tw] OR cough[tw] OR pharyngitis[tw] OR nasopharyngitis[tw] OR sinusitis[tw] OR rhinosinusitis[tw] OR rhinitis[tw] OR tonsillitis[tw] OR laryngitis[tw] OR bronchiolitis[tw] OR bronchitis[tw] OR pneumonia[tw]))) AND ((((antibiotic*[ti] OR anti-biotic*[ti] OR antimicrob*[ti] OR bacter*[ti]) AND resistance[ti])) OR ("antibiotic resistance"[tw] OR "anti-biotic resistance"[tw] OR "antimicrobial resistance"[tw] OR "bacterial resistance"[tw]))
12	Search (((cellulitis[tw] OR skin infection*[tw] OR dermatitis[tw])) OR (urine infection*[tw] OR urinary infection*[tw] OR urinary tract infection*[tw] OR cystitis[tw])) OR (respiratory infetion*[tw] OR chest infection*[tw] OR respiratory tract infection*[tw] OR "common cold"[tw] OR "sore throat"[tw] OR cough[tw] OR pharyngitis[tw] OR nasopharyngitis[tw] OR sinusitis[tw] OR rhinosinusitis[tw] OR rhinitis[tw] OR tonsillitis[tw] OR laryngitis[tw] OR bronchiolitis[tw] OR bronchitis[tw] OR pneumonia[tw])
11	Search respiratory infetion*[tw] OR chest infection*[tw] OR respiratory tract infection*[tw] OR "common cold"[tw] OR "sore throat"[tw] OR cough[tw] OR pharyngitis[tw] OR nasopharyngitis[tw] OR sinusitis[tw] OR rhinosinusitis[tw] OR rhinitis[tw] OR tonsillitis[tw] OR laryngitis[tw] OR bronchiolitis[tw] OR bronchitis[tw] OR pneumonia[tw]
10	Search urine infection*[tw] OR urinary infection*[tw] OR urinary tract infection*[tw] OR cystitis[tw]
9	Search cellulitis[tw] OR skin infection*[tw] OR dermatitis[tw]
8	Search clinic[tw] OR clinics[tw] OR practi*[tw] or primary[tw] or physician*[tw] or refer*[tw] or visit*[tw] or outpatient* or consult* or family[tw] or communit*[tw] or ambulatory[tw] or centre[tw] or centres[tw] or center[tw] or centers[tw] or office[tw] OR emergency[tw]
7	Search (((antibiotic*[ti] OR anti-biotic*[ti] OR antimicrob*[ti] OR bacter*[ti]) AND resistance[ti])) OR ("antibiotic resistance"[tw] OR "anti-biotic resistance"[tw] OR "antimicrobial resistance"[tw] OR "bacterial resistance"[tw])
6	Search "antibiotic resistance"[tw] OR "anti-biotic resistance"[tw] OR "antimicrobial resistance"[tw] OR "bacterial resistance"[tw]
5	Search (antibiotic*[ti] OR anti-biotic*[ti] OR antimicrob*[ti] OR bacter*[ti]) AND resistance[ti]

Supplementary File 2

Additional methodology (search strategy)

Reference lists of included studies and relevant systematic and narrative reviews were screened and a grey literature search was performed. One reviewer (OVH) screened all titles, with a second reviewer (KW) reviewing the list of excluded titles to see if any potentially relevant studies had been excluded. Two reviewers (OVH, KW) then independently screened through titles and abstracts. The full text of articles considered as potentially relevant based on title and abstract were independently screened by two reviewers (OVH, KW). Disagreements were resolved by consensus involving a third reviewer (CCB) where necessary.

Pilot exercise to seek additional data

We also identified studies which collected, but did not publish relevant data, and wrote to the corresponding authors to request these data, with a reminder sent six weeks later. As a pilot exercise, we contacted the authors of 19 studies (18 RCTs published in 2000 or later) that reported patient-level data on laboratory-confirmed potential pathogens and relevant outcomes to ask whether data on antibiotic resistance were also available. The cut-off of 2000 or later was chosen because we felt it was less likely that studies published less recently would have established whether or not infections were antibiotic-resistant. The authors of seven studies replied, of which one provided additional data reporting outcomes separately for antibiotic-resistant vs sensitive infection.[1] Authors that replied were unable to supply data because data were as held at a previous institution (n=1), [2] held by the study sponsor (n=3),[3-5]or the data did not fulfil the inclusion criteria (n=2). [6,7] Based on these results, we did not proceed to seek additional data from similar studies published before 2000.

Data extraction

List of extracted data on the characteristics of included studies: population demographics, country, type of health care setting, study design, year of study, infection type (i.e. respiratory; urinary tract or skin and soft tissue infection), clinical and laboratory criteria for diagnosis of bacterial infection, bacterial species, antibiotic name and class, total number of patients recruited, definition of antibiotic resistance and outcomes.

Where possible, we extracted data on the total number of laboratory-confirmed infections *Escherichia coli* (*E. coli*) UTI; *Streptococcus pneumoniae* (*S. pneumoniae*) RTI; *Staphylococcus aureus* (*S. aureus*) skin and soft tissue infection, the number of these which were defined as being antibiotic-resistant based on the laboratory criteria specified in the study, and the proportion of those patients with these resistant infections that were associated with clinical response failure.

Supplementary File 3

Risk of bias assessment tool and coding criteria for included randomised controlled studies modelled on the Cochrane Collaboration's tool for assessing risk of bias in randomised trials[8]

Item	Low risk of bias	High risk of bias	Unclear risk of bias
BIAS DOMAIN 1: SELECTION BIAS			
Patient selection (random sequence generation)	Not applicable*		
Allocation concealment	Not applicable*		
BIAS DOMAIN 2: PERFORMANCE BIAS			
Blinded participants and researchers	Not applicable*		
BIAS DOMAIN 3: DETECTION BIAS			
Blinded outcome assessment	Measures were adequately described to assess outcome blinded to knowledge of whether the infection was antibiotic-resistant or antibiotic-sensitive.	Detection bias due to knowledge of whether the infection was antibiotic-resistant or antibiotic-sensitive.	Insufficient detail to determine whether outcome assessment was blinded.
BIAS DOMAIN 4: ATTRITION BIAS			
Completeness of outcome data	All patients who entered the trial were adequately accounted for at its conclusion.	There were systematic differences between groups in withdrawals from the study or due to the amount, nature, or handling of incomplete outcome data	Insufficient detail to determine the completeness of outcome data.
BIAS DOMAIN 5: REPORTING BIAS			
Selective reporting	All clinically important outcomes were considered and reported.	There were systematic differences between reported and unreported findings.	Insufficient detail on reported outcomes.
OTHER BIAS	Did authors address any confounders?		
APPLICABILITY	❖ Is there a concern that the included patients do not match the review question? ❖ Is there concern that outcome measure(s) does not match the review question? ❖ Is there concern that the intervention given does not match the review question?		

* As randomisation was not stratified according to antibiotic resistance for RCTs, certain elements of the risk of bias assessment tool for RCTs did not apply to our research question (generation of randomisation sequence, allocation concealment, blinding of treatment allocation).

S3a. Risk of bias assessment of included randomised controlled studies

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and researches (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	Applicability
Barry et al. (1994)[9]	–	–	–	x	✓	✓	?	✓
Buchanan et al. (2005)[10]	–	–	–	x	?	✓	?	✓
Dagan et al (1992)[11]	–	–	–	✓	✓	✓	✓	✓
Dagan et al. (1996)[12]	–	–	–	x	✓	✓	?	✓
Giordano et al. (2006)[13]	–	–	–	x	?	✓	?	✓
Gupta, et al. (2007)[14]	–	–	–	x	?	✓	?	✓
Hagberg, et al. (2003)[15]	–	–	–	x	?	✓	?	✓
Hoberman et al. (2005)[16]	–	–	–	x	✓	✓	?	✓
O'Doherty et al. (1997)[17]	–	–	–	x	✓	✓	?	✓
Quinn et al. (2003)[18]	–	–	–	x	✓	✓	?	✓
van Merode et al. (2005)[19]	–	–	–	x	✓	✓	?	✓
van Rensburg et al.(2005)[20]	–	–	–	x	x	?	?	✓
Zhanel et al. (2014)[21]	–	–	–	x	✓	✓	?	✓

✓ Low risk of bias; x High risk of bias; ? Unclear risk of bias; - Not applicable

Risk of bias assessment tool and coding criteria for included observational studies based on CASP (Critical Appraisal Skills Programme) checklist for cohort studies[22]

Item	Low risk of bias	High risk of bias	Unclear risk of bias
Research question	Research question or objective was stated clearly	Research question or objective was not reported.	Insufficient information to discern objective of the study
Characteristics of study population	The study population was clearly specified and defined.	The study population was not reported.	Insufficient information to discern study population
Representative study population	Cohort of exposed and unexposed drawn for same population or administrative database of patients presenting at same points of care over the same time frame	Exposed and unexposed participants presenting to different points of care or over a different time frame or with very specific bacterial subspecies	Insufficient information to determine whether the study population was representative of the defined population
Measurement of antibiotic exposure	The exposure was accurately measured to minimise bias e.g. secure records, pharmacy records or repeated interview asking about current use/exposure	Exposure was measured following interview at a single point in time; self-reported exposure or individuals who are asked to retrospectively confirm their exposure status.	Insufficient information to determine how exposure information was obtained.
Outcome of interest ("clinical response failure")	The outcome of interest was not present at the start of the study.	The outcome of interest was present at the start of the study	Insufficient information to judge whether participants had the outcome of interest at the start of the study.
Confounding or matching (case control)	Comprehensive matching or adjustment for all plausible prognostic variables.	Matching or adjustment for a minority of plausible prognostic variables, or no matching or adjustment at all.	Insufficient information to determine whether matching or adjustment was performed.
Measurement of outcome	The outcome of accurately measured e.g. independent blind assessment or record linkage;	The outcome was assessed unblinded or self−reported.	Insufficient information given.
Follow-up	No missing outcome data or missing data unlikely to be related to true outcome. There was a sufficient timeframe to see an association between exposure and outcome. Or loss to follow-up after baseline 20% or less?	Missing outcome data likely to be related to true outcome (imbalance in numbers or reasons for missing data across intervention groups). Different length of follow-up periods across study groups.	Insufficient information about follow-up
Blinding of outcome assessment	The outcome assessors were blinded to the exposure status of participants.	There were systematic differences between groups in how outcomes are determined.	Insufficient detail to determine whether outcome assessment was blinded.
Was loss to follow-up after baseline 20% or less?	There were < 20% loss of participants at follow-up	More than 20% loss of participants at follow-up	Insufficient detail to determine.

S3b. Risk of bias assessment of included observational studies

	Brown et al. (2002) [23]	Butler et al. (2006) [1]	Cao et al. (2010) [24]	Hoberman et al. (1996) [25]	Kawai et al. (2012) [26]	Little et al. (2010) [27]	McNulty et al. (2006) [28]	Noskin et al. (2001) [29]	Raz et al. (2002) [30]	Seppala et al. (2002) [31]	Soraas et al. (2014) [32]	Vallano et al. (2006) [33]	Yanagihara et al. (2004) [34]
Was the research question or objective clearly stated?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Was the study population clearly specified and defined?	✓	✓	✓	✓	✓	✓	✓	✓	✓	?	✓	✓	✓
Was the cohort representative of the defined population?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	x	✓	✓
Was the exposure accurately measured to minimise bias?	?	✓	✓	?	?	✓	✓	✓	✓	✓	✓	✓	✓
Was the outcome of interest present at the start of the study?	✓	?	✓	✓	✓	✓	✓	✓	✓	?	✓	?	?
Did the authors attempt to identify all important confounding factors or take account of these in in the design and/or analysis?	✓	✓	x	x	✓	✓	✓	x	x	x	✓	x	x
Was the outcome accurately measured to minimise bias?	✓	✓	✓	✓	?	?	?	x	?	x	✓	?	✓
Was the follow up of cohorts adequate?	✓	✓	✓	✓	x	✓	✓	?	✓	-	✓	✓	-
Were the outcome assessors blinded to the exposure status of participants?	✓	✓	?	x	x	x	?	x	x	x	?	?	x
Was loss to follow-up after baseline 20% or less?	✓	?	?	✓	x	?	?	?	?	-	?	✓	-

✓Low risk of bias; x High risk of bias; ? Unclear risk of bias; - Not applicable

Supplementary File 4

Table 4a. Diagnostic approach of significant bacterial infection in *E. coli* urinary tract infections

Study	Clinical criteria for diagnosis of urinary tract infections	Laboratory criteria for diagnosis of significant bacterial infection	Antimicrobial susceptibility testing	Mixed infections
Brown et al. 2002 [23]	SD	$\geq 10^3$ CFU/ ml	NR	NR
Butler et al. 2006 [1]	Clinically suspected UTI	$> 10^5$ CFU/ ml	BSAC‡	Mixed infections were included if *E. coli* (71%) was reported
Gupta et al. 2007 [14]	S	$\geq 10^2$ CFU/mL of uropathogen	CLSI/NCCLS*	*E. coli* alone (82%) or in combination with another uropathogen (4%).
van Merode et al. 2005 [19]	S	NR	SWAB standard†	*E. coli* (65%) Mixed uropathogens
McNulty et al. 2006 [28]	SD[§]	$\geq 10^4$ CFU/mL of all organisms	BSAC‡	Pure coliform (89%) Mixed uropathogens
Noskin et al. 2001 [29]	SD	$\geq 10^4$cfu/ml) with no more than 2 bacteria	NCCLS*	*E. coli* alone (74%) or in combination with another uropathogen (4%)
Raz et al. 2002 [30]	SD	NR	NCCLS*	*E. coli* (78%) Mixed uropathogens
Soraas et al. 2014 [32]	NR	$>10^4$ CFU/ml of uropathogen[a]	EUCAST±	No, ESBL-*E. coli* non-ESBL-*E. coli* only
Vallano et al. 2006 [33]	NR	NR	NCCLS*	*E. coli* (75%) Mixed uropathogens

S: symptoms only; SD: symptoms and urine dipstick; NR: not reported; * Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards; †SWAB.nl (Stichting Werkgroep Antibioticabeleid); [§] Over the first 18 months of the study, clinicians used urine dipstick; ‡BSAC: British Society for Antimicrobial Chemotherapy; a: ESBL *E.coli* ; ± EUCAST: The European Committee on Antimicrobial Susceptibility Testing

Table 4b. Diagnostic approach of significant bacterial infection in community-acquired pneumonia (*S. pneumoniae*)

Study	Clinical criteria for diagnosis of community-acquired pneumonia	Laboratory criteria for diagnosis of significant bacterial infection	Antimicrobial susceptibility testing
Hagberg et al. 2003 [15]	S, R	L	NCCLS
O'Doherty et al. 1997 [17]	S, R	L	NCCLS
van Rensburg et al. 2005 [20]	S	L	NCCLS
Yanagihara et al. 2004 [34]	S, R	L	NR
Zhanel et al. 2014 [21]	NR	NR	CLSI/NCCLS*

S: Symptoms; R: radiographic evidence; L: peripheral blood (WCC) count and/or Gram-positive diplococci; NCCLS: National Committee for Clinical Laboratory Standards; NR: not reported; * Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards.

Table 4c. Diagnostic approach of significant bacterial infection in acute otitis media (*S. pneumoniae*)

Study	**Clinical criteria for diagnosis of acute otitis media**	**Laboratory criteria for diagnosis of significant bacterial infection**	**Antimicrobial susceptibility testing**
Barry et al. 1994 [9]	S, E, T	Culture	"Bacterial isolates were identified by standard methods"
Dagan et al. 1996 [12]	S, E, T	Culture	NCCLS
Hoberman et al. 1996 [25]	S,E,T	Culture	NCCLS
Hoberman et al. 2005 [16]	S, E, T	Culture	NCCLS
Zhanel et al. 2014 [21]	NR	NR	CLSI/NCCLS*

S: Symptoms; E: Examination; T: tympanocentesis or ear swab; NR: not reported; NCCLS: National Committee for Clinical Laboratory Standards; * Clinical and Laboratory Standards Institute (formerly the National Committee for Clinical Laboratory Standards.

Supplementary File 5

Table 5a. Unadjusted odds ratios (OR) for clinical response failure between antibiotic-resistant and antibiotic-sensitive infections (Group A ß-haemolytic streptococcus sore throat)

Study	*n* [a]	Treatment antibiotic arm	No. of failures/total resistant group[c]	No. of failures/total sensitive group[d]	Unadjusted OR [95% CI]
Quinn et al. 2003 [18]	187 isolates	Telithromycin	1/5	10/145	3·38 [0·34–33·11]
Quinn et al. 2003 [18]	173 isolates	Clarithromycin	2/4	10/131	12·10 [1·54–95·25]
Seppala et al. 2002 [31]	196	Erythromycin	9/19	1/26	22·50 [2·51–201·50]
Seppala et al. 2002 [31]	333	Penicillin	5/57[b]	6/171[b]	6·93 [1·02–47·23]

a: Total number of patients with GABHS unless indicated. b: numbers based on erythromycin-susceptibility. c: Total number of participants with antibiotic-resistant infections. d: Total number of participants with antibiotic-sensitive infections. OR: odds ratio. CI: confidence interval

Table 5b. Unadjusted odds ratios (OR) for clinical response failure between antibiotic-resistant and antibiotic-sensitive infections (*S. pneumoniae* acute maxillary sinusitis)

Study	*n* [a]	Treatment antibiotic arm	No. of failures/total resistant group[c]	No. of failures/total sensitive group[d]	Unadjusted OR [95% CI]
Buchanan et al. 2005 [10,b]	126	Telithromycin	0/1	9/77	2·40 [0·09–63·35]
Zhanel et al. 2014 [21]	57	Azithromycin	2/19	0/38	11·00 [0·50–241·38]

a: Total number of patients with *S.pneumoniae* b: Buchanan et al. also report outcomes for *H. influenzae* .
c: Total number of participants with antibiotic-resistant infections. d: Total number of participants with antibiotic-sensitive infections. OR: odds ratio. CI: confidence interval

Table 5c. Unadjusted odds ratios (OR) for clinical response failure between antibiotic-resistant and antibiotic-sensitive infections (*S. aureus* skin infection)

Study	*n* [a]	Treatment antibiotic arm	No. of failures/total resistant group[e]	No. of failures/total sensitive group[f]	Unadjusted OR [95% CI]
Dagan et al. 1992 [11,b]	43	Erythromycin	8/17	2/26	10·67 [1·89–60.08]
Dagan et al. 1992 [11,b]	46	Mupirocin	0/10	1/36	1·13 [0.04–29.77]
Giordano et al. 2006 [13.c]	78	Cefdinir	3/38[d]	3/40	1·06 [0·20–5.59]
Giordano et al.	73	Cephalexin	4/41[d]	3/29	1·05 [0.22–5.04]

2006 [13,c]					

a: Total number of evaluable patients with *S. aureus* where resistance and outcome data available. b:impetigo; c:Uncomplicated skin and skin structure infections (USSSI) such as impetigo, erysipelas, cellulitis, folliculitis, furunculosis, wound infection, and simple abscesses; d: isolates of *S. aureus* were tested for susceptibility to oxacillin. e: Total number of participants with antibiotic resistant infections. f: Total number of participants with antibiotic-sensitive infections. OR: odds ratio. CI: confidence interval

Supplementary File 6

Table 6a. Unadjusted odds ratios (OR) for "patient re-consultation" between antibiotic-resistant and antibiotic-sensitive urine infections

Study	Total [a]	Follow-up period	Infection type	Treatment antibiotic	Unadjusted OR [95% CI]	Re-consultations /total resistant group[b]	Re-consultations /total sensitive group[c]
Brown et al. 2002 [23]	104	14 days	*E. coli*	TMP-SMX*	18·89 [4·93–72·43]	15/33	3/71
Butler et al. 2006 [1]	862	30 days	*E. coli*	Empiric**	2·75 [1·81–4·18]	55/103	223/759
McNulty et al. 2006 [28]	317	30 days	*E. coli*	Trimethoprim	4·72 [2·39–9·31]	20/44	41/273

a: Total number of participants where resistance and outcomes data available. b: Total number of participants with antibiotic-resistant infections. c: Total number of participants with antibiotic-sensitive infection. *TMP-SMX Trimethoprim-sulfamethoxazole. ** resistant to prescribed antibiotic. OR: odds ratio. CI: confidence interval

Table 6b. Unadjusted odds ratios (OR) for "further antibiotic prescription" between antibiotic-resistant and antibiotic-sensitive infections

Study	Total [a]	Time period	Infection type	Treatment antibiotic	Unadjusted OR [95% CI]	Further antibiotic prescriptions /total resistant group[b]	Further antibiotic prescriptions /total sensitive group[c]
Cao et al. 2010 [24]	59	48-72 hours	*M. pneumoniae* CAP	Empiric**	1·67 [0·52–5·34]	20/42	6/17
Butler et al. 2006 [1]	816	30 days	*E. coli* UTI	Empiric*	2·30 [1·69–3·13]	141/391	92/467
Kawai et al. 2012 [26]	30	48-72 hours	*M. pneumoniae* CAP	Macrolides	100·43 [4·69–2,152]	18/21	0/9
Soraas et al. 2014 [32]	343	14 days	ESBL-*E. coli* UTI	Mecillinam	3·98 [1·70–6·73]	43/81	58/262

a: Total number of participants where resistance and outcomes data available. b: Total number of participants with antibiotic-resistant infections. c: Total number of participants with antibiotic-sensitive infections.
** resistant to erythromycin. *resistant to prescribed antibiotic. OR: odds ratio. CI: confidence interval

Supplementary File 7

Table 7. Symptom duration between antibiotic-resistant and antibiotic-sensitive infections

Study	Total (evaluable)	Time period	Infection type	Treatment antibiotic	Symptom duration (days) in resistant group, mean (SD) or median (IQR)	Symptom duration (days) in sensitive group, mean (SD) or median (IQR)	P-value
Cao et al. 2010 [24]	59	48-72h	*M. pneumoniae* CAP	Empiric**	10 mean 8-14)	8 mean (6-12)	0.11
Butler et al. 2006 [1]	816	30 days	*E. coli* UTI	Empiric*	7 median (3-17)	5 median (3-12)	0.12
Little et al. 2010 [27]	264	14 days	*E. coli* UTI	Empiric*	4·73 mean (2.91)	3·32 mean (2·54)	0.001[§]
McNulty et al. 2006 [28]	207	10 days	*E. coli* UTI	Trimethoprim	7 median (6.9)[†]	4 median (4.6) [†]	0.0002

SD: standard deviation; IQR: interquartile range; ** resistant to erythromycin; * resistant to one or more antibiotics; [§] multivariate analysis (age leaving full time education, marital status, number of medical problems, previous duration of symptoms, and perception of doctor communication and health anxiety (Whitely index).
[†]single value rather than range reported

Supplementary File 8

Table 8. Symptom severity* between antibiotic-resistant and antibiotic-sensitive urine infections

Study	N total (evaluable)	Time elapsed	Infection type	Treatment antibiotic	Resistant group	Sensitive group
Little 2010[27]	264	Days 2-4	*E. coli* UTI	Not specified	2·01 (mean)† SD [0·89]	1·47 (mean) SD [0·88]

*Severity of symptoms in "frequency group" at days 2 to 4 (increased day frequency, increased night frequency, and urgency and dysuria); Severity graded grading for up to 14 days: 0 (no symptoms), 1 (very slight problem), 2 (slight problem), 3 (moderately bad problem), 4 (bad problem), 5 (very bad problem), or 6 (as bad as it could be). †Adjusted multivariate analysis

References

1. 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.
2. Bjerrum L, Gahrn-Hansen B, Grinsted P. Pivmecillinam versus sulfamethizole for short-term treatment of uncomplicated acute cystitis in general practice: a randomized controlled trial. *Scandinavian journal of primary health care* 2009; **27**(1): 6-11.
3. Arredondo-Garcia JL, Figueroa-Damian R, Rosas A, et al. Comparison of short-term treatment regimen of ciprofloxacin versus long-term treatment regimens of trimethoprim/sulfamethoxazole or norfloxacin for uncomplicated lower urinary tract infections: a randomized, multicentre, open-label, prospective study. *The Journal of antimicrobial chemotherapy* 2004; **54**(4): 840-3.
4. Desrosiers M, Ferguson B, Klossek JM, Drugeon H, Mosges R. Clinical efficacy and time to symptom resolution of 5-day telithromycin versus 10-day amoxicillin-clavulanate in the treatment of acute bacterial sinusitis. *Current medical research and opinion* 2008; **24**(6): 1691-702.
5. Tellier G, Niederman MS, Nusrat R, Patel M, Lavin B. Clinical and bacteriological efficacy and safety of 5 and 7 day regimens of telithromycin once daily compared with a 10 day regimen of clarithromycin twice daily in patients with mild to moderate community-acquired pneumonia. *The Journal of antimicrobial chemotherapy* 2004; **54**(2): 515-23.
6. Monsen TJ, Holm SE, Ferry BM, Ferry SA. Mecillinam resistance and outcome of pivmecillinam treatment in uncomplicated lower urinary tract infection in women. *APMIS : acta pathologica, microbiologica, et immunologica Scandinavica* 2014; **122**(4): 317-23.
7. Syrogiannopoulos GA, Bozdogan B, Grivea IN, et al. Two dosages of clarithromycin for five days, amoxicillin/clavulanate for five days or penicillin V for ten days in acute group A streptococcal tonsillopharyngitis. *The Pediatric infectious disease journal* 2004; **23**(9): 857-65.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. 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.
14. 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.
15. 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.
16. 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.

17. 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.
18. 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.
19. 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.
20. 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.
21. 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.
22. Critical Appraisals Skills Programme (CASP). CASP Checklists. 2013. http://www.casp-uk.net/ (accessed 22/12/2015.
23. 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.
24. 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.
25. 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.
26. 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.
27. 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.
28. 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.
29. 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.
30. 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.
31. 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.
32. 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.
33. 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.

34. 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.