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Trends in the methodological quality of published randomized controlled trials on antibacterial agents

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Randomized controlled trials (RCTs) are believed to be one of the best methods of clinical research because they can minimize systematic errors of various types.
- Temporal trends in the various aspects of RCTs have been studied in several medical fields (e.g. nephrology, hepatology, oncology).
- However, there is lack of data regarding the trends in the methodological quality of RCTs focusing on antimicrobial agents.

WHAT THIS STUDY ADDS

- Several important methodological aspects of RCTs on antibacterial agents, such as description of randomization, double blinding, description of the blinding and allocation concealment, have not improved during the last 30 years.

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AIM

To investigate the trends of the methodological quality of randomized controlled trials (RCTs) of antimicrobial agents published during the last 30 years.

METHODS

We randomly selected from the Cochrane Central Register of Controlled Trials database 70 RCTs of antibacterial agents that were published during a 30-year study period (1975–2005); specifically, we randomly selected 10 RCTs published during each of the following years: 1975, 1980, 1985, 1990, 1995, 2000 and 2005. In each of the selected RCTs, we searched for information on various methodological aspects and graded the methodological quality of the RCTs to evaluate trends for possible improvement.

RESULTS

No improvement was noted in most of the analysed methodological aspects of the RCTs during the 30-year study period. Description of randomization, double blinding, description of the blinding, and allocation concealment were rather scarce among the evaluated RCTs, without observing a trend for improvement during the study period. We noted improvement in reporting power of the study calculations, baseline data as well as in reporting the presence or not of statistical significance and the statistical cut-off of significance. In only 1/70 RCTs were all 13 of the examined methodological quality aspects met and in one more RCT 12 of them were met.

CONCLUSIONS

We did not observe considerable improvement in the quality of the reporting and methodology of RCTs on antibacterial agents during the last 30 years. The methodological quality aspects that need most improvement are those that help safeguard against various types of biases.

Introduction

Randomized controlled trials (RCTs) are believed to be one of the best methods of clinical research because they can minimize systematic errors of various types. The British Medical Research Council conducted the first RCT (testing streptomycin for the treatment of tuberculosis) in 1948 [1]. Since then, many researchers have used the RCT methodology in all medical fields. Thus, the scientific community has a lot of interest in performing high-quality RCTs that will provide answers to important clinical questions.

Temporal trends in the various aspects of RCTs have been studied in several medical fields (e.g. nephrology [2], hepatology [3], oncology [4], paediatric [5], cardiothoracic surgery [6] and clinical pharmacology [7]). However, there is lack of data regarding the trends in the methodological quality of RCTs focusing on antimicrobial agents. Hence, the objective of this study was to investigate the possible changes in the reporting and methodological quality of RCTs, focusing on studies of antibacterial drugs that were published from 1975 until 2005.

Methods

Search strategy

Using the online Cochrane Central Register of Controlled Trials database (http://www.mrw.interscience.wiley.com/cochrane/cochrane_central_articles_fs.html, accessed on 3 November 2006), we searched for articles that referred to antibacterial drugs and were published in the years 1975, 1980, 1985, 1990, 1995, 2000 and 2005. The keywords used in our literature searches were: antibacterial, antimicrobial, sulfonamides, aminoglycoside, chloramphenicol, polymyxin, rifampin, lactams, penicillin, cephalosporin, carbapenem, monobactam, macrolide, tetracycline, glycopeptide, lincosamide, quinolone, fluoroquinolone, oxazolidinone and imidazole.

Selection of RCTs

The initially identified articles were put in an order as they were retrieved from our literature searches (for 1975 from 1 to 180, for 1980 from 1 to 311, for 1985 from 1 to 502, for 1990 from 1 to 636, for 1995 from 1 to 794, for 2000 from 1 to 823, and for 2005 from 1 to 596). Then, using an internet resource for derivation of random numbers (research randomizer; http://www.Randomizer.org), we randomly selected 20 articles for each year of our study (1975, 1980, 1985, 1990, 1995, 2000 and 2005), with the intent to review in detail the first 10 studies from each year that qualified for inclusion in our study, e.g. were indeed RCTs focusing on antibacterial agents. Specifically, from the retrieved articles, eligible for further evaluation of the full text and inclusion in our study were those that studied the comparative efficacy and/or safety of antibacterial treatment and included in their title and/or abstract the words randomization, randomly, or random. Articles that referred to pharmacokinetics, or dentistry or veterinary medicine, reported on local antimicrobial therapies, antimicrobial agents other than antibacterials (e.g. antifungal, antiviral or antiparasitic) were excluded from further evaluation, as were non-English language articles.

Evaluation of RCTs

In order to evaluate the methodological quality of each of the 70 RCTS reviewed (10 per selected year), predefined criteria were used. Specifically, we used a modified version of Jadad (http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat3.section.3039, accessed on 3 November 2006) criteria of evaluating the methodological quality of RCTs as well additional criteria, and we created a point grading system. One of the Jadad criteria was not used, specifically whether the study was described as randomized, because all of the articles included in our analysis were characterized as randomized in their title or abstract, based on our study design. Two of the original Jadad criteria of evaluating the methodological quality of RCTs were used: double blinding, and description of withdrawals and dropouts. In addition, we modified two criteria of the Jadad score (quality of the blinding and quality of the randomization) in order to focus more on the reporting of methodological issues of the RCTs.

Besides these four criteria from the Jadad score, nine additional criteria were used in the evaluation of the methodological quality of the reviewed RCTs. Six of them were selected from the Consolidated Standards of Reporting Trials [CONSORT (http://www.consort-statement.org, accessed on 3 November 2006)]. They mainly focus on the quality of the methodology of RCTs and are about sample size and power of the study, interventions, outcomes, allocation concealment, baseline data and adverse events. We did not use from the CONSORT statement some other criteria of quality of reporting of RCTs, specifically information regarding the scientific background and explanation of rationale, objectives, sequence generation, implementation, statistical methods, participant flow, recruitment, numbers analysed, outcomes and estimation, ancillary analyses, interpretation, generalizability, and overall evidence. Finally, three more criteria in the evaluation of the methodological quality of the reviewed RCTs were used, specifically: adequate reporting of eligibility, statistical significance, and conflicts of interest and funding of the research.

Overall, we aimed at using the most essential and crucial criteria for the quality of studies on antimicrobial agents. The choice was made after consensus of all authors (M.E.F., E.I.P., I.A.B.). In addition, we tried to use clearly defined criteria so that there would be no confusion when evaluating their presence in papers. Two reviewers independently assessed the 70 RCTs. Any disagreement was resolved by consensus.

Definitions of methodological quality criteria

Description of randomization Defines the method used to select the random numbers of allocation. One point was added if it was reported in detail, e.g. 'randomization sequence was generated by a computerized system'. Zero points were added if no data were provided regarding details of randomization.

Double blind method If the authors reported that the study was double blind (in which both the participant and the investigator are unaware of the regimen assigned to each participant), one point was added, if not 0 points.

Description of blinding Specifies the method used for the assurance of blinding. One point was added if the blinding was reported in detail, e.g. 'identical yellow tablets were used in both groups'. Zero points were added if there were no data provided regarding details of the blinding.

Description of withdrawals and drop-outs Defines the number of participants and the specific reason that led them to withdrawal and drop-out from the study. If both were reported in detail, one point was added, and if it was not, 0 points.

Eligibility of the study group Specifies criteria that qualify persons to enter the study. One point was added if the inclusion and exclusion criteria were reported in detail, and 0 points if they were not.

Interventions Defines specific details of the study drugs dosing, including the route of administration and the duration of therapy. One point was added if the description was adequate, and 0 points if not.

Outcomes One point was added if primary and secondary outcomes were clearly defined in the introduction and in the methods section of the article; if not, 0 points were added.

Allocation concealment [8] Defines the method of maintaining concealment of participant assignment until at least the point of treatment allocation. One point was added if the allocation concealment was mentioned and the description was adequate, e.g. centralized or pharmacy-controlled allocation with prenumbered/sequentially numbered, sealed, opaque envelopes. Zero points were added if the approaches to allocation concealment were not reported.

Baseline data One point was added when demographic characteristics, risk factors, or underlying diseases for each group were described and 0 points when no data were provided.

Adverse events One point was added if adverse events or side-effects were reported in each group and 0 points if they were not.

Power of the study – sample size calculation The description of the mathematical approach for calculating the statistical power of the study or the number of participants needed in each study group, in order to have sufficient statistical power (e.g. = 80%) to answer the research question. One point was added when there was power of the study calculation or presentation of the sample size calculation.

Statistical significance One point was added if in the results section of the article, details regarding the presence or not of statistical significance, as well as the exact result of the statistical testing (expressed as *P*-value or a confidence interval, for example) were reported. In case there were no data provided in the results section or there was only a report of the statistical methods used, in the methods section of the article, 0 points were added.

Conflicts of interest and funding of the research If the authors reported that the study was sponsored (or non-sponsored), 1 point was added; 0 points were added if there was lack of information regarding the financial support of the clinical trial.

Results

The 70 studies reviewed in our paper presented some degree of variability regarding the country of origin, the infections and therapies studies and, finally, their methodological characteristics. Most of the RCTs originated from the USA [23/70 (32.9%)], USA with other countries [5/70 (7.1%)], UK [6/70 (8.6%)] and UK with other countries [4/70 (5.7%)]. Only one of the 70 reviewed and analysed RCTs (originating from the USA and published in 1995) met all of the methodological quality criteria evaluated in this study.

A considerable variety of infections was studied in the reviewed RCTs, including respiratory tract, abdominal tract and urinary tract infections as well as infections caused by specific organisms such as tuberculosis, typhoid fever, syphilis, gonorrhea, as well as *Helicobacter pylori* infection. Although some small trends were noted (e.g. *H. pylori* infection was studied in more recent studies), there was no obvious bias regarding the types of infections studied over the years. Similarly, although, as expected, β-lactams and macrolides were the most commonly studied antibiotics, there was no clear clustering of a specific antibiotic within any of the study periods.

In Table 1 we present the summary data regarding the 13 evaluated methodological quality criteria for the 70 reviewed RCTs (10 in each of the 7 years studied). Overall, there were only four disagreements between the two reviewers regarding the methodological evaluation, which

Table 1

Methodological quality criteria evaluated of randomly selected randomized controlled trials (RCTs) published during the 30-year study period*

	1975 (*n* = 10)	1980 (*n* = 10)	1985 (*n* = 10)	1990 (*n* = 10)	1995 (*n* = 10)	2000 (*n* = 10)	2005 (*n* = 10)
Jadad criteria (modified)							
Description of randomization	5	5	6	3	4	2	3
Double blinding	5	2	3	4	3	3	3
Description of blinding†	2	2	2	3	3	3	2
Description of withdrawals and drop-outs	7	4	5	3	8	8	7
Additional criteria							
Eligibility	10	10	10	10	10	10	10
Interventions	10	10	10	10	10	10	10
Outcomes	10	10	10	10	10	10	10
Allocation concealment	4	1	3	2	5	2	2
Baseline data	7	9	8	10	10	10	10
Adverse events	9	8	7	8	7	10	7
Power of the study	0	0	0	1	3	4	4
Statistical significance	5	6	9	7	10	10	8
Conflicts of interest and funding of the research	9	5	4	6	5	8	9

*Numbers in the columns denote the result of the methodological quality of the evaluated RCTs based on the grading system we used and explained in Methods. †The numbers regarding quality of blinding should be interpreted in relation to the numbers of trials which were double blind [e.g. in 1975 2/5 (40%) of maximum points for double blinding were given, vs. 2/2 in 1980 (100%)].

were solved in a consensus meeting. No improvement was noted in most of the methodological quality criteria (from 1975 to 2005). The proportion of the reviewed RCTs with good reporting of randomization ranged from two in 10 to six in 10 RCTs in different years studied, with double blinding from two in 10 to five in 10 RCTs, good reporting of the blinding from two in five to three in three RCTs, and with allocation concealment from one in 10 to five in 10 RCTs.

An improvement was noted during the 30-year study period regarding three methodological quality criteria of the studied RCTs; specifically, reporting power of the study (from 0 in 10 RCTs to four in 10 RCTs in successive studied years during the study period), details regarding the presence or not of statistical significance and the statistical cut-off of significance (from five in 10 RCTs to 10 in 10 RCTs in successive studied years during the study period), and description of baseline data (from seven in 10 to 10 in 10 RCTs during the study period). All reviewed RCTs during the 30-year period reported details regarding eligibility of the study groups, interventions and outcomes. Description of withdrawals and drop-outs ranged from three in 10 to eight in 10 RCTs, whereas it ranged from seven in 10 to 10 in 10 RCTs for adverse events and from four in 10 to nine in 10 RCTs for reporting conflicts of interest and funding of the research.

Discussion

The most noteworthy finding of our study is that several methodological quality and quality of reporting aspects of RCTs on antibacterial agents have not improved during the 30-year study period (1975–2005). Specifically, no improvement was noted in four important methodological quality criteria: description of randomization, double blinding, description of blinding, and allocation concealment. It should be emphasized that these methodological aspects of RCTs are of major significance because they ensure minimization of various sources of bias; thus the finding that RCTs have not improved regarding these characteristics during the last years cannot be ignored.

In addition, inadequate improvement was noted regarding another important methodological quality criterion: description of withdrawals. Furthermore, not all evaluated RCTs reported adverse events and conflicts of interest/source of funding. Adequate reporting of information regarding these three methodological criteria is also crucial for understanding important aspects of RCTs and interpreting the research findings. An interesting observation was that there was correlation between reporting adverse events and description of withdrawals or drop-outs, a probably expected finding (data not shown).

Improvement during the 30-year study period was noted in only three methodological quality criteria: reporting of the power of the study, reporting baseline data and reporting the presence or not of statistical significance and the statistical cut-off of significance. Specifically, fewer RCTs during the early years of the study reported information regarding baseline characteristics of the enrollees and, when this happened, they usually reported information for one or two characteristics (mainly sex and age), whereas in articles of RCTs performed later long tables, including up to 20 baseline characteristics of enrollees, were common. Such characteristics frequently included demographic data, risk factors, underlying morbidity and socioeconomic status. This finding may indicate a more extensive and detailed collection of patient baseline data rather than simply a better reporting of them in research papers. It is unknown to what degree the noted improvement in base-

line data reporting is the result of the development of electronic research databases that allow easier handling of extensive datasets.

Regarding reporting the presence or not of statistical significance and the statistical cut-off of significance, an improvement was also observed during the study period: 28/30 *vs.* 27/40 articles during 1995–2005 and 1975–1990, respectively, reported details regarding the statistical analysis. This finding depicts the fact that simply reporting results without mentioning their statistical significance does not offer substantial evidence in current medical research and practice. Similarly, details on calculations of the power of the study/study sample size have been more commonly reported in recent years. Of note, they were reported in only 13 of the reviewed 70 studies and in none prior to 1990.

Adequate description was noted during the whole 30-year study period regarding three methodological quality criteria: eligibility of the study group, interventions, and outcomes. However, this is not surprising, since these characteristics are considered basic information of an RCT and, thus, reporting details regarding them does not mean that an RCT is necessarily of high quality. In this context, many medical journals and especially the so-called core journals require specific check lists with characteristics that should be included (or reported) in any study that is submitted for publication to them, in an attempt to help authors improve the quality and the quality of reporting of RCTs.

Our analysis has several limitations. First, it should be emphasized that the quality of reporting methodological aspects of research does not fully match the quality of the performed research itself. However, there is definitely significant overlapping between these two ideas. Although several factors can affect the quality of reporting of research, it is clear that for most of the methodological parameters examined in this paper, reporting them by the authors equals having performed them and vice versa. It is unclear why somebody would design an RCT on antibacterial agents and collect relevant data, but nevertheless would not report, for example, eligibility criteria, interventions, outcomes, baseline data, adverse events and withdrawals. However, it should be noted that there might be rare occasions when, due to paper length restrictions or decreased requirements from a journal, this could occur.

A second limitation is that someone could have selected another set of methodological quality criteria to evaluate. However, we selected criteria that are frequently used by the scientific community as characteristics that are important in deriving safe conclusions from an RCT and research findings with applicability in clinical practice. Third, we acknowledge that another grading system of the various methodological quality criteria that we used to evaluate the reviewed RCTs could be supported as more practical and/or valid. We acknowledge that we did not test the reproducibility of the point grading system used in our analysis. Fourth, we included in our analysis 70 RCTs. It should be acknowledged that a larger sample size would allow safer conclusions, but we believe that the number of evaluated RCTs is probably sufficient to support the qualitative statement that more attention should be paid to various methodological quality aspects of RCTs in the field of antimicrobial agents. Fifth, we included only RCTs focusing on antibacterial agents without examining RCTs studying other antimicrobial agents. However, there is no reason to believe that RCTs on antiviral, antifungal and antiparasitic agents would have more methodological quality compared with those focusing on antibacterial agents and performed during the same period. Sixth, we classified the reviewed RCTs based on the year of publication without taking into account the year of initiation of the study.

Conclusion

In summary, the findings of our mainly descriptive study suggest that several important methodological and reporting aspects of RCTs on antibacterial agents have not improved during the last 30 years. We believe that efforts to increase the methodological quality of RCTs, at least in the studied field of clinical research on antibacterial agents, are warranted.

Appendix

Grading of the various methodological quality criteria of the evaluated randomized controlled trials

Origin/reference number (Appendix) Reference number (in the Appendix)	Infection/ Antimicrobials tested	Description of randomization	Double blinding	Description of blinding	Description of withdrawals and drop-outs	Eligibility	Interventions	Outcomes	Allocation concealment	Baseline data	Adverse events	Power of the study	Statistical significance	Conflicts of interest and funding
1975														
USA[1]	Ear, nose, throat/penicillin *vs.* trimethoprim-sulfomethoxazole	0	1	0	1	1	1	1	0	0	1	0	0	0
Belgium[2]	Bacteriuria/sisomicin *vs.* gentamicin	1	0	0	1	1	1	1	1	1	1	0	1	1
UK-Hong Kong[3]	Pulmonary tuberculosis/rifampicin plus ethambutol	0	0	0	1	1	1	1	0	0	1	0	1	1
UK-Singapore[4]	Pulmonary tuberculosis/rifampicin plus isoniazid	0	0	0	1	1	1	1	0	1	1	0	1	1
South Africa[5]	Typhoid fever/amoxicillin *vs.* chloramphenicol	0	0	0	0	1	1	1	1	1	1	0	0	1
West Indies[6]	Gonorrhoea/1 *vs.* 2 dose trimethoprim-sulfamethoxazole	0	1	0	0	1	1	1	0	1	0	0	0	1
USA[7]	Intraperitoneal anaerobic bacteria/clindamycin *vs.* cephalothin	1	0	0	1	1	A1	1	0	0	1	0	0	1
USA[8]	Prophylaxis in gynaecology/cephalexin *vs.* placebo	1	1	0	1	1	1	1	1	1	1	0	0	1
USA[9]	Prophylaxis in vaginal operation/active drug *vs.* placebo	1	1	1	1	1	1	1	1	1	1	0	1	1
USA[10]	Diarrhoeal disease in apache children/oral colistin sulphate *vs.* placebo	1	1	1	0	1	1	1	0	1	1	0	1	1
1980														
USA[11]	Typhoid fever/amoxicillin *vs.* ampicillin	0	0	0	0	1	1	1	0	1	1	0	0	0
UK[12]	Urinary tract infections after lower urinary tract surgery/cephradine 500 mg *vs.* cephradine 1 g *vs.* cotrimoxazole *vs.* no treatment	0	0	0	1	1	1	1	0	0	1	0	0	1
USA[13]	Acute pulmonary exacerbations in cystic fibrosis/tobramycin *vs.* placebo	1	1	1	1	1	1	1	0	1	1	0	1	0

Appendix

Continued

Origin/reference number (Appendix) Reference number (in the Appendix)	Infection/ Antimicrobials tested	Description of randomization	Double blinding	Description of blinding	Description of withdrawals and drop-outs	Eligibility	Interventions	Outcomes	Allocation concealment	Baseline data	Adverse events	Power of the study	Statistical significance	Conflicts of interest and funding
UK[14]	Respiratory tract infection/cefaclor *vs.* amoxicillin	0	1	1	1	1	1	1	0	1	1	0	0	0
USA[15]	Gonorrhoea/bacampicillin *vs.* ampicillin	0	0	0	0	1	1	1	0	1	1	0	1	1
USA[16]	Prophylaxis of bacteriuria during intermittent catheterization/no treatment *vs.* neomycin plus polymyxin-B *vs.* nitrofurantoin macrocrystals	1	0	0	0	1	1	1	0	1	0	0	1	1
UK[17]	Prevention of chest infection after cardiac operations/cephradine *vs.* cefamandole	1	0	0	0	1	1	1	0	1	1	0	1	0
USA[18]	Vascular surgery/cephalotin *vs.* oxacillin	1	0	0	0	1	1	1	0	1	1	0	1	0
Canada[19]	Therapy for intra-abdominal and female genital tract sepsis/clindamycin *vs.* chloramphenicol *vs.* ticarcillin	1	0	0	1	1	1	1	1	1	1	0	1	1
USA[20]	Urinary tract infection/4 *vs.* 10 days of doxycycline	0	0	0	0	1	1	1	0	1	0	0	0	1
1985														
Canada[21]	Intra-abdominal infections/cefoxitin plus placebo *vs.* tobramycin plus clindamycin	1	0	0	1	1	1	1	0	1	1	0	1	0
Sweden[22]	Acute lower urinary tract infection/nalidixic acid *vs.* pivmecillinam	0	0	0	1	1	1	1	1	1	1	0	1	1
USA[23]	Streptococcal pharyngitis/penicillin *vs.* placebo	1	1	1	0	1	1	1	1	0	0	0	1	1
USA[24]	Prophylaxis during caesarean section/moxalactam *vs.* cefazolin	1	1	1	1	1	1	1	0	1	1	0	1	1
UK[25]	*Chlamydial* infection/tetracycline or erythromycin stearate *vs.* no treatment	0	0	0	0	1	1	1	0	0	0	0	1	0
USA[26]	Prophylaxis for premenopausal women undergoing vaginal hysterectomy	0	0	0	0	1	1	1	1	1	1	0	1	1

USA[27]	Acute urinary tract infection/1 dose ceftriaxone *vs.* multiple dose trimethoprim-sulfamethoxazole	1	0	0	1	1	1	1	0	1	1	0	1	0
USA[28]	Prophylaxis in caesarean section/ ceftizoxime *vs.* placebo	0	1	0	1	1	1	1	0	1	1	0	1	0
Italy[29]	Urinary tract infections/ceftizoxime *vs.* cefotaxime	1	0	0	0	1	1	1	0	1	1	0	0	0
UK-Ireland[30]	Biliary surgery/mezlocillin *vs.* netilmicin	1	0	0	0	1	1	1	0	1	0	0	1	0
1990														
Switzerland[31]	Bacterial infections/ceftriaxone	0	0	0	1	1	1	1	0	1	1	0	0	1
Canada[32]	Prophylaxis for open heart operations/ cephalothin *vs.* cefamandole	1	0	0	0	1	1	1	0	1	1	0	1	1
Japan[33]	Prophylaxis in patients with haematological disorders/aztreonam *vs.* clindamycin *vs.* amicacin plus aztreonam *vs.* clindamycin plus amicacin	0	0	0	0	1	1	1	1	1	1	0	0	0
Greece[34]	Bacteriuria/Cefadroxil *vs.* cotrimoxazole *vs.* norfloxacin	0	0	0	0	1	1	1	0	1	0	0	1	1
USA[35]	Post-caesarean section endometritis	1	1	1	0	1	1	1	0	1	1	0	1	0
The Netherlands[36]	Serious bacterial infections/aminoglycoside plus β-lactam *vs.* netilmicin plus ceftriaxone	0	0	0	1	1	1	1	0	1	1	0	1	1
USA–Zambia[37]	Resistant *Neisseria gonorrhoeae* urethritis/ciprofloxacin *vs.* ceftriaxone	1	1	1	0	1	1	1	0	1	1	0	1	1
UK[38]	Prophylaxis in total joint arthroplasty/systemic cefuroxime *vs.* cefuroxime in bone cement	0	0	0	0	1	1	1	0	1	0	0	0	1
Canada[39]	Prophylaxis in hip fracture surgery/4 doses cefazolin *vs.* 1 dose cefazolin plus 3 doses placebo *vs.* 4 doses placebo	0	1	0	0	1	1	1	1	1	1	1	1	0
Italy[40]	Arthrosis/imidazole salicylate *vs.* piroxicam	0	1	1	1	1	1	1	0	1	1	0	1	0
1995														
USA[41]	Leukocytospermia/doxycycline *vs.* trimethoprim *vs.* no treatment	0	0	0	1	1	1	1	0	1	1	0	1	0
Switzerland[42]	B-haemolytic streptococcus Pharyngotonsillitis/5 *vs.* 10 days cefetamet *vs.* phenoxymethyl penicillin	0	0	0	1	1	1	1	0	1	1	0	1	0
New Zealand–Australia[43]	Lower respiratory tract infections/ roxithromycin *vs.* amoxicillin-clavulanic acid	0	0	0	1	1	1	1	1	1	1	1	1	0

Appendix

Continued

Origin/reference number (Appendix) Reference number (in the Appendix)	Infection/ Antimicrobials tested	Description of randomization	Double blinding	Description of blinding	Description of withdrawals and drop-outs	Eligibility	Interventions	Outcomes	Allocation concealment	Baseline data	Adverse events	Power of the study	Statistical significance	Conflicts of interest and funding
USA–Canada–Nepal[44]	Typhoid fever/3 *vs.* 14 days ceftriaxone	1	0	0	1	1	1	1	1	1	1	0	1	1
Gabon–Germany–Austria[45]	Malaria/quinine plus clindamycin *vs.* quinine	0	0	0	0	1	1	1	0	1	0	0	1	0
Finland[46]	Prevention of acute otitis media after upper respiratory tract infection/amoxicillin-clavulanate *vs.* placebo	1	1	1	0	1	1	1	0	1	0	1	1	1
Sweden[47]	Recurrent respiratory tract infections/ immunoglobulin plus placebo *vs.* trimethoprim-sulfamethoxazole plus placebo *vs.* placebo plus placebo	0	1	1	1	1	1	1	1	1	0	0	1	0
USA[48]	Acute maxillary sinusitis/3 *vs.* 10 days trimethoprim-sulfamethoxazole	1	1	1	1	1	1	1	1	1	1	1	1	1
Sweden[49]	Prophylaxis in trochanteric fracture surgery/ cefadroxil *vs.* cefuroxime	0	0	0	1	1	1	1	1	1	1	0	1	1
USA[50]	Secondary bacterial infections of acute bronchitis/5 *vs.* 10 days cefuroxime axetil	1	0	0	1	1	1	1	0	1	1	0	1	1
2000														
Japan[51]	Type 2 diabetes mellitus/erythromycin *vs.* placebo	0	0	0	0	1	1	1	0	1	1	0	1	1
UK[52]	Urinary tract infection/pivmecillinam *vs.* cephalexin	0	1	1	1	1	1	1	0	1	1	0	1	0
USA[53]	Neurosyphilis in HIV patients/ceftriaxone *vs.* penicillin G	0	0	0	1	1	1	1	0	1	1	0	1	1
USA[54]	Prophylaxis against *Mycobacterium avium* in HIV patients/azithromycin *vs.* placebo	0	1	1	1	1	1	1	0	1	1	1	1	1
UK–New Zealand[55]	*Helicobacter pylori*/omeprazole plus clrarithromycin plus tinidazole or placebo	1	0	0	1	1	1	1	1	1	1	1	1	1
Croatia[56]	*Helicobacter pylori*/pantoprazole plus amoxicillin plus azithromycin or clarithromycin	0	0	0	0	1	1	1	0	1	1	0	1	1

Italy[57]	Prophylaxis in colorectal surgery/cefepime plus metronidazole *vs.* ceftriaxone plus metronidazole	1	0	0	1	1	1	1	1	1	1	1	1	1	1	1
Sweden[58]	Acute otitis media/5 *vs.* 10 days ceftibuten	0	0	0	1	1	1	1	1	0	1	1	1	1	1	1
Japan[59]	*Helicobacter pylori*/400 *vs.* 800 mg clarithromycin plus lansoprazole plus amoxicillin	0	0	0	1	1	1	1	1	0	1	1	0	1	1	0
USA[60] **2005**	Shigellosis/2 *vs.* 5 days cefixime	0	1	1	1	1	1	1	1	0	1	1	0	1	1	1
USA–Costa Rica[61]	Recurrent otitis media and acute otitis media treatment failure/gatifloxacin *vs.* amoxicillin-clavulanate	0	0	0	1	1	1	1	1	0	1	1	0	0	0	1
Italy[62]	Prophylaxis in neonatal intensive care unit/ampicillin and netilmicin	1	0	0	0	1	1	1	1	0	1	1	1	1	1	1
Argentina[63]	Acute otitis media/amoxicillin-sulbactam *vs.* amoxicillin-clavulanic acid	0	0	0	1	1	1	1	1	1	1	1	1	1	1	1
USA–South Africa–Estonia–France[64]	Skin structure infections/tigecycline *vs.* vancomycin-aztreonam	0	1	1	1	1	1	1	1	0	1	1	0	1	1	1
Iran[65]	*Helicobacter pylori*/omeprazole plus bismuth subcritrate plus metronidazole plus tetracycline *vs.* omeprazole plus bismuth subcitrate plus furqazolidone plus tetracycline *vs.* omeprazole plus bismuth subcitrate plus ciprofloxacin	0	0	0	0	1	1	1	1	0	1	0	0	1	1	1
Brazil[66]	*Helicobacter pylori*/tetracycline plus furazolidone *vs.* amoxicillin plus azithromycin	0	0	0	1	1	1	1	1	0	1	1	0	1	1	1
The Netherlands[67]	Crohn's disease/ciprofloxacin *vs.* placebo	0	1	0	0	1	1	1	1	0	1	0	0	1	1	1
Italy[68]	Prophylaxis of early-onset pneumonia in critically ill comatose patients/ampicillin-sulbactam plus standard treatment *vs.* standard treatment alone	1	0	0	1	1	1	1	1	1	1	0	1	1	1	1
USA–Argentina[69]	Mild to moderate community acquired pneumonia/ azithromycin *vs.* clarithromycin	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1
Turkey[70]	Acne vulgaris/azithromycin *vs.* doxycycline	1	0	0	1	1	1	1	1	0	1	1	0	1	1	0

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