J Antimicrob Chemother 2015; **70**: 382–395
doi:10.1093/jac/dku379 Advance Access publication 28 September 2014

Journal of Antimicrobial Chemotherapy

Bacteriostatic versus bactericidal antibiotics for patients with serious bacterial infections: systematic review and meta-analysis

Johannes Nemeth[1]*†, Gabriela Oesch[2]† and Stefan P. Kuster[1]†

[1]*Division of Infectious Diseases and Hospital Epidemiology, University Hospital and University of Zurich, Zurich, Switzerland;* [2]*University Children's Hospital, Zurich, Switzerland*

*Corresponding author. Tel: +41-44-255-21-73; Fax: +41-44-255-44-33; E-mail: johannes.nemeth@usz.ch
†The authors contributed equally to this work.

Received 2 July 2014; returned 11 August 2014; revised 26 August 2014; accepted 27 August 2014

Objectives: Antibiotics are commonly classified into bactericidal and bacteriostatic agents based on their antimicrobial action. We aimed to assess whether this distinction is clinically relevant.

Methods: OVID MEDLINE, EMBASE, The Cochrane Central Register of Controlled Trials (CENTRAL) and relevant references and conference proceedings using the Web of Science and Scopus databases were searched for randomized controlled trials comparing bactericidal with bacteriostatic antibiotics for treatment of severe infections. Main outcome measures were clinical cure rates and overall mortality. Abstracts of studies selected in the database search were screened by one reviewer; full-text screening and data extraction were performed by three independent reviewers.

Results: Thirty-three studies were included. Approximately half of patients were treated with bacteriostatic monotherapy. Infections covered were pneumonia ($n=13$), skin and soft tissue infections ($n=8$), intra-abdominal infections ($n=4$) and others ($n=8$). Neither clinical cure rates [risk ratio (RR), 0.99; 95% CI, 0.97–1.01; $P=0.11$] nor mortality rates (RR, 0.91; 95% CI, 0.76–1.08; $P=0.28$) were different between patients treated with bactericidal drugs and those treated with bacteriostatic drugs. Subgroup analyses showed a benefit for clinical cure rates associated with linezolid and increased mortality associated with tigecycline. In meta-regression, clinical cure rates remained higher in patients treated with linezolid ($P=0.01$); tigecycline displayed a close to significant association with increased mortality ($P=0.05$) if compared with other bacteriostatic agents.

Conclusions: The categorization of antibiotics into bacteriostatic and bactericidal is unlikely to be relevant in clinical practice if used for abdominal infections, skin and soft tissue infections and pneumonia. Because we were not able to include studies on meningitis, endocarditis or neutropenia, no conclusion regarding these diseases can be drawn.

Keywords: drug classes, mechanism of action, generalizability

Introduction

The distinction between bactericidal and bacteriostatic antibiotics is a successful concept to discriminate antibiotics that kill bacteria—'bactericidal'—from antibiotics that inhibit bacterial growth, i.e. 'bacteriostatic'. This classification is applied in major textbooks of medicine and infectious diseases, clinical guidelines and advertisements of novel antibiotics.[1–5] The intuitively understandable concept between the two groups of antibiotics suggests that bactericidal drugs have more powerful antibacterial action and are able to kill bacteria. In contrast, bacteriostatic antibiotics are assumed to require phagocytic cells to definitely clear bacteria and are therefore thought to be less effective without an efficient immune response. This theoretical model has led to the recommendation that severely ill and immunosuppressed patients with bacterial infections should be treated with bactericidal antibiotics.[2–4] Furthermore, some specific conditions are also thought to require bactericidal antibiotics, such as endocarditis.[1] The cardiac valves are considered as focal, immunosuppressed regions poorly accessible for phagocytic cells. Therefore, a phagocyte-independent killing by bactericidal drugs is generally recommended under such circumstances.

Unfortunately, there are no clinical data supporting the concept of bacteriostatic versus bactericidal antibiotics. This is quite remarkable given the major influence on recommendations for treatment of severely ill patients. The reason may lie in the difficulties of assessing a drug class effect in a clinically meaningful way.

The main challenge is that during bacterial infection and its treatment, relevant clinical outcomes such as cure rates and mortality are influenced by three main factors: the host, the pathogen and the drug. A drug class effect can only be secondary to these three main factors and is therefore difficult to assess. Our methodological assumption was that the drug class effect 'bactericidal versus bacteriostatic' may be measurable if the three main factors—host, drugs and pathogens—are as heterogeneous as possible. If the common denominator is limited to the difference between bacteriostatic and bactericidal drugs amongst different clinical trials, the results may be reduced to the difference between bactericidal and bacteriostatic antibiotics. This approach introduces a meta-level that is beyond the range of a single randomized trial. We therefore conducted a meta-analysis including a wide variety of prospective clinical trials using bacteriostatic versus bactericidal antibiotic drugs for the treatment of patients with severe bacterial infections. The main outcome measures were clinical outcome and overall mortality.

Methods

Definitions

Severity

Requirement of hospitalization was used as a determinant to screen for severity, unless the authors explicitly provided a definition for severity in the study. Studies including patients with different levels of severity, such as e.g. pneumonia and bronchitis, were excluded. Furthermore, studies performed with relatively benign infections were excluded (i.e. infections in the oral cavity, uncomplicated otolaryngeal infections, uncomplicated gastrointestinal infections, sexually transmitted diseases, Lyme disease, exacerbation of chronic bronchitis, pneumonia in the outpatient setting etc.). Chronic infections such as diabetic foot infections were excluded under the assumption that successful antibiotic therapy in this setting does not rely on rapid killing but rather elimination of the biofilm, vascular supply and joint and bone involvement.

Antibiotics

In the bacteriostatic antibiotic patient group, bacteriostatic single therapy only without the concomitant use of any bactericidal drug was allowed, with few exceptions: if all three authors agreed that the bactericidal component of the combination therapy had no effect on bacteria, these studies were included as well. Seven studies met these criteria.[6–12] Six out of seven allowed the use of aztreonam in case of infection with Gram-positive bacteria; one study allowed aminoglycosides in case of proven aminoglycoside resistance of *Staphylococcus aureus* infection.[6] The rate of resistance was similar between bacteriostatic and bactericidal antibiotics. For the seven studies with combination therapy, only the microbiologically confirmed cases were extracted for analysis in the clinical cure groups. In all other studies, the ITT population was assessed. If no ITT population was available, results from PP analyses were extracted.

In the bactericidal antibiotic treatment group, combination therapy was allowed. Antibiotics were defined as bactericidal and bacteriostatic according to a classification obtained from a major textbook of infectious diseases, with one important exception (Table 1).[3] Aminoglycosides act at the ribosome and are therefore classified as bacteriostatic by some authors. At higher concentrations, however, aminoglycosides display a very rapid bactericidal effect. Due to considerations regarding side effects, aminoglycosides are recommended to be given once daily at high concentrations for most indications.[13] Therefore, aminoglycosides are most likely to be bactericidal in routine clinical practice and were classified accordingly.

Table 1. Definition of bacteriostatic and bactericidal antibiotics (adapted from Cohen *et al.*[3])

Bactericidal
aminoglycosides
β-lactams
fluoroquinolones
glycopeptides
lipopeptides
nitroimidazoles and nitrofurans
Bacteriostatic
glycylcyclines
lincosamides
macrolides
oxazolidinones
streptogramins
sulphonamides

Studies using inappropriate antibiotics in terms of microbiological spectrum were excluded. Hence, possible differences are not attributable to resistance of bacteria.

Outcomes

For the primary endpoint, clinical outcome as defined by the respective study authors was used. Secondary endpoints were mortality and relapse rates. Relapse rates were defined as recurrence of signs and symptoms associated with the primary infection during follow-up after initial clinical resolution or 'relapse' as defined by the authors. Subgroup analyses for different diseases were performed.

Data sources and searches

With the help of an experienced librarian with expertise in literature search for systematic reviews and meta-analyses, we performed an electronic search of OVID MEDLINE, EMBASE and The Cochrane Central Register of Controlled Trials (CENTRAL). We also searched relevant references of included studies and conference proceedings using the Web of Science and Scopus databases. No time limits were applied. The search strategy is displayed in detail in Figure S1 (available as Supplementary data at *JAC* Online).

Study selection

We included all randomized controlled trials comparing bacteriostatic versus bactericidal antibiotics in patients with serious bacterial infections requiring hospitalization. There was no restriction by study site/country or follow-up period and there was no restriction by dose, frequency or method of drug administration. One author (J. N.) screened the title and abstract of each reference identified by the search and applied the inclusion criteria. For possibly relevant articles, the full-text article was obtained and reviewed independently by two out of the three authors (J. N., G. O. and S. P. K.). Final inclusion of studies was determined by agreement of both reviewers and involvement of a third author in case of discrepancy. After in-depth discussion of the different opinions, the authors agreed unanimously on the final classification. Only studies published in English were considered eligible.

Data extraction and quality assessment

Two out of the three authors (J. N., G. O. and S. P. K.) independently extracted data from included trials. Data extraction was performed

using a standardized data collection form. When missing data were encountered, the corresponding authors were contacted to retrieve them.

For the assessment of clinical cure, data from ITT populations were extracted if possible. Some studies did not report the clinical cure rates of the ITT population or—in case of older studies—did not discern between different study populations at all. In such a case, results from modified ITT or PP populations were extracted. In case of the seven studies with combination therapy, only the microbiologically confirmed cases were extracted.[6–12]

For mortality analysis, the ITT ('safety') population was used throughout. The primary outcome measures were (i) clinical cure rate as defined by the investigators in the study and (ii) mortality rate. Data were extracted as proportions if results were only reported as probability of events or mortality and if the number of events was not explicitly provided. Unfortunately, follow-up data and periods of follow-up after end of treatment were heterogeneous.

Subgroup analysis was performed for different diseases and different classes of antibiotics. Meta-analysis was performed only if at least three studies included the same disease or antibiotic.

To assess methodological quality and risk of bias, included articles were examined for (i) randomization process, (ii) blinding, (iii) incomplete outcome data and (iv) reporting bias/sponsorship as described in the *Cochrane Handbook for Systematic Reviews of Interventions*.[14]

Data synthesis and analysis

Data synthesis was performed using Review Manager (version 5.2, The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). *P* values <0.05 were considered statistically significant. Subgroup analyses for differences between different classes of antibiotics and differences between different diseases were performed. Because heterogeneity was anticipated between studies, a random-effects model was used for all analyses. Statistical heterogeneity was inspected graphically (forest plot) and the degree of heterogeneity quantified using the I^2 statistic. Publication bias was investigated using a funnel plot in which the standard error of the effect estimate of each study was plotted against the estimate. An asymmetric plot suggested possible publication bias.

We used STATA 13 (StataCorp 2013, College Station, TX, USA) for meta-regression assessing differences between bacteriostatic drug classes.

Results

Study selection

The literature search yielded 16490 references. After screening titles and abstracts, 81 articles were selected for full-text screening (Figure 1). Thirty-three studies met the inclusion criteria (Table 2). The bacteriostatic agents included tigecycline, linezolid, macrolides, sulphonamides, tetracyclines and streptogramins. The bactericidal agents included β-lactam antibiotics, glycopeptide antibiotics, fluoroquinolones and aminoglycosides. Diseases under study included pneumonia (13 studies[6,11,15–19,21–26]), skin and soft tissue infections (8 studies[7,8,27–32]), intra-abdominal infections (4 studies[33–36]) and others (8 studies[10,20,37–42]). No trials in neutropenic patients or patients with endocarditis or meningitis met inclusion criteria. All studies except one study on children with typhoid included adults only.[37]

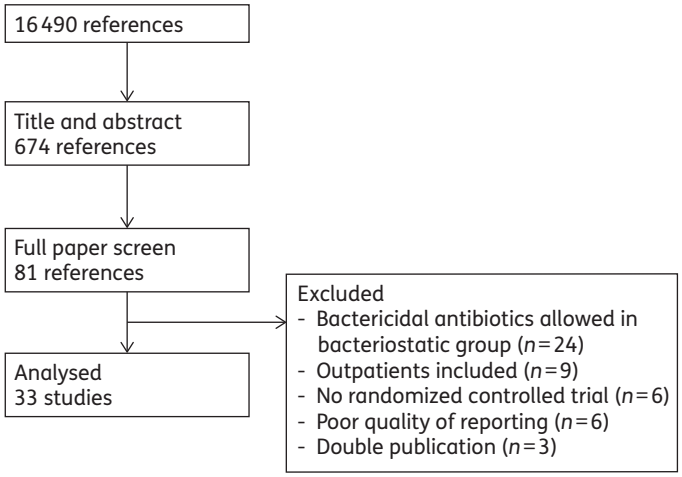

Figure 1. Study selection.

Clinical cure rates

Data from 9597 patients were available for meta-analysis of clinical cure rates. Of these patients, 4717 (49.2%) were treated with a bacteriostatic agent. Meta-analysis indicated that clinical cure rates were not different between bactericidal and bacteriostatic drugs [risk ratio (RR), 0.99; 95% CI, 0.97–1.01; $P=0.11$; Figure 2], with an overall heterogeneity of $I^2=24\%$. Analysis of subgroups was performed on studies using tigecycline, linezolid, macrolides, β-lactam antibiotics, glycopeptides and fluoroquinolones. For the other drug classes, an insufficient number of studies were found, precluding statistical analysis. Subgroup analyses revealed that treatment with linezolid appeared to be associated with better clinical cure rates compared with its bactericidal comparator (RR, 0.93; 95% CI, 0.87–0.99; $P=0.04$; Figure 2). In meta-regression, combined cure rates of trials using linezolid were better than those from tigecycline trials (RR, 1.07; 95% CI, 1.02–1.12; $P=0.01$). There was no benefit detectable for clinical cure rates among subgroups of bactericidal antibiotics (Figure 3).

Mortality

The population for the assessment of mortality consisted of 13098 patients in total. There was no significant increase in overall mortality in the patient group treated with bacteriostatic antibiotics compared with patients treated with bactericidal antibiotics (RR, 0.91; 95% CI, 0.76–1.08; $P=0.28$; Figure 4). Heterogeneity was low ($I^2=0\%$). An increased mortality was found in studies using tigecycline in the bacteriostatic regimen group (RR, 0.66; 95% CI, 0.46–0.94; $P=0.02$; Figure 4). In meta-regression, there was a strong trend towards reduced mortality in studies using linezolid compared with tigecycline trials (RR, 0.64; 95% CI, 0.41–1.00; $P=0.05$). There was no mortality benefit detectable for subgroups of bactericidal antibiotics (Figure 5).

Relapse

In 12 studies, relapse rates were reported.[7,8,17,18,20,34,35,37,39–42] Five studies included relapse rates in the clinical cure rate endpoint.[17,18,35,39,42] In the remaining seven studies, differences in relapse rates between bacteriostatic and bactericidal antibiotics were not significant (RR, 0.76; 95% CI, 0.43–1.35; $P=0.51$; data not shown).

Table 2. Study characteristics

Author	Year	Type of study	Disease	Antibiotics, bactericidal	Antibiotics, bacteriostatic
Bergallo *et al.*[15]	2009	Phase 3, multicentre, double-blind study	community-acquired pneumonia	levofloxacin	tigecycline
Bernard *et al.*[27]	1992	prospective, randomized, multicentre trial	complicated skin and soft tissue infections	penicillin	roxithromycin
Bohte *et al.*[16]	1995	open-label, randomized, multicentre study	community-acquired pneumonia	penicillin	azithromycin
Breedt *et al.*[28]	2005	randomized, double-blind, controlled, multicentre trial	complicated skin and soft tissue infections	vancomycin	tigecycline
Chen *et al.*[33]	2010	Phase 3, multicentre, open-label study	complicated intra-abdominal infection	imipenem/cilastatin	tigecycline
Chuang *et al.*[29]	2011	two Phase 3, multicentre, randomized, double-blind studies	complicated skin and soft tissue infections	vancomycin/aztreonam	tigecycline
Dartois *et al.*[17]	2008	randomized, Phase 3, multicentre trial	community-acquired pneumonia	levofloxacin	tigecycline
Ellis-Grosse *et al.*[30]	2005	two Phase 3, randomized, double-blind, multicentre studies	complicated skin and soft tissue infections	vancomycin/aztreonam	tigecycline
Frenck *et al.*[37]	2000	randomized, open-label, controlled, single-centre trial	typhoid fever	ceftriaxone	azithromycin
Genne *et al.*[18]	1997	open-label, prospective, randomized, single-centre study	community-acquired pneumonia	amoxicillin	clarithromycin
Itani *et al.*[7]	2010	prospective, randomized, open-label, controlled, multicentre, Phase 4 study	complicated skin and soft tissue infections	vancomycin	linezolid
Jauregui *et al.*[8]	2005	randomized, double-blind, controlled, multicentre, Phase 3 trial	complicated skin and soft tissue infections	dalbavancin	linezolid
Kohno *et al.*[38]	2007	randomized, open-label, comparator-controlled, multicentre study	nosocomial pneumonia, complicated skin and soft tissue infections or sepsis caused by MRSA	vancomycin	linezolid
Kuzman *et al.*[19]	2005	randomized, open-label, multicentre study	community-acquired pneumonia	cefuroxime	azithromycin
Lin *et al.*[10]	2008	randomized, double-blind, comparator-controlled, multicentre study	pneumonia or complicated skin and soft tissue infection due to suspected or known Gram-positive pathogens	vancomycin	linezolid
Markowitz *et al.*[39]	1992	randomized, double-blind, comparative, single-centre study	infection with *S. aureus*	vancomycin	trimethoprim/sulfamethoxazole
Mehtar *et al.*[20]	1982	open-label, randomized, single-centre study	severe respiratory tract infections	cefuroxime	trimethoprim/sulfamethoxazole
Mwengee *et al.*[40]	2006	randomized, controlled, comparative, open-label trial	plague	gentamicin	doxycycline

Continued

Table 2. *Continued*

Author	Year	Type of study	Disease	Antibiotics, bactericidal	Antibiotics, bacteriostatic
Mokabberi *et al.*[21]	2010	prospective, randomized, double-blind, single-centre trial	community-acquired pneumonia	levofloxacin	doxycycline
Ode *et al.*[41]	1983	open-label, randomized, prospective, single-centre, Phase 3 trial	acute pyelonephritis	ampicillin/mecillinam	trimethoprim/ sulfamethoxazole
Oliva *et al.*[34]	2005	prospective, randomized, double-blind, multicentre trial	complicated intra-abdominal infection	imipenem	tigecycline
Plouffe *et al.*[22]	2000	two multicentre, open-label Phase 3 trials, one parallel-group, randomized, one non-comparative with sequential inclusion	community-acquired pneumonia	cefuroxime	azithromycin
Qvist *et al.*[35]	2012	randomized, open-label, multicentre, Phase 3b/4 trial	complicated intra-abdominal infections	ceftriaxone/metronidazole	tigecycline
Raad *et al.*[42]	1999	evaluator-blind, prospective, randomized, Phase 2, multicentre trial	catheter-related infections	vancomycin	quinupristin/dalfopristin
Sacchidanand *et al.*[31]	2005	Phase 3, randomized, double-blind, multicentre study	complicated skin and soft tissue infections	vancomycin/aztreonam	tigecycline
San Pedro *et al.*[11]	2002	multicentre, randomized, open-label trial	pneumonia with *Streptococcus pneumoniae*	ceftriaxone/cefpodoxime	linezolid
Shanson *et al.*[23]	1984	prospective, randomized, single-centre trial	community-acquired pneumonia	ampicillin/flucloxacillin	erythromycin
Sterner *et al.*[24]	1967	randomized, open-label, single-centre trial	community-acquired pneumonia	cefaloridine	erythromycin
Stevens *et al.*[32]	2000	randomized, double-blind, multicentre trial	complicated skin and soft tissue infection	oxacillin/dicloxacillin	linezolid
Tanaseanu *et al.*[26]	2009	prospective, double-blind, non-inferiority, multicentre, Phase 3 trial	community-acquired pneumonia	levofloxacin	tigecycline
Tanaseanu *et al.*[25]	2008	two Phase 3, multicentre, randomized, double-blind studies	community-acquired pneumonia	levofloxacin	tigecycline
Towfigh *et al.*[36]	2010	multicentre, open-label, randomized, Phase 3b/4 study	complicated intra-abdominal infection	ceftriaxone/metronidazole	tigecycline
Wunderink *et al.*[6]	2012	prospective, double-blind, controlled, multicentre trial	confirmed MRSA pneumonia	vancomycin	linezolid

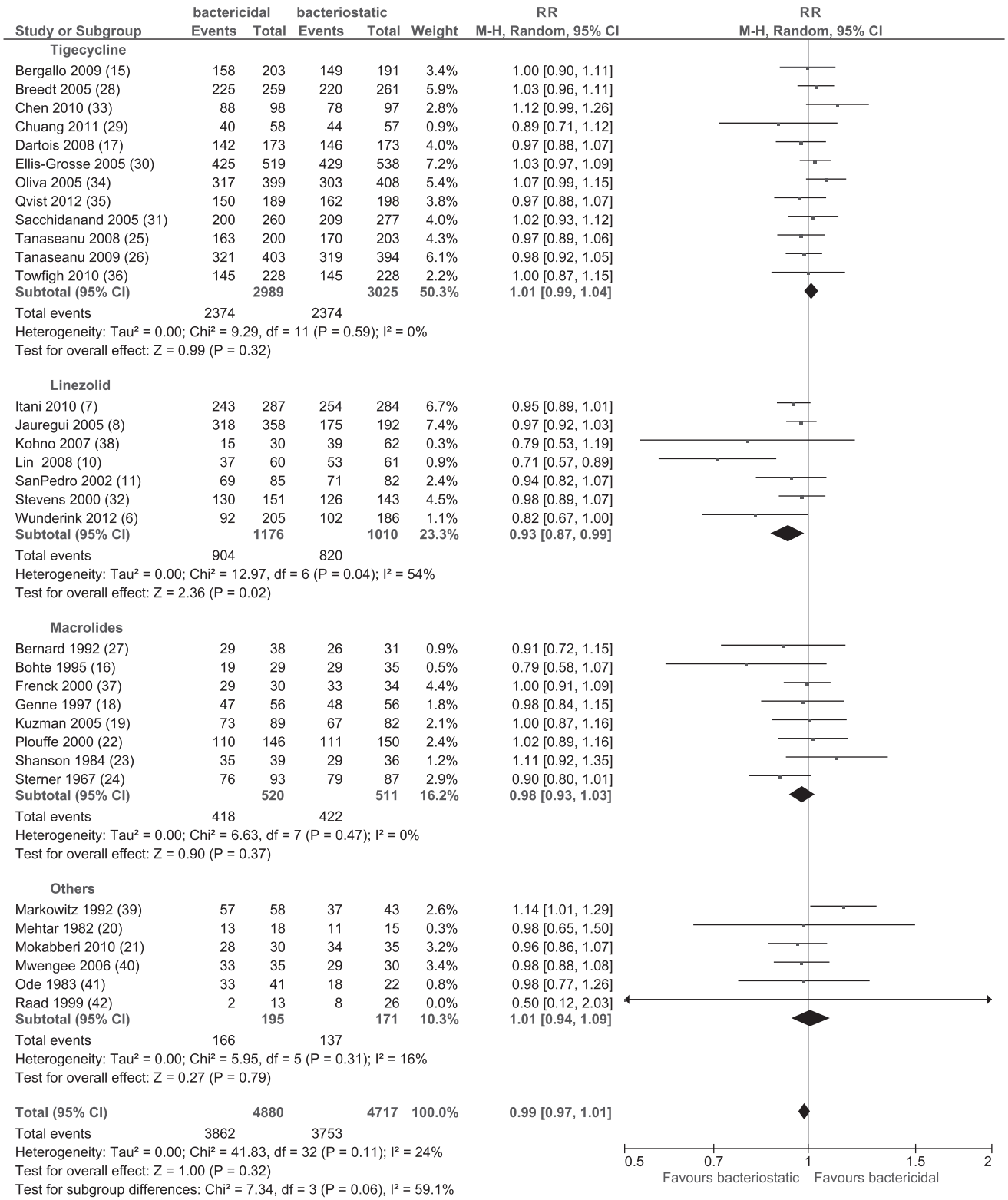

Figure 2. RRs for clinical cure rates stratified by use of different bacteriostatic antibiotics. Data markers indicate RRs and error bars indicate 95% CIs.

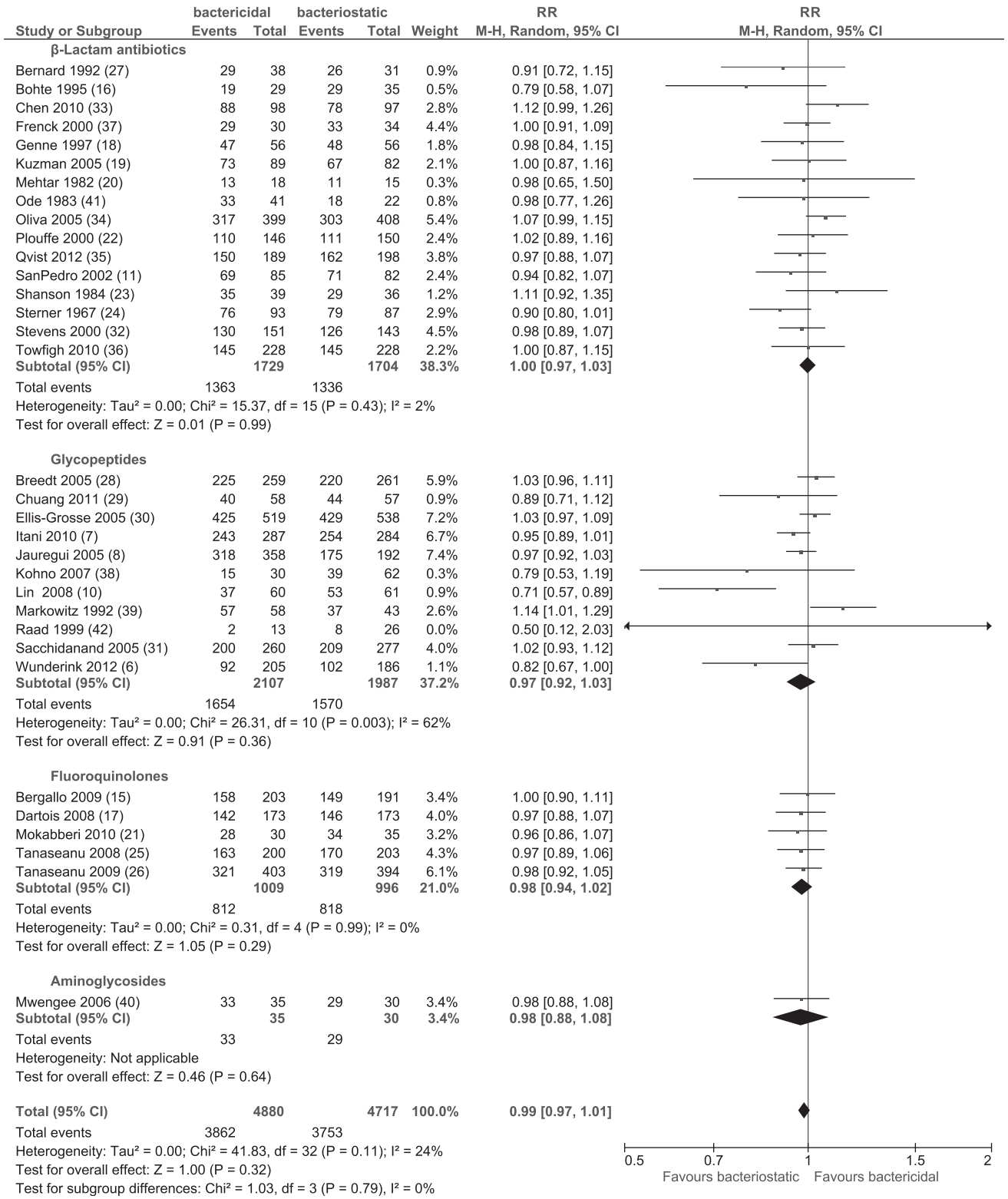

Figure 3. RRs for clinical cure rates stratified by use of different bactericidal antibiotics. Data markers indicate RRs and error bars indicate 95% CIs.

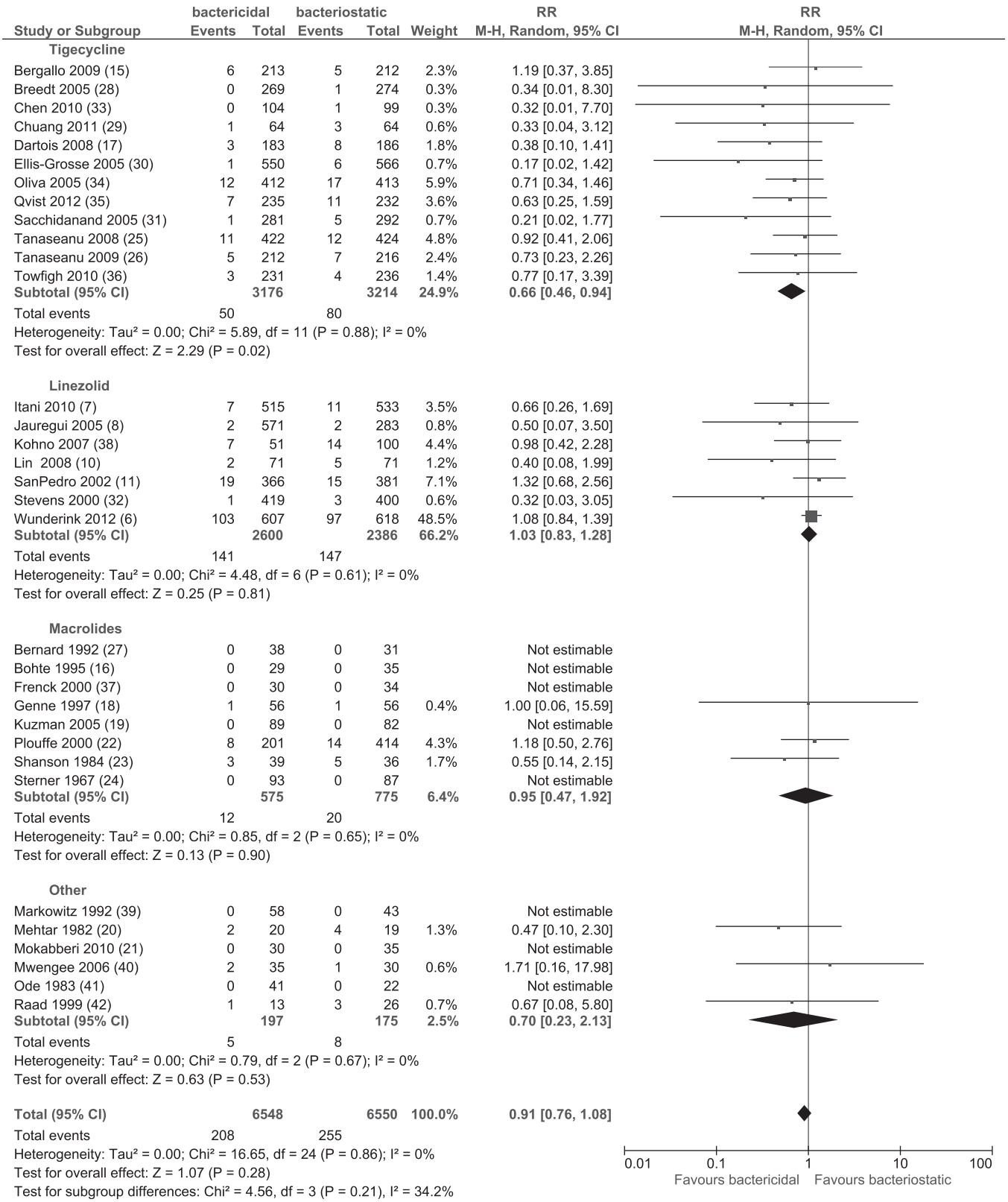

Figure 4. RRs for mortality rates stratified by use of different bacteriostatic antibiotics. Data markers indicate RRs and error bars indicate 95% CIs.

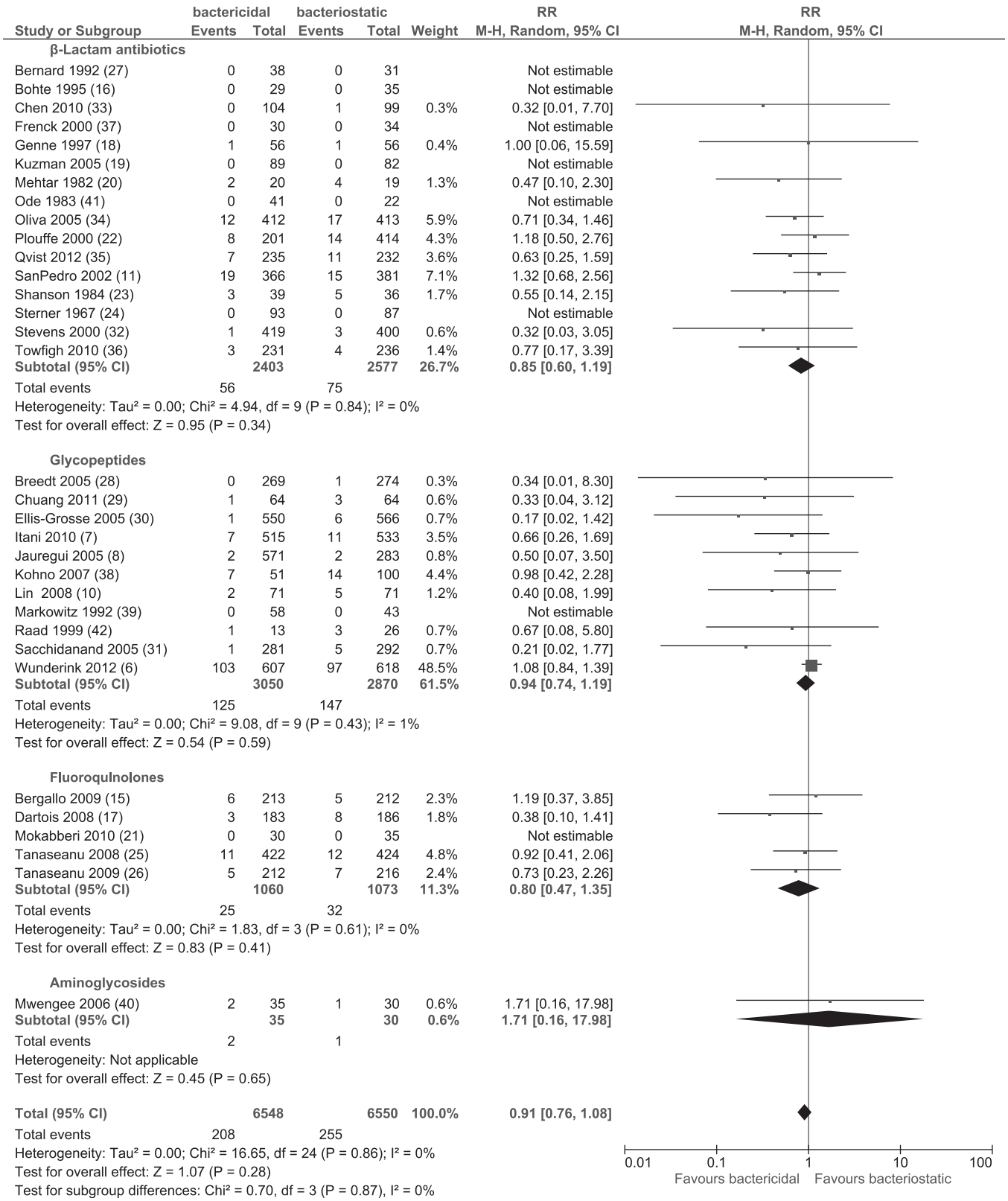

Figure 5. RRs for mortality rates stratified by use of different bactericidal antibiotics. Data markers indicate RRs and error bars indicate 95% CIs.

Different diseases

We performed subgroup analyses of the most frequent diseases: abdominal infections, skin and soft tissue infections and pneumonia. No differences in clinical outcome between diseases could be found (Figure 6). However, increased mortality was detected in skin and soft tissue infections treated with bacteriostatic agents (RR, 0.43; 95% CI, 0.23–0.84; $P=0.01$; Figure 7). If studies using tigecycline were excluded, the difference was no longer significant (RR, 0.57; 95% CI, 0.26–1.27; $P=0.17$), suggesting that this effect was again due to the increased overall mortality attributed to tigecycline. Notably, all four studies with abdominal infections had tigecycline in the bacteriostatic regimen arm without difference in mortality.

Study quality

The quality of included studies was variable (Figures S2 and S3). More than half of studies (17/33) were unblinded, resulting in significant risk of performance bias. More than 50% of studies were sponsored by the pharmaceutical company that manufactured the respective drug and were thus regarded to be at high risk of reporting bias. Funnel plots did not suggest publication bias (Figures S4–S7).

Discussion

In our meta-analysis comparing bactericidal with bacteriostatic antibiotics, no significant differences in clinical cure rates were found in the diseases under study. Subgroup analysis even suggested that linezolid may have better clinical cure rates if compared with its bactericidal comparators. This subgroup included severely ill patients with confirmed MRSA infections, amongst others.[6,38] Sufficient antibacterial action of antibiotics in such a patient group is therefore crucial. As a note of caution, involvement of the sponsor in the trials using linezolid was substantial and meta-analysis showed some heterogeneity. Furthermore, vancomycin, which is difficult to dose appropriately, was the comparator drug in the majority of studies. Therefore, it is premature to conclude that linezolid is more efficient than bactericidal antibiotics. However, our findings suggest that linezolid monotherapy is on par with the standard bactericidal therapy in this patient group.

Our meta-analysis did not detect differences in overall mortality between the patient groups. However, there was an increased mortality associated with the use of tigecycline, an observation in line with data published recently.[43] Meta-regression showed a trend towards increased mortality of patients treated with tigecycline compared with linezolid. The association between increased mortality and tigecycline was predominantly found amongst patients with severe skin infections. Remarkably, mortality was not increased in 931 patients treated with tigecycline for complicated intra-abdominal infections. An increased mortality in specific patient populations without differences in clinical cure rates may have various reasons, such as toxicity of the drug, pharmacokinetic/pharmacodynamic issues or other reasons.[43] Some authors suggest that the drug may be inadequately dosed, at least for ventilator-associated pneumonia.[44] This may well explain observed breakthrough bacteraemias as well.[45] In conclusion, increased mortality is probably a specific feature of tigecycline and not a class effect inherent to all bacteriostatic drugs. A possible difference from a previously published meta-analysis on tigecycline is the strict exclusion of concomitant bactericidal medication.[43]

It is important to note that the analysis of clinical cure rates and mortality includes two different populations. Clinical cure rates included all patients who were followed up adequately; overall and including all the older studies, they represent a sample that is closer to PP. The mortality analysis consists of safety data, resembling to a great extent an ITT population. These two populations cannot be distinguished by contemporary definitions, because we included a substantial number of older studies.

Furthermore, it is important to note that the subgroup analyses are supportive of the main research question, i.e. whether a class effect between bacteriostatic and bactericidal drugs is detectable. They should not be regarded as 'independent' investigations and their results should not be overemphasized.

Renowned textbooks suggest that immunocompromised patients should be treated with bactericidal antibiotics.[3,4] Our analyses include a wide variety of serious bacterial infections, including respiratory tract infections, complicated abdominal infections and skin infections. It is widely accepted that a central pathogenetic feature of most bacterial infections is either local (e.g. disruption of the membrane integrity, such as injury of the skin serving for severe skin infection, or obstruction, such as appendicitis caused by luminal obstruction) or systemic immunosuppression (e.g. neutropenia).[46] As it is generally assumed that bacteriostatic antibiotics require a fully functioning immune system to kill bacteria, one would expect differences in clinical cure rates in the patient group receiving bacteriostatic drugs. Our meta-analysis suggests that this is not the case. Therefore, it may be hypothesized that either the local immunosuppression in respiratory tract infections, complicated abdominal infections and skin infections is not clinically relevant enough to require the presence of a bactericidal drug or that the biology of bacterial killing is much more complex than the simplistic concept of bacteriostatic versus bactericidal drug activity suggests, even in local immunosuppression. In any case, our data suggest class indifference for infection where the immune system is intact or at least not impaired in a major way. Based on the data analysed, no conclusions regarding severely immunosuppressed patients, such as patients with neutropenia, can be drawn.

Because of our strict inclusion criteria, we were unable to include studies assessing neutropenic patients or patients with endocarditis. These are the 'classical' indications for a bactericidal drug regimen. Only one randomized controlled trial using a bacteriostatic drug—linezolid—in patients with neutropenia was found.[47] Unfortunately, a bactericidal add-on medication was allowed, precluding inclusion in our meta-analysis.[47] Thus, the findings from our work can only be applied to the diseases under study in our meta-analysis and may not be extended to endocarditis and neutropenia.

A major theoretical complication of bacteriostatic agents is relapse of infection after treatment because of the failure to clear the infection. In the current investigation, there was no detectable difference in relapse rates between bactericidal and bacteriostatic antibiotics.

Our study has limitations. To our knowledge, this is the first study to undertake a meta-analysis on a class effect of drugs. Therefore, we have no means to measure if the studies included are heterogeneous enough regarding the three main factors

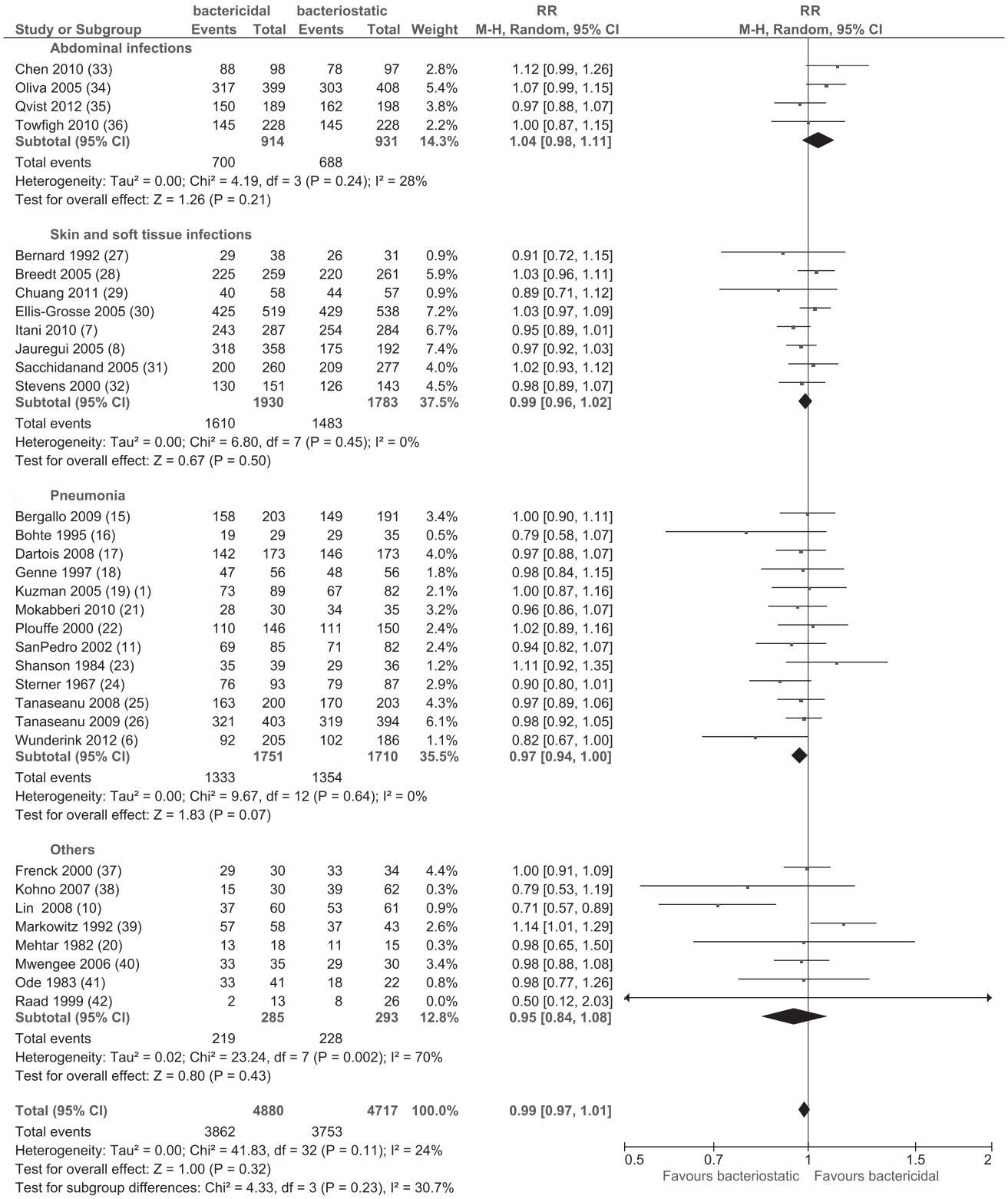

Figure 6. RRs for clinical cure rates stratified by different diseases. Data markers indicate RRs and error bars indicate 95% CIs.

(host, pathogen and drug) to conclude that the only difference between the two patient groups really is the difference between bacteriostatic and bactericidal antibiotics. There are, however, sound arguments in favour of such a conclusion. Regarding the pathogen, we included studies on a wide array of diseases, ranging from *Yersinia pestis* to methicillin-resistant staphylococci.[6,40]

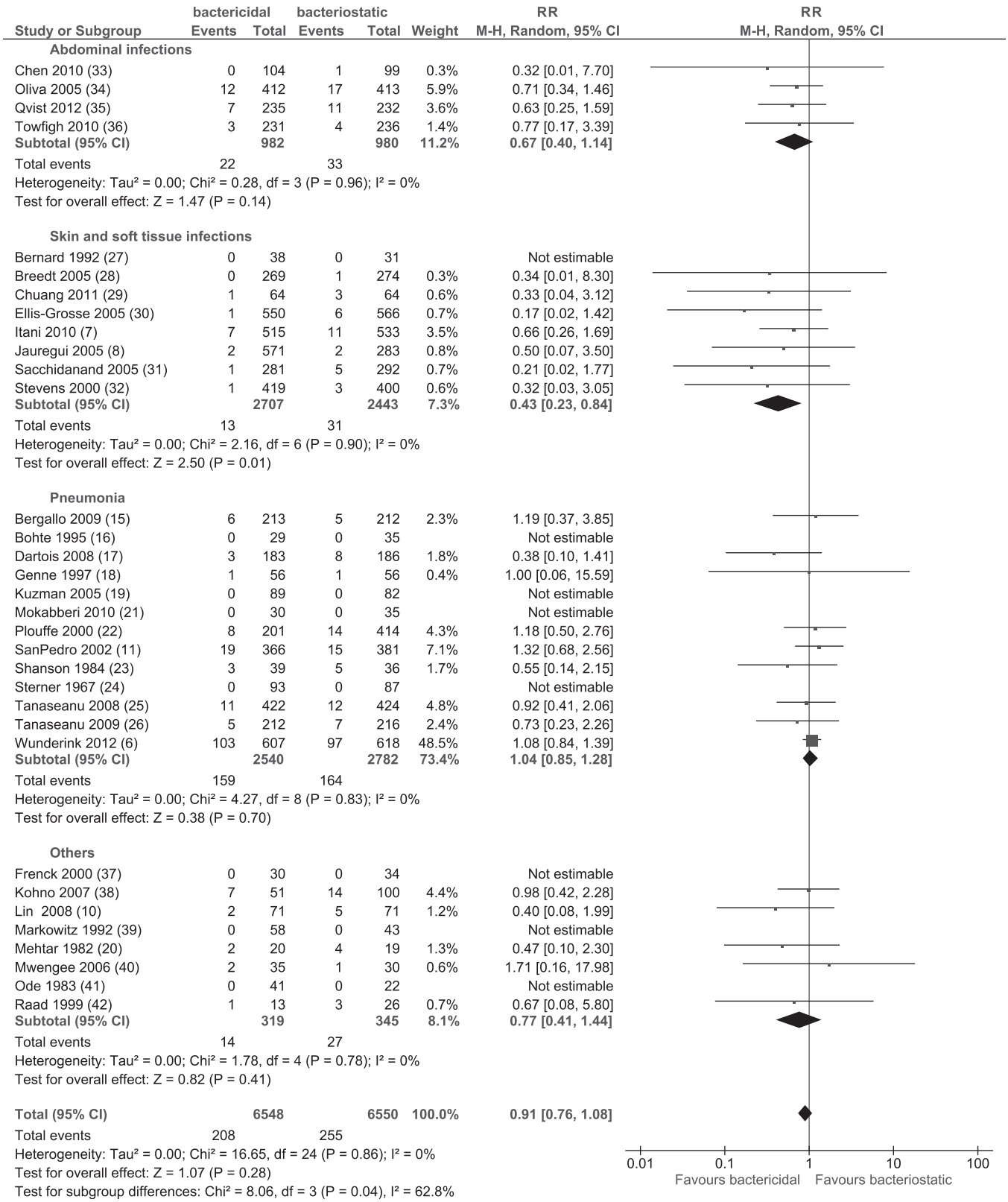

Figure 7. RRs for mortality rates stratified by different diseases. Data markers indicate RRs and error bars indicate 95% CIs.

Regarding the host, patients with severe local infections such as severe skin infections or severe abdominal infections were analysed as well as patients with systemic infections such as salmonellosis or central line-associated infections. Regarding the drugs, a total of 10 different antibiotic classes were assessed. These different drugs may vary significantly in tissue distribution and may have different effects according to their dosing schedules. Amongst the bacteriostatic drugs, the newer drugs tigecycline and linezolid are over-represented. The numbers of patients included in clinical trials increases over time, probably due to a rising standard in research practice. This may explain the observed over-representation of newer bacteriostatic drugs.

The included studies have a significant risk for performance and publication bias. In general, there may be a publication bias in favour of bacteriostatic drugs—i.e. linezolid and tigecycline. However, some studies may have a publication bias in favour of the bactericidal component as well, as in the case of dalbavancin compared with linezolid.[8]

The microbiological definition of bacteriostatic versus bactericidal suggests a degree of clarity that is not supported by the evidence. Some drugs labelled as 'bacteriostatic' do have 'bactericidal' effects under some *in vitro* conditions and vice versa.[48] For example, the exchange of culture media—media used for growing of eukaryotic cells instead of 'classical' Mueller–Hinton broth—may significantly affect drug susceptibility *in vitro*.[49] Thus, it is probably very difficult to predict the action of a given antibiotic drug in terms of bacteriostatic or bactericidal in an actual patient with an ongoing bacterial infection. Furthermore, the action of a given drug may be dependent on the bacterial load and the interaction with the immune system at the site of infection. For example, the capacity of neutrophils to phagocytose bacteria is limited by the sheer quantity of bacteria.[50]

To our knowledge, this is the first study using clinical data to investigate the difference between bactericidal and bacteriostatic antibiotics. Summarized, the data at hand suggest that this classification is clinically irrelevant if used for abdominal infections, skin and soft tissue infections and pneumonia. These findings cannot be applied directly to patients with meningitis, neutropenia or endocarditis, because we were unable to include these types of infection in our meta-analysis.

Acknowledgements

We are thankful for fruitful discussions with Rainer Weber, Nicolas Müller, Jan S. Fehr, Dominique L. Braun, Huldrych F. Guenthard, Ulrich Matt, Elisabeth and Titus Nemeth.

Funding

This study was carried out as part of our routine work.

Transparency declarations

None to declare.

Author contributions

Study concept and design: J. N., G. O. and S. P. K. Acquisition of data: J. N., G. O. and S. P. K. Statistical analysis: J. N. and S. P. K. Analysis and interpretation of data: J. N., G. O. and S. P. K. Drafting of the manuscript: J. N. and S. P. K. Critical revision of the manuscript for important intellectual content: J. N., G. O. and S. P. K.

Supplementary data

Figures S1 to S7 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

References

1 Habib G, Hoen B, Tornos P *et al*. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the International Society of Chemotherapy (ISC) for Infection and Cancer. *Eur Heart J* 2009; **30**: 2369–413.

2 American Thoracic Society. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; **171**: 388–416.

3 Cohen J, Powderly WG, Opal SM *et al*. *Infectious Diseases, 2 vols*. Mosby, 2003.

4 Fauci A, Dennis L, Longo D *et al*. *Harrison's Principles of Internal Medicine*. McGraw-Hill Professional, 2008.

5 Cubist Pharmaceuticals Inc. Lexington, MA, USA. http://www.cubicin.com/about.html.

6 Wunderink RG, Niederman MS, Kollef MH *et al*. Linezolid in methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a randomized, controlled study. *Clin Infect Dis* 2012; **54**: 621–9.

7 Itani KM, Dryden MS, Bhattacharyya H *et al*. Efficacy and safety of linezolid versus vancomycin for the treatment of complicated skin and soft-tissue infections proven to be caused by methicillin-resistant *Staphylococcus aureus*. *Am J Surg* 2010; **199**: 804–16.

8 Jauregui LE, Babazadeh S, Seltzer E *et al*. Randomized, double-blind comparison of once-weekly dalbavancin versus twice-daily linezolid therapy for the treatment of complicated skin and skin structure infections. *Clin Infect Dis* 2005; **41**: 1407–15.

9 Kohno S, Yamaguchi K, Aikawa N *et al*. Linezolid versus vancomycin for the treatment of infections caused by methicillin-resistant *Staphylococcus aureus* in Japan. *J Antimicrob Chemother* 2007; **60**: 1361–9.

10 Lin DF, Zhang YY, Wu JF *et al*. Linezolid for the treatment of infections caused by Gram-positive pathogens in China. *Int J Antimicrob Agents* 2008; **32**: 241–9.

11 San Pedro GS, Cammarata SK, Oliphant TH *et al*. Linezolid versus ceftriaxone/cefpodoxime in patients hospitalized for the treatment of *Streptococcus pneumoniae* pneumonia. *Scand J Infect Dis* 2002; **34**: 720–8.

12 Stevens DL, Smith LG, Bruss JB *et al*. Randomized comparison of linezolid (PNU-100766) versus oxacillin-dicloxacillin for treatment of complicated skin and soft tissue infections. *Antimicrob Agents Chemother* 2000; **44**: 3408–13.

13 Hatala R, Dinh T, Cook DJ. Once-daily aminoglycoside dosing in immunocompetent adults: a meta-analysis. *Ann Intern Med* 1996; **124**: 717–25.

14 Cochrane Collaboration. *Cochrane Handbook for Systematic Reviews of Interventions*. http://handbook.cochrane.org/.

15 Bergallo C, Jasovich A, Teglia O *et al*. Safety and efficacy of intravenous tigecycline in treatment of community-acquired pneumonia: results from a double-blind randomized phase 3 comparison study with levofloxacin. *Diagn Microbiol Infect Dis* 2009; **63**: 52–61.

16 Bohte R, van't Wout JW, Lobatto S *et al*. Efficacy and safety of azithromycin versus benzylpenicillin or erythromycin in community-acquired pneumonia. *Eur J Clin Microbiol Infect Dis* 1995; **14**: 182–7.

17 Dartois N, Castaing N, Gandjini H *et al*. Tigecycline versus levofloxacin for the treatment of community-acquired pneumonia: European experience. *J Chemother* 2008; **20** Suppl 1: 28–35.

18 Genne D, Siegrist HH, Humair L *et al*. Clarithromycin versus amoxicillin-clavulanic acid in the treatment of community-acquired pneumonia. *Eur J Clin Microbiol Infect Dis* 1997; **16**: 783–8.

19 Kuzman I, Dakovic-Rode O, Oremus M *et al*. Clinical efficacy and safety of a short regimen of azithromycin sequential therapy vs standard cefuroxime sequential therapy in the treatment of community-acquired pneumonia: an international, randomized, open-label study. *J Chemother* 2005; **17**: 636–42.

20 Mehtar S, Parr JH, Morgan DJ. A comparison of cefuroxime and co-trimoxazole in severe respiratory tract infections. *J Antimicrob Chemother* 1982; **9**: 479–84.

21 Mokabberi R, Haftbaradaran A, Ravakhah K. Doxycycline vs. levofloxacin in the treatment of community-acquired pneumonia. *J Clin Pharm Ther* 2010; **35**: 195–200.

22 Plouffe J, Schwartz DB, Kolokathis A *et al*. Clinical efficacy of intravenous followed by oral azithromycin monotherapy in hospitalized patients with community-acquired pneumonia. The Azithromycin Intravenous Clinical Trials Group. *Antimicrob Agents Chemother* 2000; **44**: 1796–802.

23 Shanson DC, McNabb WR, Williams TD *et al*. Erythromycin compared with a combination of ampicillin plus flucloxacillin for the treatment of community acquired pneumonia in adults. *J Antimicrob Chemother* 1984; **14**: 75–9.

24 Sterner G, Fransen H, Tunevall G *et al*. A comparative trial of cephaloridine and erythromycin in hospitalized pneumonic patients. *Postgrad Med J* 1967; **43** Suppl 43: 53–4.

25 Tanaseanu C, Bergallo C, Teglia O *et al*. Integrated results of 2 phase 3 studies comparing tigecycline and levofloxacin in community-acquired pneumonia. *Diagn Microbiol Infect Dis* 2008; **61**: 329–38.

26 Tanaseanu C, Milutinovic S, Calistru PI *et al*. Efficacy and safety of tigecycline versus levofloxacin for community-acquired pneumonia. *BMC Pulm Med* 2009; **9**: 44.

27 Bernard P, Plantin P, Roger H *et al*. Roxithromycin versus penicillin in the treatment of erysipelas in adults: a comparative study. *Br J Dermatol* 1992; **127**: 155–9.

28 Breedt J, Teras J, Gardovskis J *et al*. Safety and efficacy of tigecycline in treatment of skin and skin structure infections: results of a double-blind phase 3 comparison study with vancomycin-aztreonam. *Antimicrob Agents Chemother* 2005; **49**: 4658–66.

29 Chuang YC, Chang CM, Aradhya S *et al*. Efficacy and safety of tigecycline monotherapy compared with vancomycin-aztreonam in the treatment of complicated skin and skin structure infections in patients from India and Taiwan. *J Microbiol Immunol Infect* 2011; **44**: 116–24.

30 Ellis-Grosse EJ, Babinchak T, Dartois N *et al*. The efficacy and safety of tigecycline in the treatment of skin and skin-structure infections: results of 2 double-blind phase 3 comparison studies with vancomycin-aztreonam. *Clin Infect Dis* 2005; **41** Suppl 5: S341–53.

31 Sacchidanand S, Penn RL, Embil JM *et al*. Efficacy and safety of tigecycline monotherapy compared with vancomycin plus aztreonam in patients with complicated skin and skin structure infections: results from a phase 3, randomized, double-blind trial. *Int J Infect Dis* 2005; **9**: 251–61.

32 Stevens DL, Smith LG, Bruss JB *et al*. Randomized comparison of linezolid (PNU-100766) versus oxacillin-dicloxacillin for treatment of complicated skin and soft tissue infections. *Antimicrob Agents Chemother* 2000; **44**: 3408–13.

33 Chen Z, Wu J, Zhang Y *et al*. Efficacy and safety of tigecycline monotherapy vs. imipenem/cilastatin in Chinese patients with complicated intra-abdominal infections: a randomized controlled trial. *BMC Infect Dis* 2010; **10**: 217.

34 Oliva ME, Rekha A, Yellin A *et al*. A multicenter trial of the efficacy and safety of tigecycline versus imipenem/cilastatin in patients with complicated intra-abdominal infections [Study ID Numbers: 3074A1-301-WW; ClinicalTrials.gov Identifier: NCT00081744]. *BMC Infect Dis* 2005; **5**: 88.

35 Qvist N, Warren B, Leister-Tebbe H *et al*. Efficacy of tigecycline versus ceftriaxone plus metronidazole for the treatment of complicated intra-abdominal infections: results from a randomized, controlled trial. *Surg Infect* 2012; **13**: 102–9.

36 Towfigh S, Pasternak J, Poirier A *et al*. A multicentre, open-label, randomized comparative study of tigecycline versus ceftriaxone sodium plus metronidazole for the treatment of hospitalized subjects with complicated intra-abdominal infections. *Clin Microbiol Infect* 2010; **16**: 1274–81.

37 Frenck RW Jr, Nakhla I, Sultan Y *et al*. Azithromycin versus ceftriaxone for the treatment of uncomplicated typhoid fever in children. *Clin Infect Dis* 2000; **31**: 1134–8.

38 Kohno S, Yamaguchi K, Aikawa N *et al*. Linezolid versus vancomycin for the treatment of infections caused by methicillin-resistant *Staphylococcus aureus* in Japan. *J Antimicrob Chemother* 2007; **60**: 1361–9.

39 Markowitz N, Quinn EL, Saravolatz LD. Trimethoprim-sulfamethoxazole compared with vancomycin for the treatment of *Staphylococcus aureus* infection. *Ann Intern Med* 1992; **117**: 390–8.

40 Mwengee W, Butler T, Mgema S *et al*. Treatment of plague with gentamicin or doxycycline in a randomized clinical trial in Tanzania. *Clin Infect Dis* 2006; **42**: 614–21.

41 Ode B, Cronberg S, Flamholc L *et al*. Intravenous mecillinam, trimethoprim and ampicillin in acute pyelonephritis. *Drugs Exp Clin Res* 1983; **9**: 337–43.

42 Raad I, Bompart F, Hachem R. Prospective, randomized dose-ranging open phase II pilot study of quinupristin/dalfopristin versus vancomycin in the treatment of catheter-related staphylococcal bacteremia. *Eur J Clin Microbiol Infect Dis* 1999; **18**: 199–202.

43 Tasina E, Haidich AB, Kokkali S *et al*. Efficacy and safety of tigecycline for the treatment of infectious diseases: a meta-analysis. *Lancet Infect Dis* 2011; **11**: 834–44.

44 Ramirez J, Dartois N, Gandjini H *et al*. Randomized phase 2 trial to evaluate the clinical efficacy of two high-dosage tigecycline regimens versus imipenem-cilastatin for treatment of hospital-acquired pneumonia. *Antimicrob Agents Chemother* 2013; **57**: 1756–62.

45 Cho SY, Kang CI, Chung DR *et al*. Breakthrough bacteremia due to extended-spectrum-β-lactamase-producing *Klebsiella pneumoniae* during combination therapy with colistin and tigecycline. *Antimicrob Agents Chemother* 2012; **56**: 4994–5.

46 Mandell G, Bennett J, Dolin R. *Principles and Practice of Infectious Diseases*. Philadelphia: Churchill Livingstone, 2010.

47 Jaksic B, Martinelli G, Perez-Oteyza J *et al*. Efficacy and safety of linezolid compared with vancomycin in a randomized, double-blind study of febrile neutropenic patients with cancer. *Clin Infect Dis* 2006; **42**: 597–607.

48 Pankey GA, Sabath LD. Clinical relevance of bacteriostatic versus bactericidal mechanisms of action in the treatment of Gram-positive bacterial infections. *Clin Infect Dis* 2004; **38**: 864–70.

49 Buyck JM, Plesiat P, Traore H *et al*. Increased susceptibility of *Pseudomonas aeruginosa* to macrolides and ketolides in eukaryotic cell culture media and biological fluids due to decreased expression of oprM and increased outer-membrane permeability. *Clin Infect Dis* 2012; **55**: 534–42.

50 Drusano GL, Liu W, Fikes S *et al*. Interaction of drug- and granulocyte-mediated killing of *Pseudomonas aeruginosa* in a murine pneumonia model. *J Infect Dis* 2014; doi:10.1093/infdis/jiu237.