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MAJOR ARTICLE

The Effect of Antibiotic Restriction Programs on Prevalence of Antimicrobial Resistance: A Systematic Review and Meta-Analysis

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Background. In hospital settings, restriction of selected classes of antibiotics is usually believed to contribute to containment of resistance development. We performed a systematic review and meta-analysis to assess the effect of restricting the use of specific antibiotic classes on the prevalence of resistant bacterial pathogens.

Methods. We conducted a systematic literature search in Embase and PubMed/OVID MEDLINE. We included studies until June 4, 2020 in which a restrictive antibiotic policy was applied and prevalence of resistance and use of antibiotics were reported. We calculated the overall effect of antimicrobial resistance between postintervention versus preintervention periods using pooled odds ratios (ORs) from a mixed-effects model. We stratified meta-analysis by antibiotic-pathogen combinations. We assessed heterogeneity between studies using the I^2 statistic and sources of heterogeneity using meta-regression.

Results. We included 15 individual studies with an overall low quality of evidence. In meta-analysis, significant reductions in resistance were only observed with nonfermenters after restricting fluoroquinolones (OR = 0.77, 95% confidence interval [CI] = 0.62–0.97) and piperacillin-tazobactam (OR = 0.81, 95% CI = 0.72–0.92). High degrees of heterogeneity were observed with studies restricting carbapenem (Enterobacterales, I^2 = 70.8%; nonfermenters, I^2 = 81.9%), third-generation cephalosporins (nonfermenters, I^2 = 63.3%), and fluoroquiolones (nonfermenters, I^2 = 64.0%). Results were comparable when excluding studies with fewer than 50 bacteria. There was no evidence of publication bias for any of the antibiotic-pathogen combinations.

Conclusions. We could not confirm that restricting carbapenems or third-generation cephalosporins leads to decrease in prevalence of antibiotic resistance among Enterobacterales, nonfermenters, or Gram-positive bacteria in hospitalized patients. Nevertheless, reducing fluoroquinolone and piperacilline-tazobactam use may decrease resistance in nonfermenters.

Keywords. antibiotic restriction; antibiotic stewardship; antimicrobial resistance.

The misuse of antibiotics is known to drive the development of antimicrobial resistance [1, 2]. To counter the growing problem of antimicrobial resistance, most hospitals have adopted antimicrobial stewardship programs, whereby the goal is to optimize the beneficial effects of antibiotics, while at the same time keeping its negative consequences for both individual patients and the community to a minimum.

Many researchers have pointed out the evident relationship between use of antimicrobials and rates of resistance, and thus a decrease of overall use is generally desirable to curb resistance [1]. Indeed, a decrease in antibiotic use can be considered beneficial if there is evidence that antibiotics are being used inappropriately. However, if antimicrobial use is already optimal in a specific setting, decrease of antibiotic use might give way to undertreatment. Furthermore, a decrease in the use of one antibiotic can result in increased use of an alternative antibiotic, possibly diminishing any intended overall effect on resistance. Taken together, it is important to realize that the quantity of antimicrobial use is difficult to interpret if it is given as a sole outcome measure. The spectrum of the used antibiotics must also be taken into account [3–5].

We previously performed a systematic review and meta-analysis in which we assessed whether 14 antimicrobial stewardship objectives, such as pathogen-directed therapy or switching from intravenous to oral therapy, had tangible effects in hospitals and long-term care facilities [6]. We could establish an effect on resistance rates for only 1 stewardship objective, namely, using a list of restricted antibiotics. It is unfortunate that, due to the broad scope of that study, we were unable to

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[a]Our friend and colleague Johan Mouton regretfully passed away on July 9, 2019.

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further elaborate on other results obtained from the included studies. For that reason, in the present systematic review, we took a more in-depth look and also performed an update of the initial literature search, with the objective of systematically determining whether and which antibiotics can be restricted to help reverse antimicrobial resistance rates. More specifically, we aimed to analyze the specific effect of restricting particular antibiotic classes on the resistance rates of various bacterial pathogens. We additionally intended to assess whether other accompanying variables could influence the effect of restricted antibiotic use on resistance prevalence.

METHODS

Search Strategy

We had previously reviewed the evidence published until April 11, 2014 of the influence of 14 hospital antimicrobial stewardship objectives on 4 patient outcomes (ie, clinical outcomes, adverse events, costs, and bacterial resistance prevalence) [6]. This study encompassed individual systematic reviews for these 14 objectives, one of which involved using lists of restricted antibiotics. With the help of a clinical librarian, we performed an updated search of studies that investigated the effect of using a list of restricted antimicrobials published in Embase and PubMed/OVID MEDLINE from April 11, 2014 until June 4, 2020. Detailed search terms are presented in Supplementary A Search strategy.

All titles and abstracts were reviewed by one author (E.C.S.), and a second author (J.M.P. or J.W.M.) independently screened a random selection of 10% of all titles and abstracts. Discussion was used to resolve any discordances on inclusion or exclusion of studies, when necessary with a third reviewer. Both reviewers then assessed the eligibility of all articles initially identified as potentially relevant by reading the full text. We searched for additional studies suitable for inclusion using the reference list of the articles that were viewed in full text.

Inclusion and Exclusion Criteria

We looked for studies that assessed the effect of restrictive antimicrobial prescribing. By restrictive prescribing, we mean removal of specific antibiotics from the formulary, restriction of use by requiring preauthorization from a specialist (infectious diseases or medical microbiology), or allowing use for only 24–72 hours with mandatory approval for further use. The main antibiotic classes of interest were carbapenems, fluoroquinolones, and third-generation cephalosporins. Papers in which none of these 3 antibiotics were restricted were excluded.

Prespecified study types that were eligible for inclusion were randomized controlled trials, nonrandomized controlled trials (controlled before-after studies), interrupted time series, observational studies (including cohort, cross-sectional, and case-control studies), and systematic reviews. Excluded designs were case reports, narrative reviews, discussion papers, conference papers, letters to the editor, and editorials. We included studies in English, German, and Dutch.

We excluded studies that did not report data on both resistance prevalence and antimicrobial use. The number of isolates tested for each bacterial pathogen, with their resistance prevalence, had to be reported or calculable. If a study reported resistance percentages without the number of bacterial isolates tested, the effect size was unable to be estimated and hence the study was excluded. We did not restrict our search to a specific infection; however, study outcomes needed to relate to antibiotic treatment and be performed in hospitals or long-term care facilities. We included research in adults (18 years or older) and not in children or adolescents. We excluded studies addressing the outpatient or general practitioner setting. Studies in an outbreak setting were excluded, because these often contain multiple interventions used for infection control. Studies on methicillin-resistant *Staphylococcus aureus* or Clostridium *difficile* were not included in this study.

Data Extraction

The following parameters were extracted from the included papers: the year of publication, first author's name, study setting (intensive care unit [ICU], hospital, mixed), details and duration of the intervention and control conditions, number of individuals and number of individuals with antimicrobial-resistant bacteria in the preintervention and postintervention periods, quantity of antibiotics used in the preintervention and postintervention periods, postintervention duration, and type of infection studied (nosocomial, community-acquired, both). If bacteria were not clearly reported as nosocomial or community-acquired, we considered colonization and infection from studies conducted in the ICU department as nosocomial.

We extracted data (1) from the period before the start of the intervention and (2) at the end of the intervention or the last reported measurement. The prevalence of resistance during the preintervention and postintervention periods had to be reported for Enterobacterales, nonfermenters, or Gram-positive bacteria. If the number of susceptible bacteria were only given, we assumed that the remaining bacteria had resistance. We also extracted the use of nonrestricted antibiotics, if reported, to assess whether there was any carryover effect of restrictive use to other antibiotics, which could then influence resistance prevalence. We limited these antibiotics to cotrimoxazole, piperacillin-tazobactam, and first- and second-generation cephalosporins.

We extracted data from either the manuscript text and/or tables. If necessary, we extracted data by estimating the approximate number from a graph. When 2 or more antibiotics with comparable resistance prevalence were reported within a class, we used the mean number of isolates with resistance across antibiotics divided by the total number of isolates tested

to calculate the resistance prevalence for that class. We included all measures for use of antibiotics, such as defined daily doses or the amount of antibiotics in grams, and reported the difference in use between preintervention and postintervention periods as percentages. We did not extract data on costs.

The information from all included studies was extracted by one reviewer (E.C.S.) and fully checked for accuracy by a second reviewer (J.M.P.). Missing data were not requested from study authors, and if the predefined data were not present, incomplete, or not interpretable, the study was excluded.

Quality Assessment

The quality of each included study was assessed independently by 2 reviewers (E.C.S. and J.M.P.) using the Cochrane Risk of Bias tool for randomized controlled trials and the Newcastle-Ottawa Quality Assessment Scale for nonrandomized studies [7, 8]. Disagreement between the reviewers was resolved by discussion, with the involvement of a third reviewer if necessary.

Statistical Analysis

We carried out all analysis using STATA (version 15.1; College Station, TX) and R (version 3.6.1; Vienna, Austria). For each study, we calculated odds ratios (ORs) comparing the odds of having antimicrobial resistance during the preintervention versus postintervention periods. We conducted meta-analyses of the calculated ORs using the "metan" command in STATA. We stratified meta-analysis by all combinations of antibiotic targeted (carbapenem, fluoroquinolones, third-generation cephalosporins, cotrimoxazole, piperacillin-tazobactam, and first- and second-cephalosporins) and bacteria (Enterobacterales, nonfermenters, or Gram-positive bacteria). We used a random-effects model to calculate DerSimonian and Laird pooled ORs. We also conducted sensitivity analyses in which studies with fewer than 50 participants in either the preintervention or postintervention period were excluded.

We assessed heterogeneity between studies using the I^2 statistic with an I^2 of >75% indicating substantial heterogeneity [9]. We explored sources of heterogeneity with meta-regression using the "metareg" command in STATA. The unit of measure analyzed was antibiotic-pathogen combination, and we stratified meta-regression by antibiotic targeted where there were more than 5 antibiotic-pathogen combinations available. The covariates in the meta-regression included difference in antibiotic usage in the postintervention versus preintervention period (relative change in percentage), type of bacteria (Enterobacterales, Gram-positive, or nonfermenters), prevalence of antimicrobial resistance in the preintervention period, duration of the postintervention period (in years), type of infection (nonspecified or nosocomial), and setting (hospital or ICU). We assessed the influence of outlying studies within antibiotic-pathogen combinations, provided there were more than 3 studies within a subgroup, using the method developed by Viechtbauer and Cheung [10] in the "metafor" package in R. We removed studies identified as outlying in a sensitivity analysis. We also assessed for publication bias using the Egger test of bias [11] with $P < .05$ indicating significant publication bias.

RESULTS

Search Results

Figure 1 summarizes the selection of studies for this updated systematic review. In our initial systematic review [6], we included 26 studies reporting data on resistance prevalence after applying a restrictive antibiotic policy. After excluding 16 studies that did not meet inclusion criteria for this analysis, 10 studies remained.

During the updated search (June 4, 2020), we found 911 new citations after removing duplicates: 447 in Embase and 464 in PubMed/MEDLINE. After screening titles and abstracts, we selected 44 potentially relevant studies for full-text screening. Less than 2.5% of the papers screened by the second author were missed as eligible by the first author. We identified 2 relevant papers after reviewing reference lists. Five studies were eligible for final inclusion (Figure 1, flowchart of systematic search; Supplementary A, search strategy). The main reasons for excluding studies were as follows: lack of data on predefined outcomes, study design and publication format, written in a language other than those of the search parameters, or missing data. Ten studies were excluded for not providing the number of isolates tested for each bacterial pathogen [12–21].

Combined with the 10 studies from the previous systematic review, 15 articles were included in the present analysis (Figure 1, flowchart of systematic search). The 15 studies originated from 11 countries, covering 5 continents (Supplementary B, characteristics). The duration of restrictive policies differed between studies, varying from 6 months to 10 years. Most studies [8] reported data from hospital wards, 6 from the ICU exclusively and 1 study from both settings. Only 1 study was performed in more than 1 hospital, whereas the remainder were single-center studies set at university [1], general care [5], and tertiary care hospitals [8]. No studies were performed in long-term care facilities. All studies were observational with a serious risk of qualitative bias, and thus the quality of research was judged to be poor (Supplementary B, characteristics of included studies).

Studies were grouped based on the restriction of the 3 main antibiotic classes: carbapenems [6, 22–27], fluoroquinolones [8, 22, 23, 28–33], and third-generation cephalosporins [9, 22–24, 29, 31, 32, 34–36]. In addition, we found studies on use and resistance prevalence of nonrestricted antibiotics for piperacillin-tazobactam [3, 22, 24, 36] and first- and second-generation cephalosporins [3, 22, 23, 31], but not for cotrimoxazole. For both restricted and nonrestricted antibiotics, most studies reported

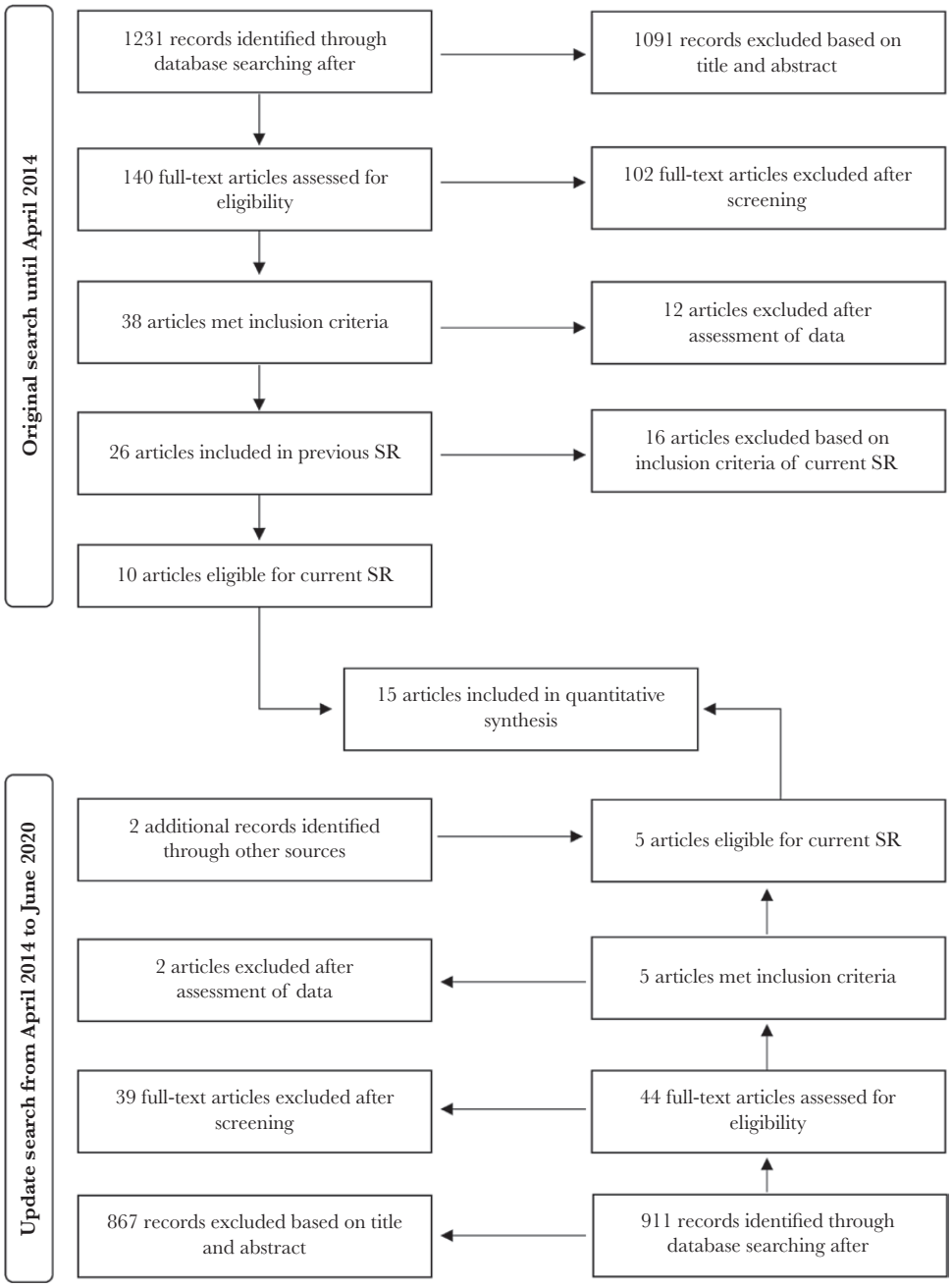

Figure 1. Flowchart of systematic search. SR, systematic review.

resistance prevalence in Enterobacterales and nonfermenters, whereas only 2 studies reported resistance prevalence in Gram-positive bacteria [23, 31]. Antibiotic use during preintervention and postintervention periods are provided according to study in Supplementary C, antibiotic use per study.

Effect of a Restrictive Intervention

Figure 2 displays a forest plot with individual ORs, indicating the effect sizes of each study. We observed a high degree of heterogeneity (I^2) across studies for most antibiotic-pathogen combinations, indicating large between-study variability. Exceptions were piperacillin-tazobactam/nonfermenters (I^2 = 0.0%), piperacillin-tazobactam/Enterobacterales (I^2 = 0.0%), and fluoroquinolones/Enterobacterales (I^2 = 0.0%). We did observe a significant effect for several antibiotic-pathogen combinations in individual studies. For example, data from Zhang et al [27] showed a significant 41% decrease in the odds of resistance of nonfermenters to carbapenems during the postintervention versus preintervention period (OR = 0.59, 95% confidence interval [CI] = 0.44–0.78). However, the pooled OR for this antibiotic-pathogen combination was not significant (OR = 0.87, 95% CI = 0.70–1.08). For 2 antibiotic-pathogen

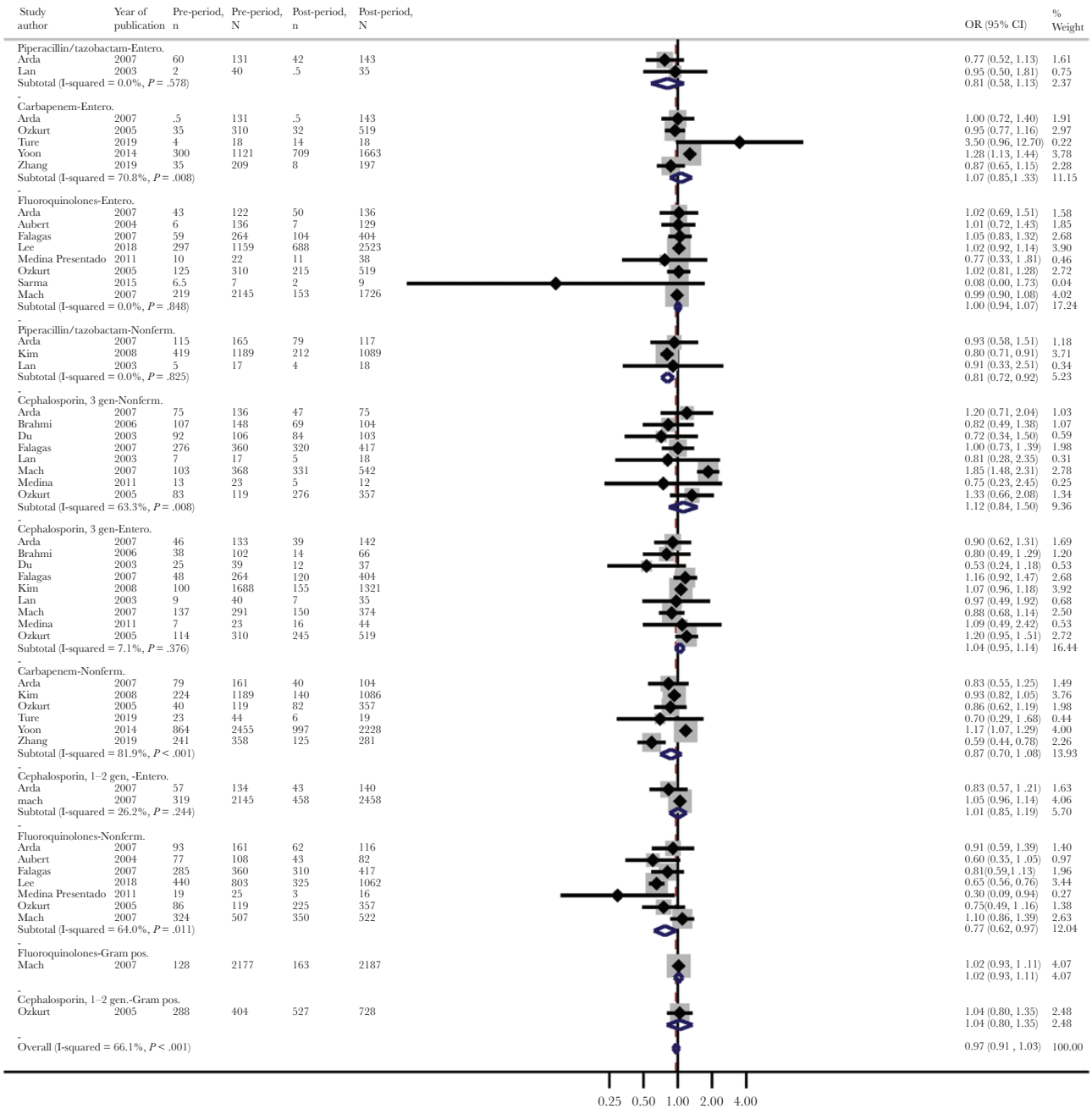

Figure 2. Effect sizes (odds ratios) comparing the prevalence of antibiotic resistance before and after implementing interventions to restrict antibiotic usage, analyzed in subgroups of antibiotic pathogen.

combinations, we did find a modest effect of restriction when comparing the pooled odds of having resistance during the postintervention versus preintervention periods: a 23% decrease in resistance to nonfermenters after restricted use of fluoroquinolones (OR = 0.77, 95% CI = 0.62–0.97) and a 19% decrease in resistance to nonfermenters after restricted use of piperacillin-tazobactam (OR = 0.81, 95% CI = 0.72–0.92). It is notable that, in these studies, piperacillin-tazobactam was not a part of the restricted antibiotics during the postintervention period. Due to a limited number of studies, a possible carryover effect could not be investigated for the remaining nonrestricted antibiotics (first- and second-generation cephalosporins and cotrimoxazole).

Results were comparable when excluding studies with fewer than 50 bacteria in either the preintervention or postintervention period (Supplementary D, forest plot of studies with ≥50 individuals in both periods). We identified 5 outlying studies for the bug-drug combinations that could be evaluated. When excluding these studies, we obtained comparable results, yet heterogeneity overall was reduced, and a significant 20% reduction

in resistance to nonfermenters was observed after restricted use of carbapenems (Supplementary E, influential studies removed). There was no evidence of publication bias for any of the antibiotic-pathogen combinations (Supplementary F, funnel plots).

In Table 1, we summarized the results of the meta-regression stratified on specific classes of antibiotics. Studies performed in the ICU versus other settings had significantly higher increases in resistance after restricting carbapenems (exp(β) = 2.78, 95% CI = 1.01–7.65, P = .04), whereas this was the opposite after restricting cephalosporins (exp(β) = 0.41, 95% CI = 0.20–0.84). The preintervention prevalence of antimicrobial resistance did not significantly change the effect on resistance after restricting carbapenems or third-generation cephalosporins (Figure 3A and B, respectively). However, higher preintervention prevalence of resistance did lead to stronger reductions in resistance after restricting cephalosporins (exp(β) percent = 0.98, 95% CI = 0.97–0.99) and fluoroquinolones (exp(β) percent = 0.98, 95% CI = 0.97–0.99), yet the observation with fluoroquinolones seems to be driven by 2 smaller studies with high preintervention prevalence (Figure 3C). No other factors, such as nosocomial infections, postintervention antibiotic use, or intervention duration, were found to explain the heterogeneity between studies within the same class of antibiotics.

DISCUSSION

Our systematic review and meta-analysis of 15 studies indicates that applying restrictive antibiotic interventions has a significant effect on the resistance of nonfermenters to fluoroquinolones. Reducing piperacillin-tazobactam use, although not through a restrictive intervention, also showed to have a significant effect on resistance of nonfermenters. For the other antibiotic-pathogen combinations, restriction did not result in a reduction of resistance. After excluding outlying studies in a sensitivity analysis, we obtained comparable results, while heterogeneity overall was reduced and a significant 20% reduction in resistance to nonfermenters was also observed after restricted use of carbapenems. In an exploratory analysis, no consistent factors were identified explaining the heterogeneity between studies within the same class of antibiotics.

Our findings are in disagreement with current in-hospital practice and with individual studies. It is therefore important to consider the substantial inconsistencies in the direction of effect sizes between included studies, which led to a high degree of heterogeneity, and the generally low quality of evidence. Sensitivity analyses excluding small studies yielded comparable results, and they did not indicate the presence of publication bias. The potential bias of analyzing aggregated data instead of individual-patient data could have also influenced the lack of observed relationships between antibiotic use and resistance [37]. Based on the present comprehensive overview of the available evidence, it is therefore perhaps too straightforward to conclude that applying a restrictive antibiotic policy is in general ineffective. However, high-quality research is lacking and is clearly needed before concluding otherwise.

This study has several strengths. First, we designed a broad search strategy and did not limit the search to specific antibiotics or bacterial species. Second, the risk of bias was assessed for each study by 2 independent authors, with a scale that was most suitable to the study design. Third, we looked for evidence for possible carryover effects of restriction by examining whether restrictive use of one antibiotic led to an increase in the use of other, nonrestricted antibiotics, with resulting increased resistance prevalence to these antibiotics. Finally, many of these

Table 1. Univariate Meta-Regression for the Effects of Antibiotic Restriction on Prevalence of Antimicrobial Resistance[a]

	Carbapenem			Cephalosporins			Fluoroquinolones		
	N	exp(β) (95% CI)	*P*	N	exp(β) (95% CI)	*P*	N	exp(β) (95% CI)	*P*
Relative difference in antibiotic usage (%)	11	0.99 (0.97–1.01)	.17	9	1.00 (0.99–1.02)	.60	14	1.01 (1.00–1.02)	.07
Bacteria									
Enterobacterales	5	Ref		9	Ref		8	Ref	
Nonfermenters	6	0.63 (0.16–2.51)	.47	8	1.19 (0.57–2.50)	.62	7	0.63 (0.34–1.16)	.13
Gram-positive	0	--		0	--		1	1.34 (0.44–4.05)	.58
Prevalence antimicrobial resistance preintervention (%)	11	0.99 (0.94–1.04)	.73	17	0.98 (0.97–0.99)	.04	14	0.98 (0.97–0.99)	.04
Duration of intervention (years)	11	0.86 (0.66–1.14)	.26	14	1.34 (0.83–2.17)	.21	16	0.98 (0.88–1.09)	.69
Type of Infection									
Nonspecified	5	Ref		8	Ref		13	Ref	
Nosocomial	6	1.57 (0.33–7.39)	.53	6	0.60 (0.26–1.38)	.21	3	1.03 (0.38–2.76)	.95
Setting									
Hospital	7	Ref		7	Ref		10	Ref	
ICU	4	2.78 (1.01–7.65)	.04	7	0.41 (0.20–0.84)	.02	6	0.74 (0.35–1.55)	.40

Abbreviations: CI, confidence interval; ICU, intensive care unit; N, number of antibiotic-pathogen combinations included; Ref, Reference variable.

[a]The reduction in resistance prevalence after antibiotic restriction was significantly stronger because the exponentiated regression coefficient (β) was significantly less than one and vice versa. "—," no studies pertained to these categories and hence the parameter estimate could not be calculated. Analysis was not performed for first- and second-generation cephalosporins and piperacillin-tazobactam due to limited numbers of antibiotic-pathogen combinations.

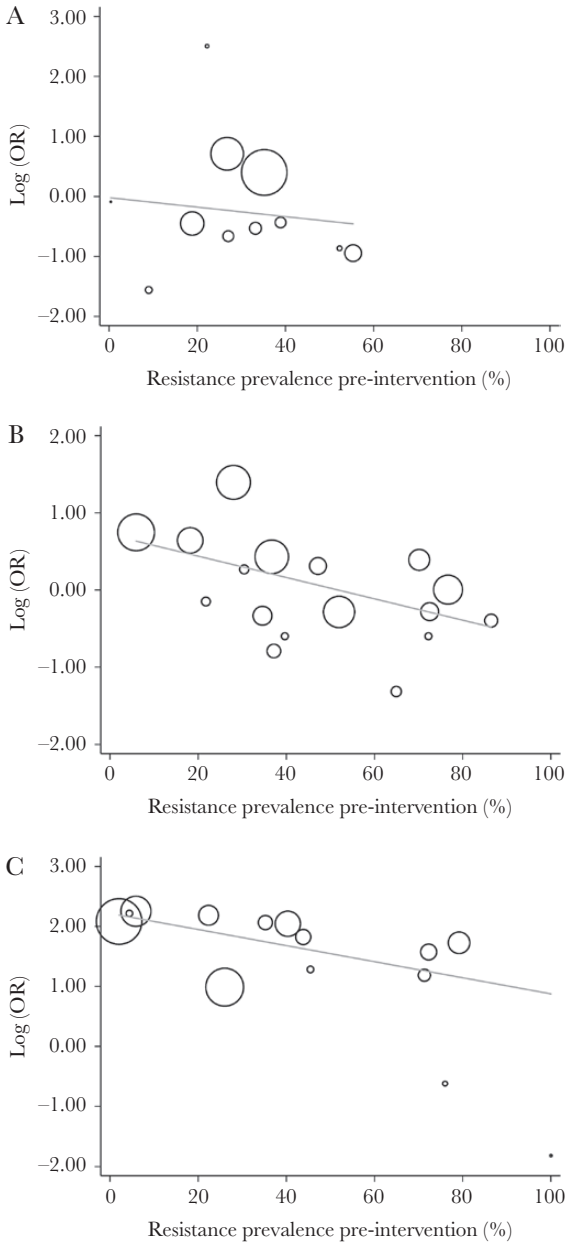

Figure 3. Effect size in relation to resistance prevalence preintervention for carbapenems (A), third-generation cephalosporins (B), and fluoroquinolones (C). OR, odds ratios.

studies included low numbers of isolates and might not have been sufficiently powered to describe the effect of a restrictive intervention on a given antibiotic-pathogen combination. By pooling these studies together, we are able to offer a more robust picture of the effect that these interventions have on resistance.

However, we should be aware that 4 studies did not clearly report whether bacteria were nosocomial or community-acquired [23, 29–31]. Second, only a limited number of studies were included per antibiotic group, and, although we carefully assessed factors influencing resistance rates, it is possible that certain variables affecting antimicrobial resistance were left out of the meta-regression. Third, we did not perform a search of gray literature and restricted our search to Embase and PubMed/OVID MEDLINE. This may have resulted in some relevant studies being missed. We did not apply a filter for publication date in our search, and the final analysis included studies published between 1985 and 2020. The resistance rates and antibiotics used have changed considerably over this period. Finally, we only focused on 3 restricted antibiotic classes in this systematic review, and thus we are unable to draw any conclusions on the effect of restrictive antibiotic policies for other antibiotics.

It has been commonly understood that increased antibiotic use is correlated with the development of antimicrobial resistance at the population level [38]. Furthermore, restricting overall antibiotic use has been shown to decrease antibiotic resistance in livestock, in outpatients, and during infection outbreaks [39–44]. In our previous systematic review[6], we reported that "Restrictive antibiotic policies were associated with reduced resistance rates in most of the studies we assessed, but inconsistent relations between antibiotic use and resistance rates were also found." A recent qualitative systematic review also provided support towards a beneficial effect of these policies for several antibiotic-pathogen combinations [45]. In our current, in-depth analysis, which only included studies reporting the number of isolates tested, we conclude that, in contrast to interventions in livestock and in the community, restrictive antibiotic policies as a single intervention might not be an effective tool to achieve decreases in the prevalence of resistance in hospitalized adults. Considering that most studies reported nosocomial infections or were conducted in an ICU setting, resistance in these patients was probably acquired or selected during admission.

A systematic review and meta-analysis by Baur et al [46] has shown a significant reduction in the incidence of infections and colonization with antibiotic-resistant bacteria through implementation of antibiotic stewardship programs. This indicates a beneficial effect of a multifactorial intervention. However, the direct effect of a single stewardship improvement strategy, such as restriction, could not be assessed in their study.

CONCLUSIONS

The currently available evidence for the selected antibiotic-pathogen combinations in hospitalized patients is insufficient to conclude that applying a short-term restrictive antibiotic prescribing policy has the generally presumed effect of decreasing bacterial resistance. A restrictive intervention might be useful when specifically targeting a decrease in resistance of nonfermenters. Long-term effects cannot be excluded, because the time window of these interventions was often relatively short. Given the poor quality of studies with regard to methods used and reporting of data, we feel that there is a strong need for high-quality studies to address this question and to explore alternative interventions that could bring way to reduced prevalence of antimicrobial resistance.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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