Computerized Clinical Decision Support Systems and Antibiotic Prescribing: A Systematic Review and Meta-analysis

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ABSTRACT

Purpose: The aim of this study was to perform a systematic review and meta-analysis of studies performed in primary care centers and hospital facilities that evaluated the effectiveness of computerized clinical decision support systems (CDSSs) in decision making on the prescription of any given antibiotic.

Methods: We conducted a search of the MEDLINE and EMBASE databases. A meta-analysis was then conducted of all variables with results reported in >2 studies.

Findings: A total of 42 of the 46 studies included in the review identified a statistically significant advantage for CDSSs in ≥1 study variables. The effect of CDSSs on the percentage accuracy of the antibiotic spectrum prescribed empirically with respect to the microbial agent's susceptibility, which is one of the most frequently studied outcome variables, was examined in 7 studies, all undertaken in hospital settings. In all these studies but one, CDSSs resulted in a statistically significant increase in percentage accuracy. The other study variables present in >2 studies had more inconsistent results. Although the results of the meta-analysis of the variables percentage accuracy, antibiotic prescription rate in hospital, percentage adherence to antibiotic prescription guidelines in primary care or hospital, and percentage of inappropriate prescriptions for antibiotics in primary care were statistically significantly favorable to CDSSs; in the case of hospital length of stay and mortality, they were favorable although not statistically significantly.

Implications: CDSSs appear to be useful for variables such as the percentage of appropriate empirical treatment in the hospital setting or to induce changes in antibiotics prescription rate. Even so, more better quality studies are required to draw clearer conclusions in respect of morbidity and mortality outcome variables and other settings. (*Clin Ther*. 2019;41:552–581)

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INTRODUCTION

Currently, antibiotic resistance is one of the main threats to public health. One of the principal reasons for this is the high antibiotic misprescription rate.[1] Such antibiotic misuse can further drive the emergence of antibiotic-resistant pathogens. Analysis of these prescriptions reveals a wide variability among countries[2] and physicians, variations that are not accounted for by differences in disease incidence.[3] This finding indicates that although there is scientific evidence of the treatment of choice in each infectious disease, the degree of follow-up is low.[1,4]

One of the strategies for enhancing the incorporation of scientific evidence is to implement clinical decision support systems (CDSSs) in the form of computerized expert systems. These systems, which incorporate an underlying algorithm for clinical decision making, are an important method for improving decision making in clinical practice.[5] Many clinical trials and observational studies have been conducted to assess the effectiveness of computerized CDSSs for improving antibiotics' prescription in both primary care centers and hospitals. However, as far as we know, no meta-analysis that includes both settings has been performed so far.

Therefore, we conducted a systematic review and meta-analysis of studies performed in primary care centers and hospital facilities that evaluated the effectiveness of these expert computerized systems in decision making on the prescription of any given antibiotic. The primary objective of this study is to examine whether the use of a CDSS is associated with improved antibiotic prescribing, and the secondary objective is to determine whether CDSSs are associated with lower morbidity and mortality.

METHODS

We followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[6] to perform the following systematic review and meta-analysis. We conducted a bibliographic search of the MEDLINE and EMBASE databases, covering the end of 2017 to the previous 21 years and using the following keywords: (*antibiotic** OR *antimicrobial**) AND (*clinical-decision-support-system* OR *decision-support-system* OR *computer-assisted decision making* OR *expert-system* OR *decision-support*). These keywords were selected to make it possible to retrieve articles known to the authors regarding CDSS and antibiotics.

Of the total number of articles retrieved, a selection performed by 2 reviewers (E.C.M. and A.T.R.) was made by reference to the language used and the topic addressed in the title and/or abstract. This resulted in all articles that were not written in English, Spanish, or French or that did not address the designated study topic being discarded.

Articles cited as references in those yielded by the search were also selected. The inclusion criteria were as follows: the article had to be exclusively confined to the study of antibiotics (articles that studied the effect of CDSS only on a mix of antibiotics and antifungal agents or antibiotics and medications for rhinorrhea or antipyretics were not included); statistical analysis had to be by intention to treat; there had to be a comparison group without a CDSS; the control group had to be concurrent or pre-post; at minimum, the CDSS had to focus on prescribing physicians (which did not exclude the possibility of it also focusing on other professionals); the study had to analyze the effect of CDSS on clinical variables or variables of cost or antibiotic consumption (excluding studies that only expressed an opinion on CDSSs or solely addressed the workload of the hospital pharmacy department); the study had to be longitudinal; and the sample sizes of groups had to be available.

Two reviewers (E.C.M. and A.T.R.) independently abstracted the following data from all studies that met the eligibility criteria: study setting, study methods, country of study, year of publication, target population, sample size, study period, study design, funding, CDSS characteristics, patient characteristics, and study outcomes (in studies with several outcomes, those outcomes not with intention-to-treat analysis or not exclusively confined to the study of antibiotics were not included). Disagreements were resolved by a third reviewer (A.F.).

With regard to CDSS characteristics, CDSSs were classified into not web computer programs or web pages. CDSSs belonged in the latter category when authors of the study denote the CDSS as web and it has interlinks with internet or intranet.

Measure of Quality

Two reviewers (E.C.M. and A.T.R.) independently measured studies quality, and disagreements were resolved by a third reviewer (A.F.). To measure quality, we relied on a classification used in previous studies,[5,7] with a possible score range of 0 to 10 points. The 10-point scale consists of 5 potential sources of bias. In brief, we considered the following: method of allocation to study groups (random [2] vs quasi-random [1] vs selected concurrent controls [0)]; unit of the allocation (a cluster, such as a practice [2] vs physician [1] vs patient [0]); presence of any baseline differences between the groups that were potentially linked to study outcomes (no baseline differences present or appropriate statistical adjustments made for differences [2] vs baseline differences present and no statistical adjustments made [1] vs baseline characteristics not reported [0]); the objectivity of the outcome (objective outcomes or subjective outcomes with blinded assessment [2] vs subjective outcomes with no blinding but clearly defined assessment criteria [1] vs subjective outcomes with no blinding and poorly defined [0]); and the completeness of follow-up for the appropriate unit of analysis (>90% [2] vs 80% to 90% [1] vs <80% or not described [0]).

Statistical Analysis

To ascertain whether there had been an increase in study quality across time, we applied the Mann−Whitney statistical test to compare pre-2010 to 2010 and post-2010 quality scores, as in previous studies.[5] The Mann−Whitney statistical test is used because the distribution of the quality across time does not follow a normal distribution.

To determine whether studies characteristics such as clinical setting (hospital or primary care), kind of CDSS initiation (system or user), mode of CDSS delivery (multifaceted or CDSS only), or total quality score (<5 or >5) had any influence on results being statistically favorable to CDSS we used the χ^2 test.

We used 2 main effect estimates in the meta-analysis, depending on which data were available in the studies: odds ratios (ORs) for noncontinuous data (events, mortality) and standardized mean differences (SMDs) for continuous data (mean change). SMDs, also called the Cohen d or effect size, compare treatment and placebo and are weighted by the pooled SD of both arms. An SMD of zero signifies no difference between intervention and control; a negative result favors intervention in our case (because scores for medication costs, length of stay, and prescription rate decrease when the intervention is effective), whereas a positive result favors control. A large effect is defined as >0.8 units, a medium effect as >0.5 units, and a small effect as <0.2 units.[8]

In the case of SMDs, we weighted the study-specific SMDs by the inverse of their variance to compute a pooled effect size and its 95% CI. We assessed heterogeneity using the Cochran Q-statistics and the proportion of total variance attributable to between-study variance I^2 to obtain fixed-effect estimates or pooled random-effect estimates, using the latter when heterogeneity was present.

Funnel plots were used to assess publication bias visually. However, such plots have several limitations and are purely an informal way of detecting publication bias. Because we could not use the total sample of the review, we therefore performed more formal testing using the test proposed by Egger et al.[9]

All statistical analyses were performed using Comprehensive Meta-analysis Software (Biosta, Englewood, New Jersey).

RESULTS

Selection of Articles

Figure 1 shows the flow of studies through the review. Although 45 articles met the inclusion criteria,[10−54] 1 article reported 2 different types of studies,[16] thereby making a total of 46 studies (14 conducted in a primary care setting and the remainder in a hospital setting). Of the 46 studies, 35 had outcome variables that were present in >2 studies and thus where included in the meta-analysis.

Study Description

Table I gives the characteristics of the studies. Although 30 of the 46 studies focused on a single professional (ie, the physician), the remainder jointly targeted a series of professionals that comprised a team (physicians plus nurses or pharmacists). Study quality is given in Table II, with a mean score of 5.15 and a median score of 4 (range, 2-10). The statistical analysis failed to find any increase in study quality across time ($p = 0.596$).

The characteristics of CDSSs used in the various studies are given in Table III. Although most of the CDSSs ($n = 41$) consisted of not web computer

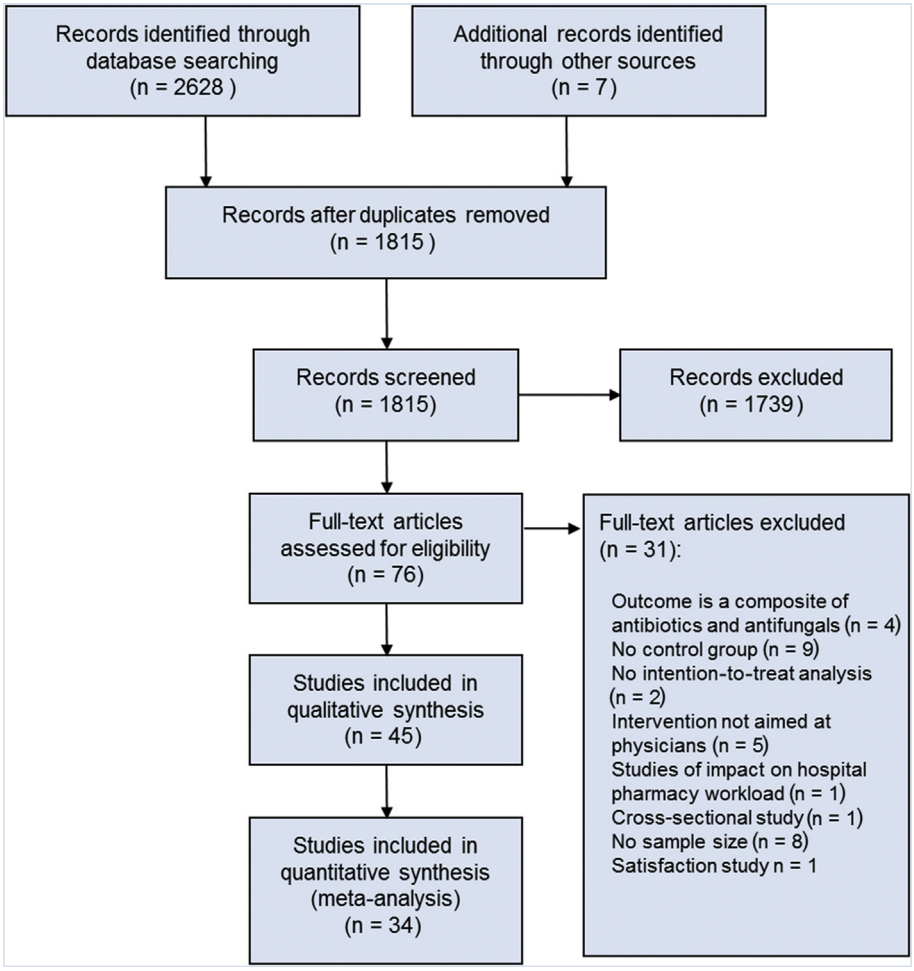

Figure 1. Flow diagram.

programs, on 5 occasions they were in the form of web pages. On 2 occasions, the computer program was only available in a mobile electronic device, namely, a personal digital assistant, and on 1 occasion, the program was available for both smartphones and desktop computers. Whereas most CDSSs functioned on a step-by-step basis (going from using the patient data provided to generating an antibiotic recommended for that same patient), on 5 occasions they only provided information on different aspects, such as local recommendations, on 6 occasions they provided alerts, and on 2 occasions they acted as a dose calculator. In 19 studies, the use of a CDSS was voluntary on the part of a prescriber, consisting of user initiation of CDSS, and in 24 studies such use was obligatory, consisting of system initiation of CDSS.

Tables IV and V list the various outcome variables analyzed in the different studies, and Table VI gives a stratification by factors that could intervene in CDSS effectiveness. None of the factors analyzed (type of CDSS initiation, clinical setting, mode of delivery, or quality score) appeared to influence the proportion of studies that reported significant results. On the other hand, in all studies there was at least 1 variable that proved favorable to CDSSs, and no study reported unfavorable results for all variables. Only 1 study[36] reported results that were significantly unfavorable to CDSSs, and this was only in respect to one of this study's outcome

Table I. Characteristics of the studies.

Study	Country	Setting	Target population	Patient age group, diagnosis	Sample size	Study period, mo		Study design
						Baseline	Follow-up	
Leibovici et al,[10] 1997	Israel	Hospital	Physician	Older adults, NS	219 patients	13		Cohort
Shojania et al,[11] 1998	United States	Hospital	Phyician	NS, NS	198 physicians (CG); 198 physicians (CDSSG)	9		RT
Christakis et al,[12] 2001	United States	Primary care	Physician, Nurse	Children, otitis media	488 visits (CG);851 visits (CDSSG)	7	8	RT
Mullet et al,[13] 2001	United States	Hospital	Physician, Nurse	<16 years, patients in ICU	809 patients (pre-);949 patients (post-)	6	6	Pre-post
Mullet et al,[14] 2004	United States	Hospital	Physician	NS, NS	226 patients	6		Cohort
Samore et al,[15] 2005	United States	Primary care	Physician, Nurse	NS, NS	19,310 inhabitants (CG);30,960 inhabitants (EMG);32,490 inhabitants (CDSSG)	9	9+9	CRT
Sintchenko et al,[16] 2005	Australia	Hospital	Physician	NS, patients in ICU	362 hospital admissions (CG);390 hospital admissions (CDSSG)	6	6	Pre-post
Paul et al,[17] 2006	Israel, Germany, Italy	Hospital	Physician	>18 years, NS	350 patients	6		Cohort
				>18 years, NS	273 patients (CG);297 patients (CDSSG)	7		CRT

Table I. (*Continued*)

Study	Country	Setting	Target population	Patient age group, diagnosis	Sample size	Study period, mo		Study design
						Baseline	Follow-up	
McGregor et al,[18] 2006	United States	Hospital	Physician, Pharmacist	NS, NS	2237 patients (CDSSG);2270 patients (CG)	3		RT
Thursky et al,[19] 2006	Australia	Hospital	Physician	NS, patients in ICU	524 patients (pre-);536 patients (post-)	6	6	Pre-post
Davis et al,[20] 2007	United States	Primary care	Physician, Nurse	Children, otitis media	6318 visits (CG);5877 visits (CDSSG)	50		CRT
Buising et al,[21] 2008	Australia	Hospital	Physician	>18 years, pneumonia in the community	215 patient (CG);133 patients (CDSSG)	9	6	Pre-post
Kofoed et al,[22] 2009	Denmark	Hospital	Physician	>18 years, sepsis	65 patients	14		Cohort
Linder et al,[23] 2009	United States	Primary care	Physician, Nurse	NS, ARI	10,007 ARI visits (CG);11,954 ARI visits (CDSSG)	7		CRT
Bourgeois et al,[24] 2010	United States	Primary care	Physician, Nurse	<18 years, ARI	5007 visits (CG);14,934 visits (CDSSG)	7		CRT
Tafelski et al,[25] 2010	Germany	Hospital	Physician	>18 years, severe sepsis	88 patients (pre-); 98 patients (post-)	3	3	Pre-post
Yong et al,[26] 2010	Australia	Hospital	Physician	NS, patients in ICU	2838 g-negative isolates	30	138	Pre-post
Rattinger et al,[27] 2012	United States	Primary care	Physician	>16 years, ARI	717 visits (pre-);3117 visits (post-)	12	48	Pre-post
Mainous et al,[28] 2012	United States	Primary care	Physician, Nurse	NS, ARI	125,477 visits (CG);17,271 visits (CDSSG)	3	15	Quasi-experimental trial

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Table I. (*Continued*)

Study	Country	Setting	Target population	Patient age group, diagnosis	Sample size	Study period, mo		Study design
						Baseline	Follow-up	
Gonzales et al,[29] 2013	United States	Primary care	Physician, Nurse	>13 years, uncomplicated acute bronchitis	4145 visits (CG);3991 visits (CDSSG)	18	6	CRT
Forrest et al,[30] 2013	United States	Primary care	Physician	>2 months and <12 years, acute otitis media	23,033 visits (CG);38,215 visits (CDSSG);45,843 visits (CDSSG and feedback group)	12	11+10	CRT
Filice et al,[31] 2013	United States	Hospital	Physician	NS, NS	246 antimicrobial courses (CG);254 antimicrobial courses (CDSSG)	12		Cohort
Leibovici et al,[32] 2013	Israel	Hospital	Physician	>18 years, NS	823 patients (CG);860 patients (CDSSG)	7		CRT
McGinn et al,[33] 2013	United States	Primary care	Physician, Nurse	NS, pharyngitis or pneumonia	398 patients (CG);586 patients (CDSSG)	12		RT
Demonchy et al,[34] 2014	France	Hospital	Physician	<16 years, UTI	448 patients (pre-);307 patients (post-)	4	4	Pre-post
Dumkow et al,[35] 2014	United States	Hospital	Physician, Pharmacist	>18 years, NS	124 patients (pre-);197 patients (post-)	4	3	Pre-post quasi-experimental
Gulliford et al,[36] 2014	United Kingdom	Primary care	Physician	18−59 years, respiratory infection	285,692 patients (CG);317,717 patients (CDSSG)	12	12	CRT
Nachtigall et al,[37] 2014	Germany	Hospital	Physician	>18 years, admitted to ICU >48 h	328 patients (CG); 988 patients (CDSSG)	4	8	Pre-post

Table I. (*Continued*)

Study	Country	Setting	Target population	Patient age group, diagnosis	Sample size	Study period, mo		Study design
						Baseline	Follow-up	
Ng et al,[38] 2014	Singapore	Hospital	Physician	NS, complicated urinary tract infection	44 patients (CG); 22 patients (CDSSG)	4		Cohort
Hamad et al,[39] 2015	United Kingdom	Hospital	Physician	Adults, kidney failure, prescribed vancomycin or gentamicin	350 patients (pre-); 357 patients (post-)	8	2	Pre-post
Dean et al,[40] 2015	United States	Hospital	Physician	NS, pneumonia	2071 patients (CG);2687 patients (CDSSG)	12	12	Pre-post quasiexperimental
Hingorani et al,[41] 2015	United States	Primary care	Physician	NS, ARI	1002 patient (CG);240 patients (CDSSG)	69	10	Pre-post
Faine et al,[42] 2015	United States	Hospital	Physician	NS, patients in ICU, prescribed vancomycin	100 patients (CG);178 patients (CDSSG)	15	18	Pre-post
Beeler et al,[43] 2015	Switzerland	Hospital	Physician	NS, prescribed IV antibiotic	10,441 patients (CG);10,410 patients (CDSSG)	12	12	Pre-post
Shakib et al,[44] 2015	United States	Hospital	Physician	Newborns, mother had chorioammonitis	698 patients (CG);698 patients (CDSSG)	150		Cohort
Kandel et al,[45] 2016	Canada	Hospital	Physician	Adults, NS	21,542 patientp-days (CG);10,763 patient-days (CDSSG)	12	6	Pre-post
Kerste et al,[46] 2016	Netherlands	Hospital	Physician	Newborns;NS	108 patients (CG); 108 patients (CDSSG)	12		Cohort
Kuzniewicz et al,[54] 2017	United States	Hospital	Physician	Infants, NS	95,543 patients (CG);56,261 patients (CDSSG)	35	18	Pre-post

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Table I. (*Continued*)

Study	Country	Setting	Target population	Patient age group, diagnosis	Sample size	Study period, mo		Study design
						Baseline	Follow-up	
Gifford et al,[47] 2017	United States	Primary care	Physician, Nurse	>18 years, ARI	115 patients (CG);44 patients (CDSSG)	68	28	Pre-post
Sharp et al,[48] 2017	United States	Primary care	Physician, Nurse	>18 years, sinusitis	10,491 patients (CG);11,458 patients (CDSSG)	8		RT
Berrevoets et al,[49] 2017	Netherlands	Hospital	Physician	NS, NS	2960 patients (CG); 2925 patients (CDSSG)	13	13	Pre-post
Haque et al,[50] 2017	Bangladesh	Hospital	Physician	NS, diarrhea	325 patients (CG);516 patients (CDSSG)	2.5	2.5	Pre-post
Hincker et al,[51] 2017	United States	Hospital	Physician, Nurse	NS, using perioperative cefazolin	597 patients (CG); 127 patients (CDSSG)	5	1	Pre-post
Blumenthal et al,[52] 2017	United States	Hospital	Physician	NS, patients with possible penicillin allergy	148 patients (CG);199 patients (CDSSG)	5	6	Pre-post
Money et al,[53] 2017	United States	Hospital	Physician	Newborns, mother had chorioammonitis	362 patients (CG);362 patients (CDSSG)	88		Cohort

ARI = acute respiratory infection; CDSSG = clinical decision support systems group; CG = control group; CRT = cluster randomised trial; EMG = educational material group; ICU = intensive care unit, IV = intravenous; NS = not stated; RT = randomized trial; UTI = urinary tract infection.

Table II. Summary of quality assessment of included studies.

Study	Potential sources of bias					Total quality Score
	Method of allocation*	Unit of the allocation†	Baseline differences‡	Objectivity of the outcome§	Completeness of follow-up‖	
Leibovici et al,[10] 1997	0	0	0	2	0	2
Shojania et al,[11] 1998	2	1	2	2	0	7
Christakis et al,[12] 2001	2	1	2	2	0	7
Mullet et al,[13] 2001	0	0	2	2	0	4
Mullet et al,[14] 2004	0	0	2	2	0	4
Samore et al,[15] 2005	2	2	2	2	0	8
Sintchenko et al,[16] 2005	0	0	2	2	0	4
Paul et al,[17] 2006 (observational study)	0	0	0	2	0	2
Paul et al,[17] 2006 (clinical trial)	2	2	2	2	2	10
McGregor et al,[18] 2006	2	0	2	2	0	6
Thursky et al,[19] 2006	0	0	2	2	0	4
Davis et al,[20] 2007	2	1	2	2	2	9
Buising et al,[21] 2008	0	0	2	2	0	4
Kofoed et al,[22] 2009	0	0	0	2	0	2
Linder et al,[23] 2009	2	2	2	2	0	8
Bourgeois et al,[24] 2010	2	2	2	2	0	8
Tafelski et al,[25] 2010	0	0	2	2	0	4
Yong et al,[26] 2010	0	0	2	2	0	4
Rattinger et al,[27] 2012	0	0	2	2	0	4
Mainous et al,[28] 2012	1	2	2	2	0	7
Gonzales et al,[29] 2013	2	2	2	2	0	8
Forrest et al,[30] 2013	2	2	2	2	2	10
Filice et al,[31] 2013	0	0	2	2	0	4
Leibovici et al,[32] 2013	2	2	2	2	0	8
McGinn et al,[33] 2013	2	1	2	2	0	7
Demonchy et al,[34] 2014	0	0	2	2	0	4
Dumkow et al,[35] 2014	0	0	2	2	0	4
Gulliford et al,[36] 2014	2	2	2	2	0	8
Nachtigall et al,[37] 2014	0	0	2	2	0	4
Ng et al,[38] 2014	0	0	2	2	0	4
Hamad et al,[39] 2015	0	0	2	2	0	4
Dean et al,[40] 2015	0	2	2	2	0	6
Hingorani et al,[41] 2015	0	0	0	2	0	2
Faine et al,[42] 2015	0	0	2	2	0	4
Beeler et al,[43] 2015	0	0	0	2	0	2
Shakib et al,[44] 2015	0	0	2	2	0	4
Kandel et al,[45] 2016	0	0	2	2	0	4
Kerste et al,[46] 2016	0	0	2	2	0	4
Kuzniewicz et al,[54] 2017	0	0	2	2	0	4

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Table II. (*Continued*)

Study	Potential sources of bias					Total quality Score
	Method of allocation*	Unit of the allocation†	Baseline differences‡	Objectivity of the outcome§	Completeness of follow-up‖	
Gifford et al,[47] 2017	0	0	2	2	0	4
Sharp et al,[48] 2017	2	2	2	2	0	8
Berrevoets et al,[49] 2017	0	2	2	2	0	6
Haque et al,[50] 2017	0	0	2	2	0	4
Hincker et al,[51] 2017	0	0	2	2	0	4
Blumenthal et al,[52] 2017	0	0	2	2	0	4
Money et al,[53] 2017	0	0	2	2	0	4

* Random, 2; quasi-random, 1; and selected concurrent controls, 0.
† A cluster, such as a practice, 2; physician, 1; and patient, 0.
‡ No baseline differences present or appropriate statistical adjustments made for differences, 2; baseline differences present and no statistical adjustments made, 1; and baseline characteristics not reported, 0.
§ Objective outcomes or subjective outcomes with blinded assessment, 2; subjective outcomes with no blinding but clearly defined assessment criteria, 1; and subjective outcomes with no blinding and poorly defined, 0.
‖ >90%, 2; 80% to 90%, 1; and <80% or not described, 0.

variables. With respect to prescribing domain, most of the studies analysed only the effect of CDSSs on initiation of antibiotics; only 3 studies analysed the effect of the CDSS on antibiotic monitoring.[10,12,37]

Results of the Meta-analysis

Figures 2–8 show the results of performing a meta-analysis of variables that were analyzed in >2 studies.

Variables That Analyzed the Quantity of Antibiotic Prescriptions

Prescription rates were reported in 12 studies (7 in hospital setting and 5 in primary care). In all studies but 1, CDSSs significantly decreased the prescription of antibiotics. Our meta-analysis results indicated that CDSSs in hospital setting reduced the antibiotic prescription rate by a mean of 70% (random OR = 0.30; 95% CI, 0.21–0.44).

Five studies reported data on cost reduction in medication, all in the hospital setting, but in 2 studies the results of the meta-analysis were not estimable because SD data were not reported. Although the other 3 articles included in the meta-analysis reported a statistically significant decrease in costs, there was a high degree of heterogeneity among them ($I^2 = 99.8$), which meant that when random models were applied, the global effect was not statistically significant (random SMD = –1.17; 95% CI, –3.03 to 0.69).

Variables That Analyzed Antibiotic Prescription Quality

Seven studies reported results on the percentage of appropriate empirical prescription, all in the hospital setting. All but 1 study found that CDSSs significantly increased the probability of accuracy of empirical treatment. Indeed, the meta-analysis indicated that CDSSs doubled the probability of accuracy (random OR = 1.93; 95% CI, 1.21–3.08).

Compliance with prescription guidelines was reported in 10 studies (7 in the hospital setting and 3 in primary care). In the hospital setting, all studies found an increased probability of guidelines being followed, and all but 1 study reported a significant effect; we found that CDSSs increased the likelihood of guidelines being followed by almost 4-fold (random OR = 4.22; 95% CI, 1.89–9.42).

Four studies presented data on the percentage of prescriptions in inappropriate indications, all in primary care. Not all studies reported a statistically significant effect, but the meta-analysis found that CDSSs result in a 50% reduction in inappropriate

Table III. Characteristics of computerized clinical decision support systems (CDSSs) used.

Study	Type (function)	Initiation of CDSS	Multifaceted (if yes, type of intervention)	Funding
Leibovici et al,[10] 1997	CP on DT (SbS)	System	No	No
Shojania et al,[11] 1998	CP on DT (provides information)*	System	No	Public
Christakis et al,[12] 2001	CP on DT (provides information)†	System	No	NS
Mullet et al,[13] 2001	CP on DT (SbS)	System	Yes (CDSS-T)	Public
Mullet et al,[14] 2004	CP on DT (SbS)	System	No	Public
Samore et al,[15] 2005	CP on PDA (SbS)	User	Yes (F, I, EL)	Public
Sintchenko et al,[16] 2005	CP on PDA (provides information)‡	User	Yes (CDSS-T)	No
Paul et al,[17] 2006 (observational study)	CP on DT (SbS)	System	No	Public
Paul et al,[17] 2006 (clinical trial)	CP on DT (SbS)	User	No	Public
McGregor et al,[18] 2006	Web on DT (alerts)§	System	No	Public
Thursky et al,[19] 2006	CP on DT (SbS)	System	Yes (CDSS-T)	Public
Davis et al,[20] 2007	Web on DT (provides information)†	System	No	NS
Buising et al,$_{21}$ 2008	web on DT (SbS)	User	Yes (CDSS-T)	Public
Kofoed et al,[22] 2009	CP on DT (SbS)	System	No	Public
Linder et al,[23] 2009	CP on DT (SbS)	User	Yes (F,R)	Public
Bourgeois et al,[24] 2010	CP on DT (SbS)	User	Yes (R, CDSS-T)	Public
Tafelski et al,[25] 2010	Web on DT (SbS)	Unclear	Yes (CDSS-T)	Public
Yong et al,[26] 2010	CP on DT (SbS)	System	No	Public
Rattinger et al,[27] 2012	CP on DT (SbS)	Unclear	No	Public
Mainous et al,[28] 2012	CP on DT (SbS)	User	Yes (F,CDSS-T, EM, EL)	Public/private
Gonzales et al,[29] 2013	CP on DT (SbS)	User	Yes (F, CDSS-T, EM)	Public
Forrest et al,[30] 2013	CP on DT (SbS)	User	Yes (F)	Public
Filice et al,[31] 2013	CP on DT (provides information)‖	User	No	Public
Leibovici et al,[32] 2013	CP on DT (SbS)	User	No	No
McGinn et al,[33] 2013	CP on DT (SbS)	User	Yes (CDSS-T)	NS
Demonchy et al,[34] 2014	CP on DT (SbS)	User	Yes (CDSS-T)	No
Dumkow et al,[35] 2014	CP on DT (alerts)¶	System	No	Private
Gulliford et al,[36] 2014	CP on DT (SbS)	User	Yes (CDSS-T)	Public/private
Nachtigall et al,[37] 2014	CP on DT (SbS)	System	Yes (CDSS-T)	Public
Ng et al,[38] 2014	CP on DT (SbS)	System	No	NS
Hamad et al,[39] 2015	CP on DT (dose calculator)	User	Yes (CDSS-T)	Private
Dean et al,[40] 2015	CP on DT (SbS)	User	Yes (CDSS-T)	Public/private
Hingorani et al,[41] 2015	CP on DT (SbS)	User	Yes (F, R, EM, EL)	No

(*continued on next page*)

Table III. (*Continued*)

Study	Type (function)	Initiation of CDSS	Multifaceted (if yes, type of intervention)	Funding
Faine et al,[42] 2015	CP on DT (dose calculator)	System	No	NS
Beeler et al,[43] 2015	CP on DT (alerts)[#]	System	No	No
Shakib et al,[44] 2015	CP on DT (SbS)	system	No	NS
Kandel et al,[45] 2016	CP on DT (alerts)[**]	System	No	Public
Kerste et al,[46] 2016	CP on DT (SbS)	System	No	No
Kuzniewicz et al,[54] 2017	CP on DT (SbS)	System	Yes (CDSS-T)	NS
Gifford et al,[47] 2017	CP on DT (SbS)	System	No	Public
Sharp et al,[48] 2017	CP on DT (SbS)	System	Yes (CDSS-T)	Private
Berrevoets et al,[49] 2017	CP on DT (alerts) [#]	System	Yes (F, EM, EL)	No
Haque et al,[50] 2017	CP on DT and smartphone (SbS)	User	Yes (CDSS-T)	NS
Hincker et al,[51] 2017	CP on DT (alerts)[↑↑]	System	Yes (EM)	Public
Blumenthal et al,[52] 2017	Web on DT (SbS)	User	No	Public/private
Money et al,[53] 2017	CP on DT (SbS)	System	No	NS

CP = not web computer program; CDSS-T = clinical decision support systems training session; DT = desktop; EL = educational lectures; EM = educational materials; F = feedback; I = incentives; NS = not stated; PDA: personal digital assistant; R = reminders. SbS = step by step (the user enters data on the patient and disease into the program and the program provides the recommended treatment); web = web page with hyperlinks to internet or intranet.

[†] Provided information based on their selection of medication, indication, or duration. The first screen contained a short summary of the evidence supporting or refuting the current choice of medication, indication, or duration. The provider could then choose to view more information about this evidence.

[‡] Provided information on microbiological outcomes-guidelines-resistance rates calculator of the severity of the infection.

[*] Provided information on vancomycin prescription guidelines.

[§] Provided alerts about previously initiated antibiotics where inappropriate use was detected.

[||] Provided information on disease, syndrome, pathogen, adverse effects of antimicrobials, and diagnosis and treatment by pathology, according to local recommendations.

[¶] Alert about microbiology laboratory new positive urine or blood culture results for patients.

[#] Alert about the possibility of changing the intravenous antibiotic to an oral one.

[**] Alert about using an antibiotic and a protom pump inhibitor increases the risk of *Clostridium difficile* infection.

[↑↑] Alert about the antibiotic is due to be redosed.

antibiotic prescriptions (random OR = 0.45; 95% CI, 0.28–0.74).

Morbidity and Mortality Variables

Of the 32 studies undertaken in a hospital setting, 6 reported duration of hospital stay as an outcome, but in 1 study the result of the meta-analysis was not estimable because of the number of days data were not reported (only a *P* and sign of effect were reported). When the meta-analysis was performed, heterogeneity was observed (I^2 = 98.3), with the result that, when the random models were applied, the reduction in duration of stay did not prove statistically significant (SMD = –0.23; 95% CI, –0.49 to 0.02).

Mortality data were available from 8 studies, all in the hospital setting, but in no case did the results prove statistically significant, and the meta-analysis found no statistically significant effect (random OR = 0.98; 95% CI, 0.84–1.14). Neither the funnel plot nor the Egger test found publication bias for any of the variables.

DISCUSSION

To our knowledge, this is the first systematic review to use meta-analysis to assess the effectiveness of CDSSs

Table IV. Results of hospital studies for different dependent variables.*

Study	Outcomes**							
	Percentage of appropriate empirical antibiotic treatment	Total antibiotic prescription rate	Direct cost of antibiotics	Mortality	Length of hospital stay	Individual antibiotic prescription rate	Percentage adherence to guidelines and evidence	Other
Leibovici et al,[10] 1997	++							
Shojania et al,[11] 1998								Number of patients for whom each physician had prescribed vancomycin (++); number of days of vancomycin per course of treatment (++)
Mullet et al,[13] 2001			++					Rate of plasma antibiotic concentrations within the therapeutic range (++); no. of antibiotics per patient (++)
Mullet et al,[14] 2004	++							
Sintchenko et al,[16] 2005		++		−	++	(++/+/-)†		
Paul et al,[17] 2006 (observational study)	++							
Paul et al,[17] 2006 (clinical trial)	+		++	+	+			
McGregor et al,[18] 2006			+	−	+			
Thursky et al,[19] 2006	++	+	+			(+/++)†		
Buising et al,[21] 2008							++	Percentage of inappropriate prescription of antibiotics to patients with allergy to that same antibiotic (+)

(*continued on next page*)

Table IV. (*Continued*)

Study	Outcomes**							
	Percentage of appropriate empirical antibiotic treatment	Total antibiotic prescription rate	Direct cost of antibiotics	Mortality	Length of hospital stay	Individual antibiotic prescription rate	Percentage adherence to guidelines and evidence	Other
Kofoed et al,[22] 2009	++		++					
Tafelski et al,[25] 2010							++	No. of antibiotics per patient (++)
Yong et al,[26] 2010								Changes in susceptibility rate to microorganisms (++/+/−)[‡]
Filice et al,[31] 2013				−				Percentage of appropriate antibiotics courses (++)
Leibovici et al,[32] 2013				+				
Demonchy et al,[34] 2014							+	
Dumkow et al,[35] 2014								Percentage of emergency department revisits within 72 h (+); percentage of hospital admissions at 30 days of discharge (+)
Nachtigall et al,[37] 2014				+	−−		++	
Ng et al,[38] 2014	++				−		++	Percentage of patients with correct antibiotic dosage (++)
Hamad et al,[39] 2015								Percentage of patients with correct dosage for gentamicin (++); percentage of patients with correct dosage for vancomycin (++)
Dean et al,[40] 2015				+	+			
Faine et al,[42] 2015				−				

Table IV. (*Continued*)

Study	Outcomes**							
	Percentage of appropriate empirical antibiotic treatment	Total antibiotic prescription rate	Direct cost of antibiotics	Mortality	Length of hospital stay	Individual antibiotic prescription rate	Percentage adherence to guidelines and evidence	Other
Beeler et al,[43] 2015								Percentage of patients with correct dosage for vancomycin (++) Mean time to change from an IV antibiotic to an oral one (++)
Shakib et al,[44] 2015		++						
Kandel et al,[45] 2016		++						
Kerste et al,[46] 2016		++						
Berrevoets et al,[49] 2017								Percentage of patients who use IV antibiotic for >72 h (++)
Haque et al,[50] 2017							++	
Hincker et al,[51] 2017							++	
Blumenthal et al,[52] 2017								Percentage of patients reporting penicillin allergy using a penicillin or cephalosporin (++)
Money et al,[53] 2017		++						Mean length of antibiotic therapy (++)
Kuzniewicz et al,[54] 2017		++						

*Study outcomes (results for each variable) are classified as follows: ++, intervention results favored clinical decision support system (CDSS) and were statistically significant; +, intervention results favored CDSS but were not statistically significant or statistical significance test was not applied; −, intervention results favored the comparison group but were not significant or statistical significance test was not applied; −−, intervention results favored the comparison group and were statistically significant.

†The result varies depending on the individual antibiotic.

‡The result varies depending on the individual antibiotic and microorganism.

Table V. Results of studies performed in primary care for different dependent variables.

Study	Outcomes*				
	Total antibiotic prescription rate	Prescription of total antibiotics in inappropriate indications, %	Individual antibiotic prescription rate	Adherence to guidelines and evidence, %	Other
Christakis et al,[12] 2001					Percentage of cases without antibiotics (+); percentage of cases of otitis with duration of antibiotic treatment <10 days (++)
Samore et al,[15] 2005	++		++		
Davis et al,[20] 2007				++	Percentage of prescription of amoxicillin in line with scientific evidence (-); percentage of cases of otitis with duration of antibiotic treatment <10 days (-)
Linder et al,[23] 2009	+	+			
Bourgeois et al,[24] 2010	+		++		Percentage of prescription of total antibiotics in sinusitis (+), otitis (+); percentage of prescription of macrolids in sinusitis (++), otitis (++)
Rattinger et al,[27] 2012		++			
Mainous et al,[28] 2012		Adults (++) Children (+)	(++/+)†		
Gonzales et al,[29] 2013		++			
Forrest et al,[30] 2013					Percentage of use of amoxicillin as first-line treatment (++); delayed prescription (-)
McGinn et al,[33] 2013	++		(++/+) †		
Gulliford et al,[36] 2014	++				
Hingorani et al,[41] 2015				++	

Table V. (*Continued*)

Study	Outcomes*				
	Total antibiotic prescription rate	Prescription of total antibiotics in inappropriate indications, %	Individual antibiotic prescription rate	Adherence to guidelines and evidence, %	Other
Gifford et al,[47] 2017				++	
Sharp et al,[48] 2017					Percentage of prescription of total antibiotics in sinusitis (++)

* Study outcomes (results for each variable) are classified as follows: ++, intervention results favored clinical decision support system (CDSS) and were statistically significant; +, intervention results favored CDSS but were not statistically significant or statistical significance test was not applied; -, intervention results favored the comparison group but were not significant or statistical significance test was not applied; −−, intervention results favoured the comparison group and were statistically significant.
† The resultvaries depending on the individual antibiotic.

to improve antibiotic prescribing using studies performed in primary care centers besides hospital facilities. A total of 46 studies were identified that evaluated a wide variety of outcome variables. Most of these studies found a positive effect of CDSSs on all or some of the outcome variables described. Mean study quality was not high, something that must be borne in mind when it comes to interpreting the results.

The outcomes of the studies were of a varied nature and ranged from improvement in antibiotic prescribing to a reduction in mortality. These outcomes can be

Table VI. Distribution of the number of studies according to the proportion of variables with a statistically significant result that is favorable for the computerized clinical decision support system (CDSS).

	No. (%) of studies			P (χ2 Test)
	All variables	Some variables	None of the variables	
CDSS initiation				0.5312
System	15 (60.0)	8 (32.0)	2 (8.0)	
User	8 (42.1)	9 (47.4)	2 (10.5)	
Unclear	2 (100)	0 (0)	0 (0)	
Clinical setting				0.2264
Hospital	18 (62.1)	8 (27.6)	3 (10.3)	
Ambulatory care	7 (41.2)	9 (52.9)	1 (5.9)	
Mode of delivery				0.4919
Multifaceted	11 (47.8)	9 (39.2)	3 (13.0)	
CDSS only	14 (60.9)	8 (34.8)	1 (4.3)	
Total quality score				0.1759
5−10	7 (41.2)	7 (41.2)	3 (17.6)	
<5	18 (62.1)	10 (34.5)	1 (3.4)	

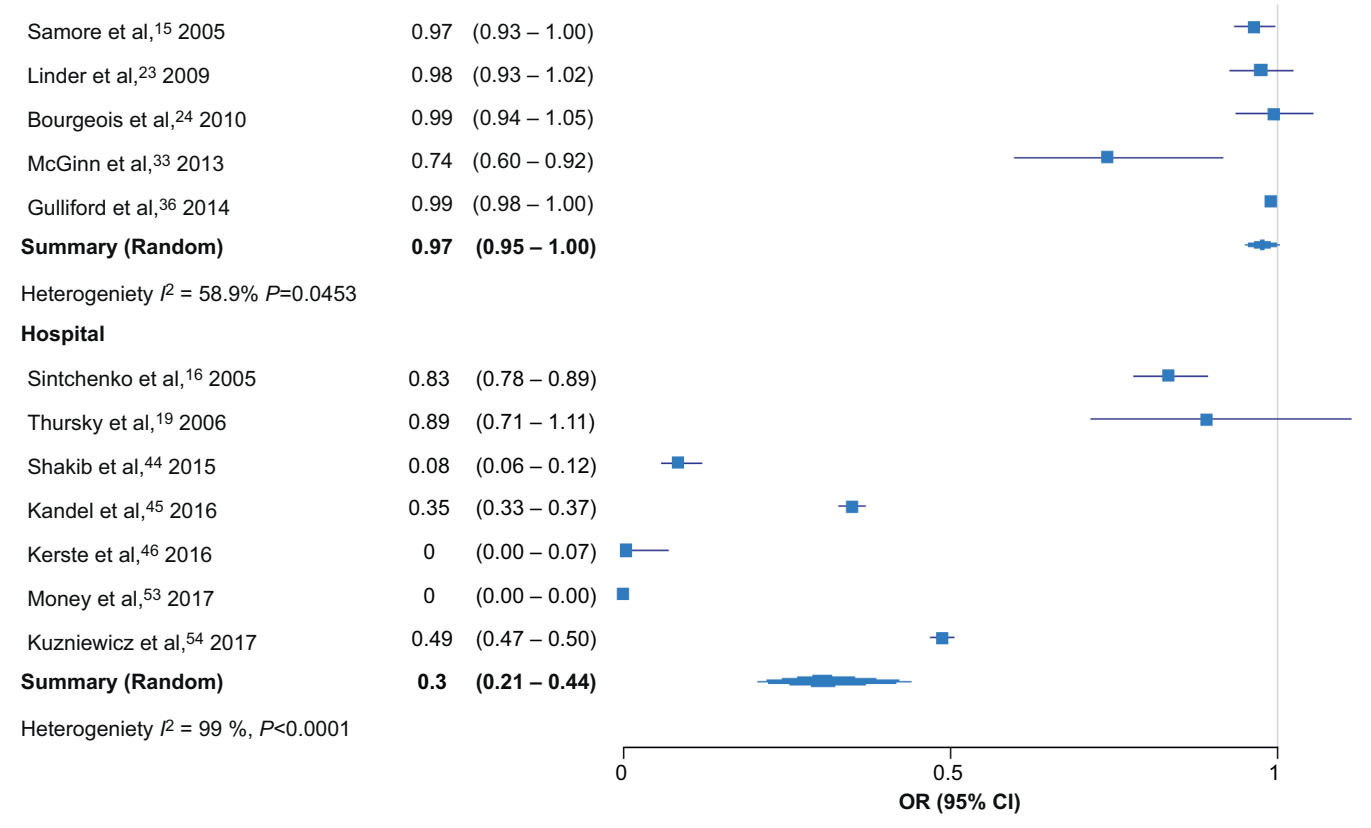

Figure 2. Results of meta-analysis for the variable antibiotics prescription rate in hospital or primary care. OR = odds ratio.

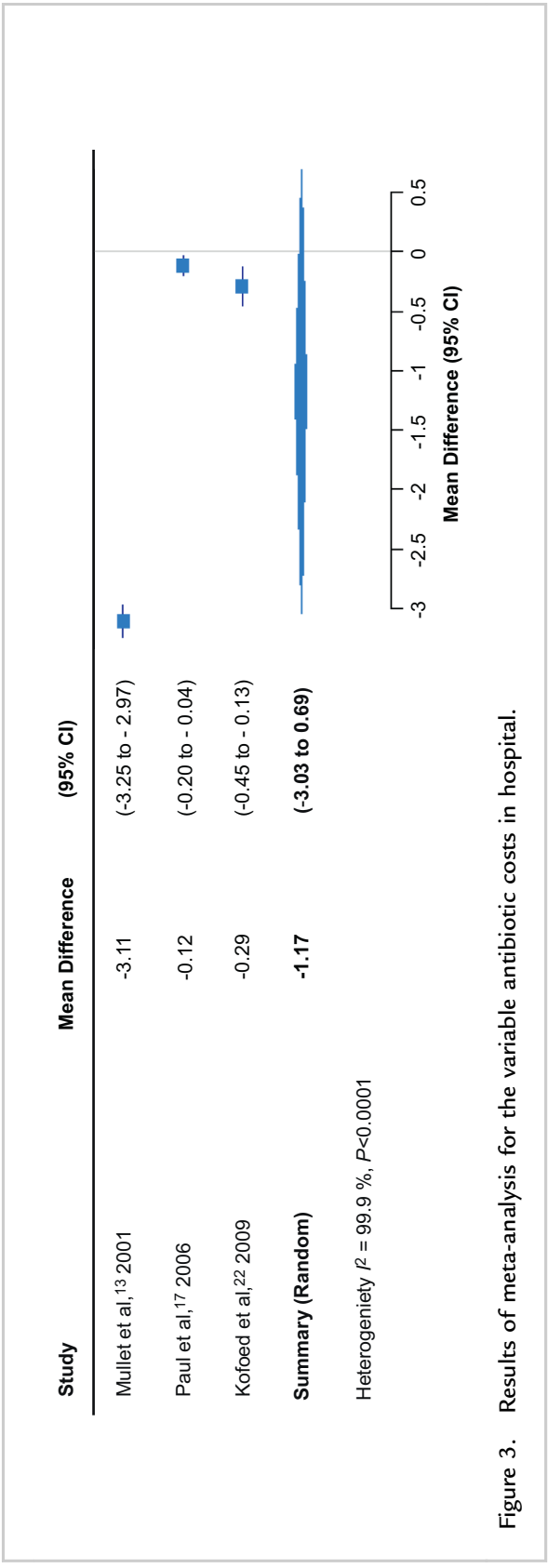

Figure 3. Results of meta-analysis for the variable antibiotic costs in hospital.

modeled hierarchically using a pyramid (Figure 9), which gives changes in the quantitative indicators of antibiotic consumption (eg, fewer prescriptions) at level 4, the association between clinical practice and the bacteria (percentage accuracy of the prescription with respect to the bacteria, following of clinical practice guidelines) at level 3, morbidity indicators (days of hospital stay) at level 2, and mortality at the top (level 1).

Our results indicate that although CDSSs are capable of modifying aspects of clinical practice (eg, adherence to guidelines), to date it has not been possible to determine their ability to affect clinical variables (decrease in morbidity and mortality), possibly because the effect of improvement in prescriptions is *diluted* by many other factors, which can influence patient health. This would explain why the effects of CDSSs on the variables of the upper levels (levels 1 and 2 in Figure 9) are far smaller and, by extension, more difficult to detect. To detect these small effects, very large samples (ie, sizes not found in most of the studies in this review) would be required.

Although one might think that, because they address more aspects, multifaceted interventions would be more effective than using a CDSS alone, the results of our review do not suggest this, a finding in line with the results of the review by Pearson et al.[6] There are a number of mechanisms whereby CDSSs can improve clinical practice: (1) by reducing the gap between scientific knowledge and its application in clinical practice[55] and (2) by reducing the insecurity and fear of complications of infectious disease in the event of an antibiotic not being used.[56] At all events, it has to be borne in mind that there a percentage of physicians that pay no attention to CDSS-based advice or warnings[57] because of a phenomenon known as alert fatigue.[58]

Although 90% of antibiotics are consumed in a community setting,[59] only 50% of the studies in our review had been conducted in primary care. In addition, reports have found that an extremely high percentage of resistance at a hospital level is of community origin[60] and that a very high percentage of antibiotic prescriptions in primary care are unnecessary.[61] Therefore, more CDSSs need to be developed and properly evaluated for this setting.

Patients can influence prescribing in primary care inasmuch as patients with respiratory infections for

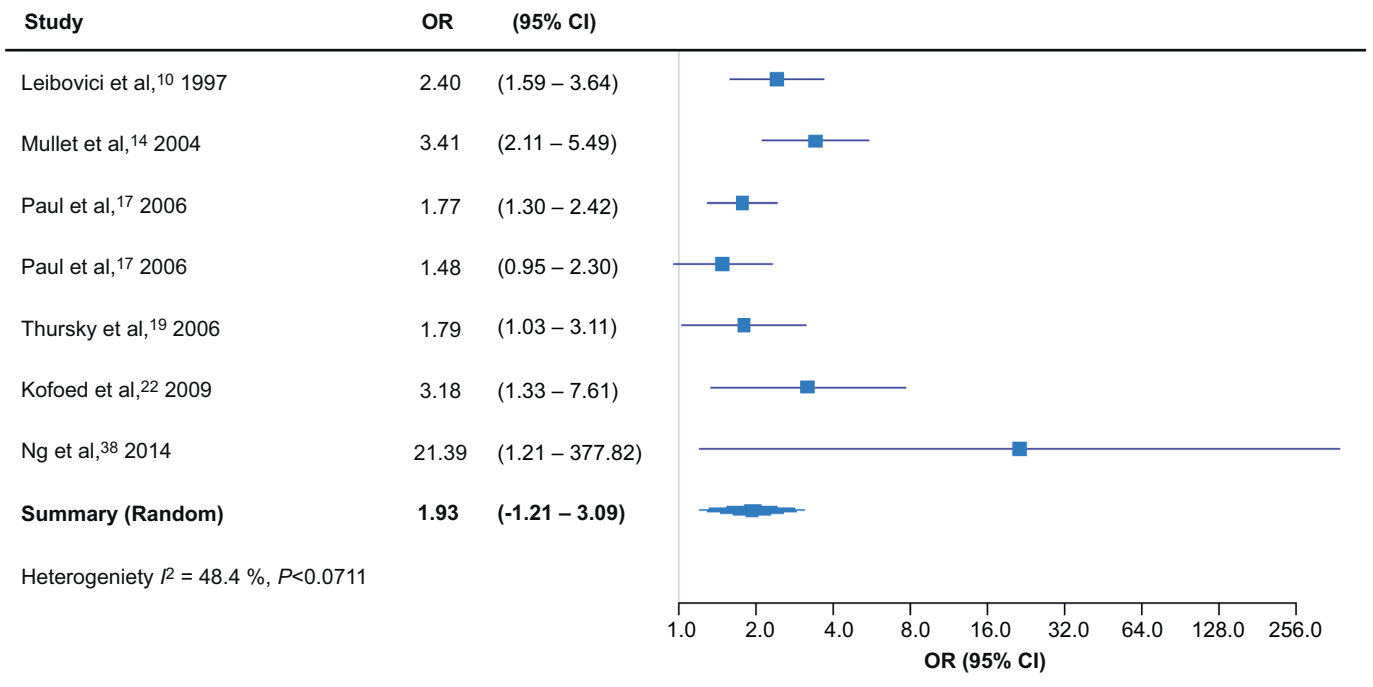

Figure 4. Results of meta-analysis for the variable percentage of appropriate empirical antibiotic treatments in hospital. OR = odds ratio.

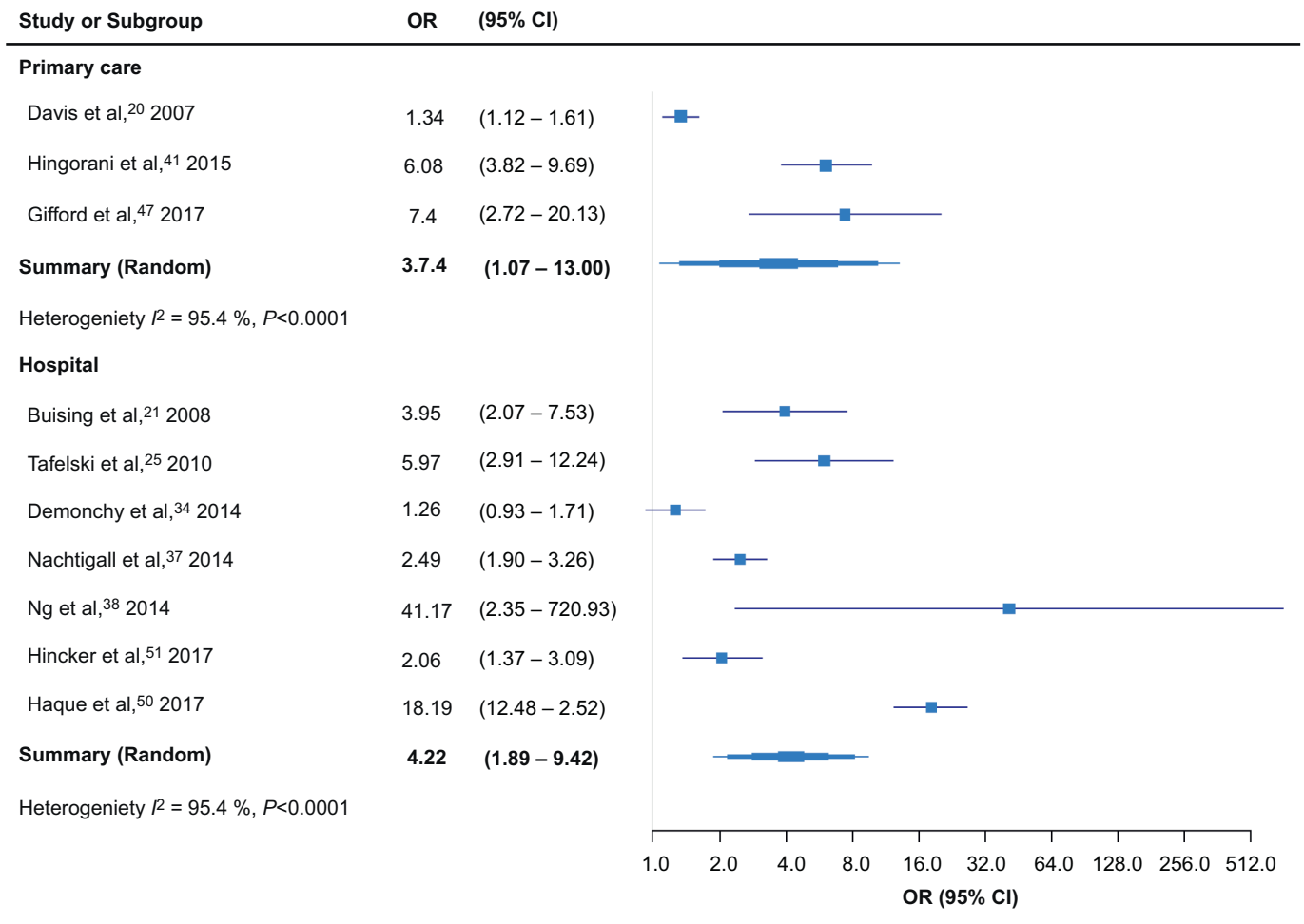

Figure 5. Results of meta-analysis for the variable accordance to antibiotic prescription guidelines in hospital or primary care. OR = odds ratio.

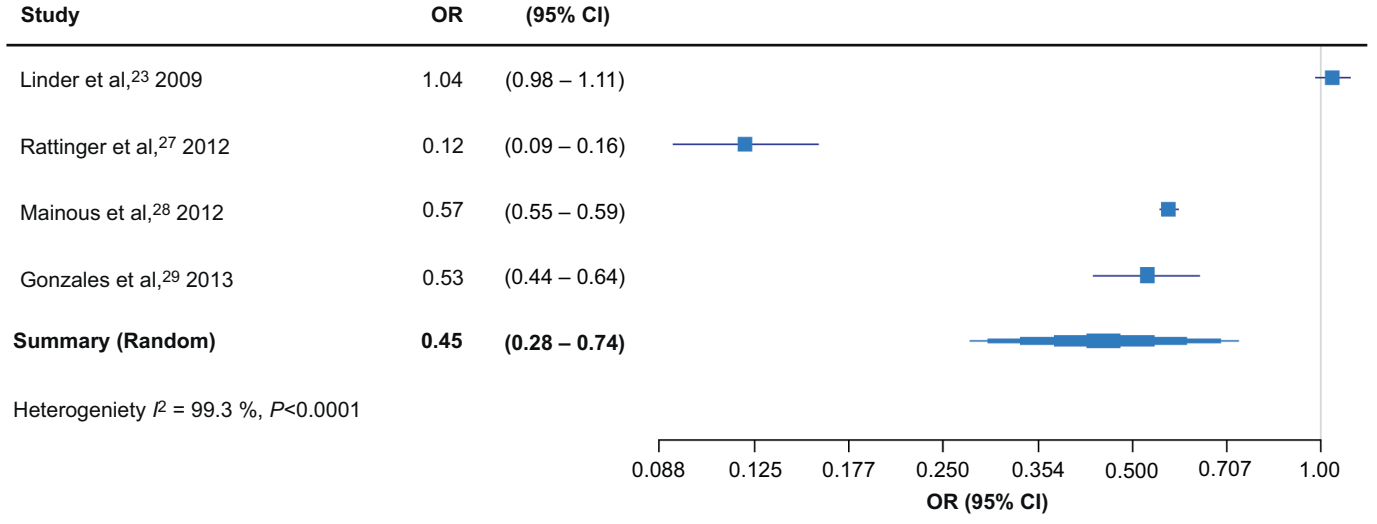

Figure 6. Results of meta-analysis for the variable percentage of antibiotic prescriptions for inadequate indications in primary care. OR = odds ratio.

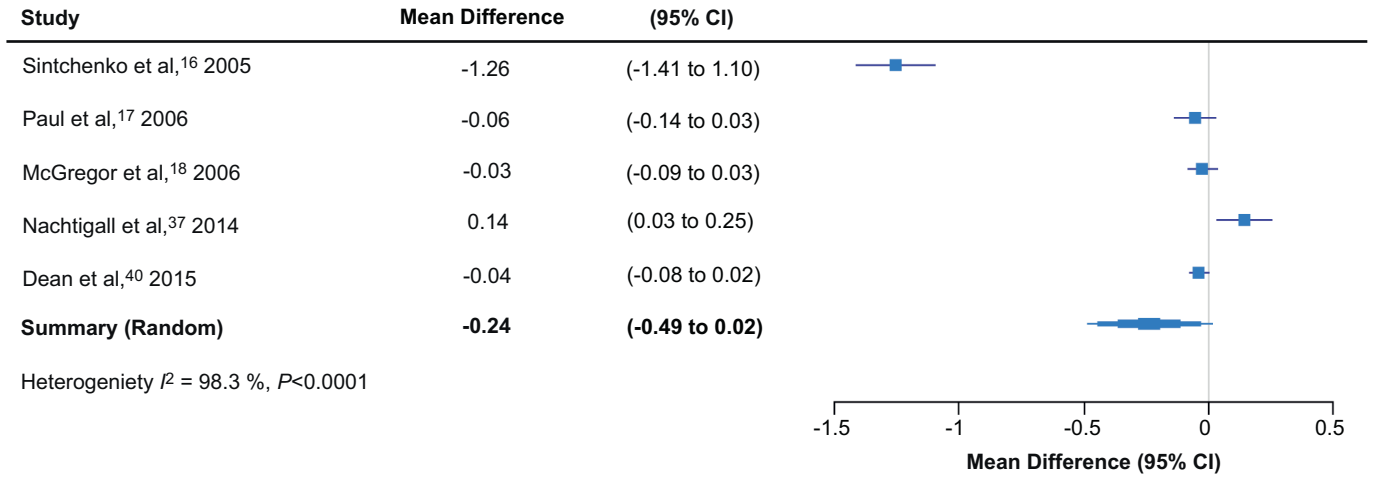

Figure 7. Results of meta-analysis for the variable length of hospital stay.

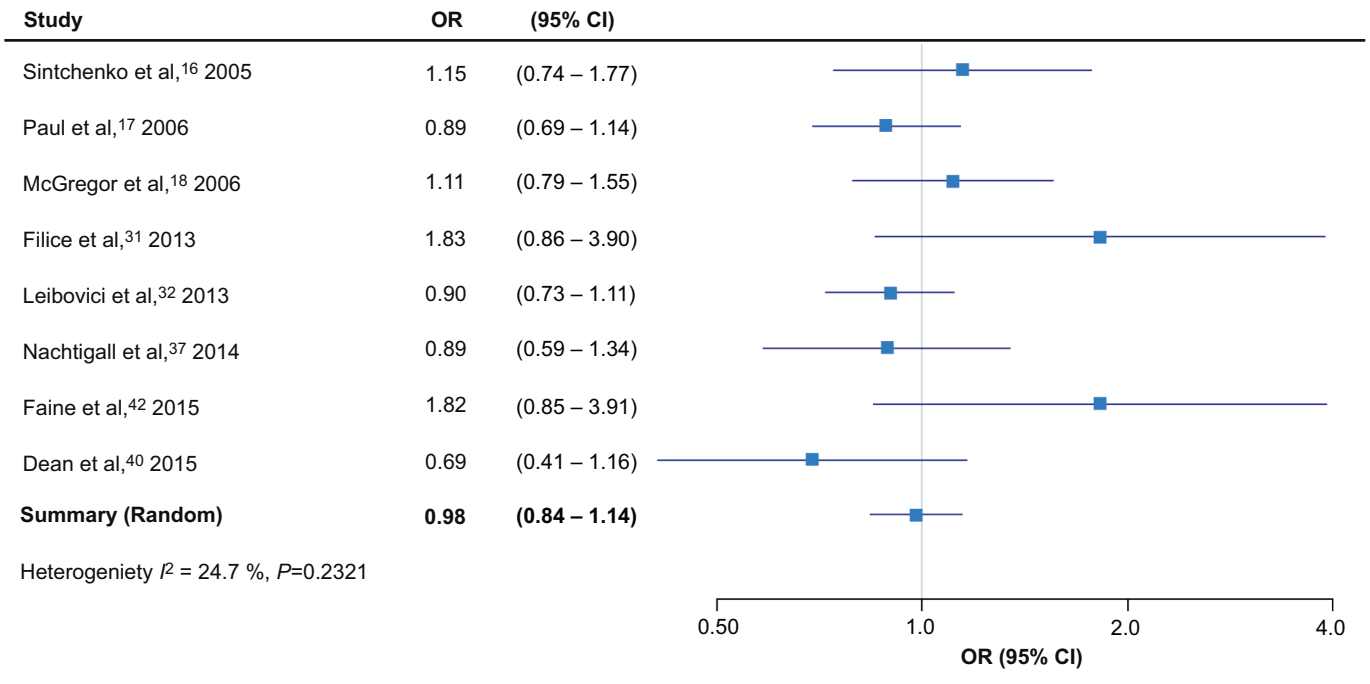

Figure 8. Results of meta-analysis for the variable mortality in hospital. OR = odds ratio.

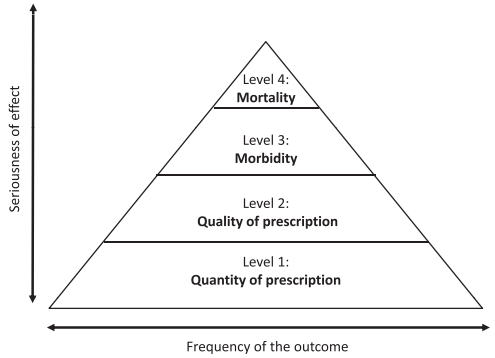

Figure 9. Hierarchy of outcomes.

whom antibiotics are prescribed have greater satisfaction.[62] The role that a CDSS can play in the patient–physician relationship remains to be studied. On the one hand, it could be beneficial by informing patients that decisions were being taken on the basis of preestablished target criteria; on the other hand, it could prejudice communication by reducing visual contact as a result of reliance on an electronic device.

Another aspect to be considered is that of access to antibiotics without medical prescription, a phenomenon that is important in areas outside North America, Northern Europe, and Australia, where high percentages of antibiotics are dispensed by community pharmacies without the mandatory medical prescription.[63,64] Accordingly, decision support systems should not be restricted to physicians. Instead, they could also be geared to pharmacists and patients, something that would improve treatment, particularly in the case of viral diseases.

Countries

In previous reviews,[65,66] all or almost all of the studies included had been undertaken in the USA. In our review, half of the studies had been conducted in the USA and the remainder in other countries, though all of these were, but one, developed countries.

The fact that most of the studies have been undertaken in developed rather than developing countries may possibly be attributable to the latter's relative lack of devices such as tablets, lower degree of internet access and program development, and greater difficulty in ensuring that reports are published.[67] However, given that the use of antibiotics is increasing worldwide, and in developing countries in particular,[68] more study should be devoted to the use of CDSSs in such countries. Furthermore, in these countries, a high degree of self-medication and dispensing without a prescription has been detected, partly because of the critical shortage of health workers and poor distribution of services. In these settings, the development and study of CDSSs tailored to persons who dispense antibiotics would be of great interest.

Many of our subgroup analyses presented high levels of heterogeneity of effects as measured by the I^2 statistic. We should emphasize, together with several experts of meta-analysis methods, that heterogeneity is a characteristic of a particular meta-analysis not a nuisance. Heterogeneity describes the meta-analysis at hand, and its exploration may shed light on other interesting features. Higgins[69] emphasizes that "heterogeneity is to be expected in a meta-analysis" and that "it would be surprising if multiple studies, performed by different teams in different places with different methods, all ended up estimating the same underlying parameter." Higgins[69] also comments that any amount of heterogeneity is acceptable, providing that the predefined eligibility criteria for the meta-analysis are sound and that the data are correct.

Furthermore, we should bear in mind the fact that apparent heterogeneity (ie, results of opposite directions of individual studies) is probably the best reason to perform a meta-analysis. If there is a unanimous verdict and all studies on a particular exposure-outcome association indicate a risk increase, then a meta-analysis would be of less interest, if not completely useless.

Future Directions

The small number and the different characteristics and setting of studies involving exclusively mobile devices in our review (one in primary care and another in the hospital setting) meant that it was not possible to draw comparisons between mobile and fixed devices. It is to be expected in future that studies will appear with CDSSs in the form of applications (apps) for smartphones because of the spread of these types of mobile devices and their acceptance and use by health care professionals.[70]

The use of smartphones as CDSS devices could be especially important in resource-poor countries because it is a low-cost way of accessing CDSS applications. In low-income countries, there is little likelihood of health systems having the necessary resources to install fixed computers with an internet link-up in all physicians' practices. However, the increased use of smartphones among physicians in low- and middle-income countries[71] may well make these an element that could catapult the use of CDSSs in the form of mobile apps.

Quality

In terms of quality, the mean score of the studies included in our review (5.15 points) was lower than that reported by previous reviews on the use of medical drugs in general (7 points), which indicates that studies on the effect of CDSSs on antibiotics have a worse methodologic quality than do studies on other drug groups or other types of therapeutic interventions.[5] Unlike other reviews,[5] we also failed to find any increase in quality scores across time.

Limitations

Among this study's limitations is the possibility of publication bias, which is possible with any systematic review. Similarly, our review encountered studies that had been undertaken with varying designs and/or used varied outcome variables or different types of patients. Moreover, identification of study design or CDSS characteristics proved a complex task, and it is therefore possible that some studies may have been misclassified in terms of design or CDSS characteristics because of an incomplete description of the methods used. In many cases, shortcomings in the design and description of the intervention and identification of the sample made it difficult to tabulate a study's characteristics.

The Egger test was not statistically significant for outcomes in which a meta-analysis was performed. However, this result must be viewed with caution because of the low number of studies in most of the variables.

Some outcome variables were not studied in all settings: for instance, the variable percentage of appropriate empirical prescription was only studied in a hospital setting because no studies in primary care were available, and the variable cost of antibiotic treatment was likewise studied only in hospitals. It would be desirable for studies with these variables to be conducted in other settings because, for instance in the case of cost, it is in primary care and not in the intrahospital setting that the greatest part of a country's expenditure on medications tends to take place.[72]

CONCLUSION

CDSSs can be said to increase the percentage of appropriate empirical treatment in the hospital setting, lower the antibiotic prescription rate, enhance guideline adherence and reduce inappropriate indications. Even so, more better-quality studies are required to draw clearer conclusions in respect to heath outcome variables (morbidity and mortality) and other settings. These data support the use of CDSSs to improve antibiotic prescribing until more adequately powered high-quality randomized trials for health outcomes have been performed.

TRANSPARENCY DECLARATION

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