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Misprescription of antibiotics in primary care: a critical systematic review of its determinants

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Abstract

Background Antibiotic resistance is one of the principal public health problems worldwide. Currently, inappropriate use of antibiotics is regarded as the principal determinant of resistance, with most of these drugs being prescribed outside a hospital setting. This systematic review sought to identify the factors, attitudes and knowledge linked to misprescription of antibiotics.

Methods A systematic review was conducted using the MEDLINE-PubMed and EMBASE databases. The selection criteria required that papers: (1) be published in English or Spanish; (2) designate their objective as that of addressing attitudes/knowledge or other factors related with the prescribing of antibiotics; and (3) use quality and/or quantity indicators to define misprescription. The following were excluded: any paper that used qualitative methodology and any paper that included descriptive analysis only.

Results A total of 46 papers that met the inclusion criteria were included in the review. They were very heterogeneous and displayed major methodological limitations. Doctors' socio-demographic and personal factors did not appear to exert much influence. Complacency (fulfilling what professionals perceived as being patients'/parents' expectations) and, to a lesser extent, fear (fear of possible complications in the patient) were the attitudes associated with misprescription of antibiotics.

Conclusions Before designing interventions aimed at improving the prescription and use of antibiotics, studies are needed to identify precisely which factors influence prescribing.

Introduction

Bacterial resistance has become an important public health problem. According to a World Health Organization report, prevalence of antibiotic resistances may reach values of 70% for *Streptococcus pneumoniae*, which is the most frequent extrahospital pathogen and causes otitis media in children and invasive infections in adults [1]. Many of the most frequent pathogens have become resistant to conventional antimicrobial treatments, thereby leading to a loss of efficacy in such treatments and an increase in the use of broad-spectrum combinations [2].

At present, few doubts exist as to the relationship between the use of antibiotics and the spread of antimicrobial resistance. Ecologic studies undertaken as a result of European initiatives, for example, European Surveillance of Antimicrobial Consumption and European Antimicrobial Resistance Surveillance System, suggest that in Europe there is a clear association between the use of penicillin and the rate of penicillin-non-susceptible pneumococci, and likewise, between the use of fluroquinolones and the rate of *E. coli* resistant to this group[3]. The conclusion to be drawn from these studies and another, earlier, related study conducted in the same field [4], is that such great differences in use

would not appear to be justified on the basis of differences in the prevalence of the infectious pathology. Accordingly, improving the pattern of antibiotic use would seem to be a fundamental measure for controlling bacterial resistance.

Different actors, such as doctors, patients, pharmacists and health authorities, are involved in this inappropriate and excessive use of antimicrobials. In view of the fact that, here in Europe, antibiotics are medications which must be sold under medical prescription, doctors are a fundamental target for any action aimed at improving the use of antimicrobials.

As a preliminary step in designing really effective interventions in this field, better knowledge is needed about the reasons for these drugs being prescribed [5]. Accordingly, the aim of this systematic review was precisely to identify the factors, attitudes and knowledge related with the misprescription of antibiotics.

Method

Literature search methodology

For the purpose of this systematic bibliographic review, a search was made of the scientific MEDLINE and EMBASE databases from January 1987 to February 2008. In addition, manual searches of journals, particularly those less likely to be indexed, and of references cited by the retrieved papers, were used to locate further papers. The following search terms and their equivalents were used in MEDLINE and EMBASE: (attitud* OR knowle* OR percept*) AND (physician* OR doctor* OR practitioner*) AND (antibiotic OR antimicrobial*).

Our selection criteria required that papers: (1) be published in English or Spanish, with those in any other language being ruled out for bibliographic review purposes; (2) designate their objective as that of addressing attitudes/knowledge or other factors related with the prescription of antibiotics; (3) define what was understood by 'misprescription'; (4) use quality and/or quantity indicators to define 'misprescription'; and, lastly (5) be included whatever the infectious disease studied. The following were excluded: any paper that used qualitative methodology and any paper that included descriptive analysis only. In the case of papers that included various study subpopulations (e.g. doctors, pharmacists and patients), data were exclusively collected on the subpopulation of doctors and the pertinent results. Similarly, in the case of papers that included substudies with qualitative and quantitative methodology, data were collected solely on the quantitative substudy and its related results.

Data extraction

For each study included in this review, a table (see Table 1) with the following parameters was drawn up: author (publication year), country, study population, workplace, method of assessment, pathology, type(s) of patient, antibiotics, sample size, participation, questionnaire distribution and type of analysis (bivariate, multivariate).

A second table was drawn up using the following data: author and year of publication, factors intrinsic to the professional (sociodemographic data and attitudes); a third table was including the external factors associated to the prescribing process: characteristics of the patients, the health system and the pharmaceutical industry (see Table 2). In the review process itself, as there was no previously proposed classification such as Inman's [in the case of attitudes associated with adverse drug reaction (ADR) underreporting], attitudes and other factors were added as they were extracted from the respective papers.

Therefore, socio-demografic factors analysed in the diferent estudies were: age, gender, medical speciality, years of practice, school/residence training and continuous medical education.

Attitudes found in the review are given in the results section. As explained previously, attitudes were identified as they were reading included papers. The selection criteria of attitudes were based on the results provided by these papers and their results. This is summarized in Table 3.

Regarding extrinsic factors: (1) As patient-related factors were defined as follows: patient's age, patient's gender, race, co-morbidity, symptoms, signs, anxiety because of illness, socioeconomic and educational levels, type of insurance and other patient-related factors. (2) As factors related with health care system were identified: practice location, patient volume, type of practice, working alone or as part of a group, accreditation level of practice setting and other factors related with health care system.

Finally, we also studied the influence of the pharmaceutical companies.

To evaluate the relationship offers these factors with inappropriate prescribing of antibiotics, we define:

- Direct relationship: In the primary studies selected, the presence of the studied factor increased inappropriate antibiotic's prescriptions. We believe that this was significant when the measure of association provided in the primary studies was >1 and had an associated *P*-value ≤0.05. This is represented in Tables 1 and 4 as (↑).
- Inverse relationship: In the primary studies selected, the presence of the studied factor decreased inappropriate antibiotic's prescriptions. We believe that this was significant when the measure of association provided in the primary studies was <1 and had an associated *P*-value ≤0.05. This is represented in Tables 1 and 4 as (↓).
- No relationship: In the primary studies selected, the presence of the studied factor presented no influence in inappropriate antibiotic's prescriptions. We believe that this was accomplished when the measure of association provided in the primary studies had an associated *P*-value >0.05, was not statistically significant. This is represented in Tables 1 and 4 as (=).

The papers obtained were reviewed by two of the authors (JVL and PLV), who decided whether or not these met the selection criteria. Finally, papers as to which there was some disagreement were examined by a third author (AFG), who took the final decision.

Results

Selection of papers

A total of 785 papers were located in PubMed and 1215 in EMBASE. After the titles and abstract were examined, 144 were selected for perusal of the complete text, and two more were added after the search of papers cited. Finally, 46 papers were included in the review (Fig. 1) [6–45,47–51].

Table 1 Studies that analyse attitudes/knowledge or other factors related with the prescription of antibiotics: description of methods

Author (year)	CO	SP	WP	EVAL	Pathology	Type of patient	Sample size	% *R*	QD	SA
Beltran Brotons (1990) [6]	SP	gps	PC	PR			174	99.8	o	M
Vinson and Lutz (1993) [7]	USA	gps	PC	CR	Cough	Paediatric	44 gps	100	o	M
Nazareth and King (1993) [8]	UK	gps, pa	PC	CR	UTIs	Women	6 gps	100	sa	M
Kuyvenhoven *et al.* (1993) [9]	NL	gps	PC	CR	URIs		161 gps	na		M
Carr *et al.* (1994) [10]	AU	gps	PC	SR	Sore throat	Clinical cases	400	77.4	pd	B
Hamm *et al.* (1996) [11]	USA	gps, pa	PC	SR	URIs	Outpatients	13 gps	100	sa	M
White *et al.* (1996) [12]	USA	gps, ps, o	H, PC	CR	AOM	Paediatric	7 357	100	o	B
Cars and Hakansson (1997) [13]	SE	gps, ps, o	PC	PR	URIs	Paediatric	3 047 prescriptions	na	nm	M
Steffensen *et al.* (1997) [14]	DK	gps	PC	PR	URIs, UTIs, Skin infections, Genital tract infections	Adult + paediatric	145	95.80	nm	M
Macfarlane *et al.* (1997) [15]	UK	gps, pa	PC	SR	LRIs	Outpatients	76 gps	100	nm	B
Davy *et al.* (1998) [16]	CA	gps, ps	PC	EO	URIs	Paediatric	181	75	pd	M
Pradier *et al.* (1999) [17]	FR	gps, ps	PC	SR	Viral pharyngitis	Paediatric	674	84.5	o	M
Mangione-Smith *et al.* (1999) [18]	USA	ps, pa	PC	SR + CR	URIs	Paediatric	10 doctors (306 patients)	77	sa	M
Watson *et al.* (1999) [19]	USA	gps, ps, pa	PC	SR + CR	URIs	Paediatric	1 541 doctors	43	pd	B
Dosh *et al.* (2000) [20]	USA	gps, ps, o, pa	PC	SR	URIs, bronchitis, sinusitis	Outpatients	55 doctors + 3 nurses	100	sa	M
McIsaac and Butler (2000) [21]	CA	gps	PC	SR	Sore throat	Outpatients	31 doctors	100	sa	M
Murray *et al.* (2000) [22]	AU	gps	PC	SR	URIs	Outpatients	nm	nm	nm	M
Steinke *et al.* (2000) [23]	UK	gps	PC	PR		Outpatients	231 gps	na	na	M
Gorecki *et al.* (2000) [24]	HK	o	H	EO	Surgical infections		911 (396 medical infectious specialists, 515 surgeons)	14	pd	B
Lin PL *et al.* (2000) [25]	USA	ps, o	H	SR		Paediatric	287 doctors	62	pd	B
Walker *et al.* (2001) [26]	UK	gps	PC	SR	Sore throat	Outpatients	185	76.2	pd	M
Lam and Lam (2001) [27]	hk	gps	PC	SR	URIs	Outpatients	1 248	65	pd	M
De Sutter *et al.* (2001) [28]	be	gps	PC	EO	URIs	Outpatients	80 doctors	nm	nm	M
Metlay (2002) [29]	USA	gps, o	H, PC	SR	CAP		1 600	53	pd	M
Metlay *et al.* (2002) [30]	USA	gps, o	H, PC	SR	CAP		1 600	52	pd	M
Nash *et al.* (2002) [31]	AU	gps	PC	NAMCS	URIs/LRIs/OM	Paediatric	13 078 medical visits	na	na	M
Cho and Kim (2002) [32]	KR	gps	PC	Actors	Common cold		149 doctors	100	na	M
Liabsuetrakul *et al.* (2003) [33]	TH	o	H	SR	Prophylaxis in Caesarean section	Women	50	100	sa	M/Q

Table 1 *Continued*

Author (year)	CO	SP	WP	EVAL	Pathology	Type of patient	Sample size	% *R*	QD	SA
Fakih *et al*. (2003) [34]	USA	gps, o	H, PC	SR	URIs		379 doctors	48	pd	B
Mangione-Smith *et al*. (2004) [35]	USA	ps, pa	PC	SR	URIs	Paediatric	59 paediatricians (43 gps)	64	sa	M
Thorpe *et al*. (2004) [36]	USA	o	H	NAMCS	URIs	Emergencies	nm	nm	o	M
Teng *et al*. (2004) [37]	MY	gps	PC	PR/SR	URIs	Outpatients	12 doctors	100	sa	B
Chamany *et al*. (2005) [38]	USA	o	H, PC	SR	URIs	Women	1 031 obstetrician/gynecologists	50	pd	M
Finkelstein *et al*. (2005) [39]	USA	gps, ps	PC	SR	AOM	Paediatric	292 doctors	58	pd	M
Liabsuetrakul and Islam (2005) [40]	TH	o	H	CR	Prophylaxis in Caesarean section	Women	232 records	na	na	M
Akkerman *et al*. (2005) [41]	NL	gps	PC	SR	URIs		84 gps	nm	nm	M
Akkerman *et al*. (2005) [42]	NL	gps	PC	SR + CR	AOM	Paediatric	600 gps	24.3	na	M
Akkerman *et al*. (2005) [43]	NL	gps	PC	SR + CR	URIs		600 gps	24.3	na	M
Fischer *et al*. (2005) [44]	DE	gps	PC	EO	URIs		62 gps	48.5	na	M
Huang *et al*. (2005) [45]	TW	gps	PC	CR	URIs and acute bronchitis, nasopharyngitis		128 260 files	na	na	M
Bharathiraja *et al*. (2005) [46]	IND	gps, ps	PC	CR	URIs, acute diarrhoea and viral fever	Paediatric	nm	nm	na	B
Ciofi Degli Atti *et al*. (2006) [47]	IT	ps, pa	PC	SR	URIs	Paediatric	150 paediatricians	47	sa	M
Mangione-Smith *et al*. (2006) [48]	USA	ps, pa	PC	SR	URIs	Paediatric	59 paediatricians (43 practices)	64	sa	M/Q
Fakih *et al*. (2006) [49]	USA	gps, ps, o	H	CR	URIs		90 doctors	na	na	M
Cadieux *et al*. (2007) [50]	FR	gps	PC	CR/PR	URIs/UTIs		852 gps	na	na	M
Cotter and Daly (2007) [51]	IE	gps	PC	SR			100	76.5	pd	M

Each study variable is accompanied by (0) (+) or (–) as follows: (+) where an increase in the variable was associated with an increase in the prescription of antibiotics; (–) where an increase in the variable was associated with a decrease in the prescription of antibiotics; and (0) where there was no association.

CO, country (Internet domain).

EVAL, evaluation: method of assessing the dependent variable (CR, clinical record; AR, selfreporting; PR, prescriptions; EO, external observer; NAMCS, National Ambulatory Medical Care Survey).

QD, questionnaire distribution: sa, self-administered; pd, postal distribution; o, others; na, not applicable; nm, not mentioned.

WP, workplace; H, hospital; PC, primary care.

Pathology (URIs, upper respiratory infections; UTIs, urinary tract infections; AOM, acute otitis media; LRIs, lower respiratory infections; CAP, community acute pneumonia)

SA, statistical analysis; M, multivariate; B, bivariate; M/Q, multivariate/qualitative.

SP, study population; gps, general practitioners; ps, paediatricians; o, others; pa, patients.

Table 2 Studies that analyse attitudes/knowledge or other factors related with the prescription of antibiotics: factors extrinsic to health care professional

	Factors extrinsic to the health professional		
Authors (year)	Patients	Health care system	Pharmaceutical companies
Beltran Brotons (1990) [6]		pl(↓), pv(↑), x(=)	
Vinson and Lutz (1993) [7]	pa(↑), co(↑), sy(↑), si(=), op(↑)		
Nazareth and King (1993) [8]	pa(↑), si(↑), se(↑)	x(=)	ph(=)
Kuyvenhoven *et al.* (1993) [9]		pv(↑)	
Carr *et al.* (1994) [10]	pa(↑), sy(↑)		ph(↑)
Hamm *et al.* (1996) [11]	pa(↑), in(↑)		
White *et al.* (1996) [12]	pa(↓), r(↑), co(↑)		
Cars and Hakansson (1997) [13]	op(↑/↓)	pv(↑),	
Steffensen *et al.* (1997) [14]		pv(↑), x(=)	
Macfarlane *et al.* (1997) [15]	se(↑), op(↑)	pv(↑)	
Davy *et al.* (1998) [16]	pa(↑), sy(↑), si(↑), an(↑), op(↑)		
Pradier *et al.* (1999) [17]	in(=)	pv(=)	
Mangione-Smith *et al.* (1999) [18]	r(=), sy(=), si(=), se(=)		
Watson *et al.* (1999) [19]	r(↑), in(↑)	x(=)	
Dosh *et al.* (2000) [20]	pa(=), co(=), si(↑)		
McIsaac and Butler (2000) [21]	pa(=), sy(↓), si(↑), pg(=)		
Murray *et al.* (2000) [22]	pa(=), si(↑)		
Steinke *et al.* (2000) [23]	pa(=)		
Gorecki *et al.* (2000) [24]	pa(=)		
Lin PL *et al.* (2000) [25]	pa(=)		
Walker *et al.* (2001) [26]	se(↑)		
Lam and Lam (2001) [27]		o(↑)	
De Sutter *et al.* (2001) [28]	pa(=), co(=), sy(=/↑), si(=/↑)	o(=)	
Metlay (2002) [29]			
Metlay *et al.* (2002) [30]	op(↑)		
Nash *et al.* (2002) [31]	pa(↑), si(=), in(=)	pl(=)	
Cho and Kim (2002) [32]		oh(=)	
Liabsuetrakul *et al.* (2003) [33]		pv(=)	
Fakih *et al.* (2003) [34]			
Mangione-Smith *et al.* (2004) [35]	r(=), si(↑)		
Thorpe *et al.* (2004) [36]	pa(↑), r(↑), sy(↑), si(↑), in(=), pg(=)	o(=)	
Teng *et al.* (2004) [37]		pv(=)	
Chamany *et al.* (2005) [38]		pl(↑)	
Finkelstein *et al.* (2005) [39]		oh(↓)	
Liabsuetrakul and Islam (2005) [40]	si(↑)		
Akkerman *et al.* (2005) [41]			ph(=)
Akkerman *et al.* (2005) [42]	pa(↓)		
Akkerman *et al.* (2005) [43]	pa(=), sy(=,↑, ↓), in(=/↓)		
Fischer *et al.* (2005) [44]	pa(=), sy(=)	pv(=)	
Huang *et al.* (2005) [45]	pa(↓), r(↑), co(↑), se(=), pg(↓), op(=)	pl(↑), pv(↑), o(↑), al(↑), oh(↑)	
Bharathiraja *et al.* (2005) [46]	pa(=)	pv(=), oh(↑)	Ph(↑)
Ciofi Degli Atti *et al.* (2006) [47]	si(↑), an(↑), e(=), op(=)		
Mangione-Smith *et al.* (2006) [48]	r(↑), sy(↑/↓), an(↑), se(↑), op(=)		
Fakih *et al.* (2006) [49]			
Cadieux *et al.* (2007) [50]		pv(↑)	
Cotter and Daly (2007) [51]		pl(↑), pv(=)	

Patient-related factors: pg, patient's gender; pa, patient's age; r, race; co, co-morbidity; sy, symptoms; si, signs; an, anxiety; se, socio-economic level; e, educational level; in, insurance; op, other patient-related factors.

Factors related with the health care system: pl, practice location; pv, patient volume; o, ownership of practice setting; x, working alone or as part of a group; al, accreditation level of practice setting, oh, other health care system factors; ph, pharmaceutical companies.

Table 3 Process for extraction of attitudes from papers included in the review

Examples of sentences in the primary article	Attitude identified
'Doctor prescribes antibiotics significantly more when their patients request it'	Complacency
'Doctors believe that the antibiotics prescribed in primary care do not influence the genesis of resistances'	Indifference
'The antibiotics commonly used in primary care are not broad spectrum antibiotics'	Ignorance
'If in doubt, the primary care physicians prefer to prescribe a broad spectrum antibiotics'	Fear
'Antibiotics use without prescription by patients is cause of emergence of resistances'	Responsibility of others professionals
'Doctors prescribes antibiotics due patients demand'	Complacency

Methods used in the studies selected

The 46 papers included could be separated into two blocks, according to whether the unit of analysis used was doctors (31 studies) [10,11,15–22,24–30,32–35,37–39,41–44,47,48,51] or some other item (clinical histories, prescriptions, etc.) [6–9,12–14,23,31,36,40,45,49,50]. In the 15 remaining studies [6–9,12–14,23,31,36,40,45,49,50], the unit of analysis used was: clinical histories in eight [7–9,12,40,45,49], prescriptions in four [6,13,14,23], both in one [50] and annual survey data in two (National Hospital Ambulatory Medical Care Survey) [31,36].

In the 31 studies included in the block which studied doctors [10,11,15–22,24–30,32–35,37–39,41–44,47,48,51], the median percentage participation was 65%, and the data were collected by means of questionnaires in 27 cases [10,11,15–22,25–27,29,30,33–35,37–39,41–43,47,48,51] (with this procedure being combined with collection based on a review of clinical histories in four cases [18,19,42,43] and a review of prescriptions in one case) [37], and through observers/actors present at the medical visit in four cases [24,28,32,49]. Questionnaires were distributed by post in over 50% of cases [10,16,19,24–27,29,30,34,38,39,51]; nine were self-administered [11,18,20,21,33,35,37,47,48], four made no mention of the method of distribution [15,22,28,41] and one took the form of a telephone survey [17].

In terms of the disease treated, most studies focused on respiratory infection in its different spectra (ranging from the common cold to acute bronchitis) [7,9–13,15–22,26–32,34,36–39,41–45,47–49]. In four no specific disease was mentioned [6,23,25,51], in three respiratory infection was combined with others, such as urinary tract infections or diarrhoea [14,46,50], two addressed the topic of prophylaxis in Caesarean section [33,40], and surgical infection was targeted in one [24] and urinary infection in another [8].

The study setting was primary care in 35 of the 46 studies [6–11,13–23,26–28,31,32,35,37,39,41–45,48,50,51], hospital care in six [24,25,33,36,40,49] and both in the remainder (five papers) [12,29,30,34,38]. The most widely studied professionals were general practitioners (GPs), followed by paediatricians. Insofar as the study population (major type of patient) was concerned, 14 studies made no mention of this [6,9,24,29,30,32,34,41,43–45,49–51], 15 focused on the paediatric population [7,12,13,16–19,25,31,35,39,42,46–48] (with it being noted that the most frequently studied disease in this population was acute otitis media), 10 targeted the ambulatory adult population [11,15,20–23,26–28,37], four centred on women [8,33,38,40] (two addressing the topic of prophylaxis in Caesarean section, one addressing urinary tract infections and the other addressing clinical management of upper respiratory infections by specialists in gynecology and obstetrics) and one reported on the emergency room population [36]. One study simultaneously assessed both ambulatory adult and paediatric patients [14], and another conducted its evaluation on the basis of clinical cases [10].

Three of the studies concentrated on the factors that influenced the prescription of specific antibiotics [10,13,25] (penicillins, other broad-spectrum cephalosporins, vancomycin and macrolides).

Results of the studies selected

The median number of factors studied in the studies selected was five (range 1–11).

Socio-demographic factors of doctors

Few studies assessed all socio-demographic characteristics, with the most widely studied being age, years of practice and medical specialty.

Age was assessed in 12 [6,9,10,14,17,27,32,37,40,44,45,51] of the 46 studies, with a direct relationship being found in eight [6,10,14,27,32,44,45,51], a inverse relationship in one [9] and no relationship in three [17,37,40].

Medical specialty was assessed in 15 [6,12,17,19,20,24,25,29–32,39,45,49] of the 46 studies, with a direct relationship being found in nine [12,17,19,24,29,30,39,45]. Furthermore, the medical specialty evaluated was seen to vary depending on the study, although a more marked trend towards misprescribing was observed among GPs in the case of studies in which the paediatric population was studied. In one of the studies [31], a direct relationship was found for GPs in the misprescription of antibiotics for upper respiratory infections and bronchitis, whereas no relationship was found in prescriptions for otitis and sinusitis. The remaining studies [6,20,25,32,49] that assessed medical specialty reported no relationship between this factor and misprescription of antibiotics. It should just be noted, however, that we located no study in which this relationship was inverse.

In 14 studies [9,10,19,25,27,34,36–39,41,44,46,50], years of clinical practice were assessed, with a direct relationship being found in nine [10,27,34,36,38,39,41,46,50], a inverse relationship in one [9] and no relationship in four [19,25,37,44].

Sex was another variable assessed by several studies [17,27,28,32,38,41,51], with a direct relationship for male gender being observed in two [27,38]. In the remainder [17,27,32,41,51], no relationship was observed between sex and misprescription of antibiotics.

Other socio-demographic variables, such as continuous education, doctors' original university or medical school, etc., were evaluated by few studies (see Table 4).

Doctors' attitudes

The attitudes envisaged by studies as possible factors underlying the misprescribing of antibiotics were complacency, indifference,

Table 4 Studies that analyse attitudes/knowledge or other factors related with the prescription of antibiotics: factors intrinsic to health care professional

	Factors intrinsic to the health professional	
Authors (year)	Socio-demographic factors	Attitudes
Beltran Brotons (1990) [6]	a(↑), s(=)	
Vinson and Lutz (1993) [7]		c(↑)
Nazareth and King (1993) [8]	om(↑)	c(↑)
Kuyvenhoven *et al.* (1993) [9]	a(↓), p(↓)	
Carr *et al.* (1994) [10]	a(↑), p(↑)	i(↑), c(↑), f(↑)
Hamm *et al.* (1996) [11]	sr(↑)	i(↑), c(↑), f(↑), r(↑)
White *et al.* (1996) [12]	s(↑)	
Cars and Hakansson (1997) [13]		
Steffensen *et al.* (1997) [14]	a(↑), om(↑/↓)	
Macfarlane *et al.* (1997) [15]		c(↑), r(↑)
Davy *et al.* (1998) [16]		f(↑)
Pradier *et al.* (1999) [17]	a(=), g(=), s(↑)	
Mangione-Smith *et al.* (1999) [18]		c(↑)
Watson *et al.* (1999) [19]	s(↑), p(=)	
Dosh *et al.* (2000) [20]	s(=)	
McIsaac and Butler (2000) [21]		
Murray *et al.* (2000) [22]		
Steinke *et al.* (2000) [23]		
Gorecki *et al.* (2000) [24]	s(↑)	
Lin PL *et al.* (2000) [25]	s(=), p(=), om(↑)	
Walker *et al.* (2001) [26]		i(↑), ii(↑), c(↑), f(↑)
Lam and Lam (2001) [27]	a(↑), male(↑), p(↑), sr(↑), om(↑)	
De Sutter *et al.* (2001) [28]	g(=), sr(=), om(↑)	f(↑)
Metlay (2002) [29]	s(↑)	ii(↑)
Metlay *et al.* (2002) [30]	s(↑)	
Nash *et al.* (2002) [31]	s(=/↑)	
Cho and Kim (2002) [32]	a(↑), g(=), s(=), om(↑)	
Liabsuetrakul *et al.* (2003) [33]	om(↑)	i(↑), c(=)
Fakih *et al.* (2003) [34]	p(↑)	
Mangione-Smith *et al.* (2004) [35]		c(↑)
Thorpe *et al.* (2004) [36]	p(↑)	
Teng *et al.* (2004) [37]	a(=), p(=), om(=)	c(=)
Chamany *et al.* (2005) [38]	male(↑), p(↑)	c(↑), r(↑)
Finkelstein *et al.* (2005) [39]	s(↑), p(↑)	ii(↓)
Liabsuetrakul and Islam (2005) [40]	a(=)	
Akkerman *et al.* (2005) [41]	g(=), p(↑), om(↓)	
Akkerman *et al.* (2005) [42]		c(↑), f(↑)
Akkerman *et al.* (2005) [43]		c(↑), f(↑)
Fischer *et al.* (2005) [44]	a(↑), p(=)	
Huang *et al.* (2005) [45]	a(↑), s(↑)	c(↑)
Bharathiraja *et al.* (2005) [46]	s(↑), p(↑), cme(↓)	
Ciofi Degli Atti *et al.* (2006) [47]		c(↑)
Mangione-Smith *et al.* (2006) 48]		c(↑)
Fakih *et al.* (2006) [49]	s(=)	
Cadieux *et al.* (2007) [50]	p(↑), sr(↑)	
Cotter and Daly (2007) [51]	a(↑), g(=)	

Doctor-related factors: a, age; g, gender; s, medical specialty; p, years of practice; sr, school/residency; cme, continuous medical education; i, ignorance; ii, indifference; c, complacency; f, fear; r, responsibility; om, other doctor-related factors.

ignorance, fear and responsibility of other professionals. Found attitudes were defined as:

- Complacency: attitude that motivates the prescription of antibiotics to fulfill the expectations that professionals believe they have patients/parents.
- Fear: attitude related to the fear of possible complications in the patient.
- Ignorance: lack of relationship between overprescribing and antibiotic resistances.
- Indifference: lack of motivation to feel positive or negative slope to the problema of antibiotic resistance.
- Responsibility of other professionals: attitude that motivates the belief that responsibility in the generation of antibiotic resistances is from other professionals.

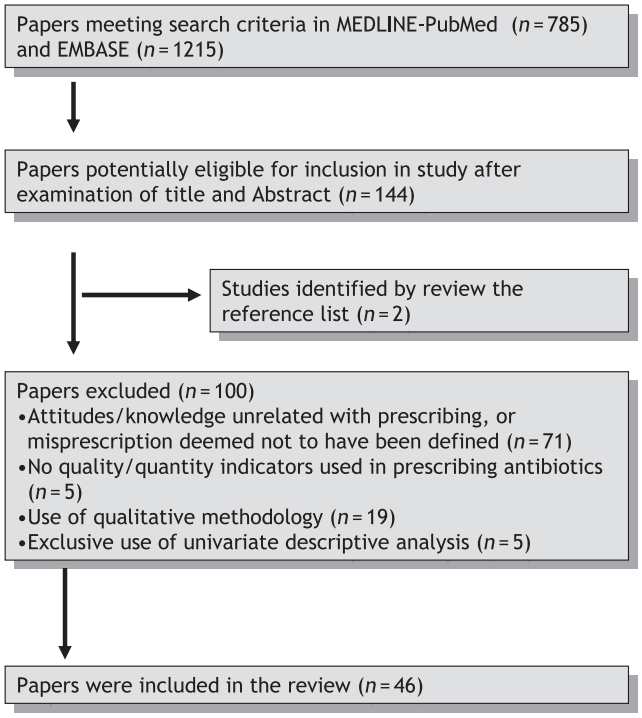

Figure 1 Identification and inclusion of studies.

The number of attitudes assessed was as follows: none in 26 studies [6,9,12–14,17,19–25,27,30–32,34,36,40,41,44,46,49–51]; one in 12 studies [7,8,16,18,28,29,35,37,39,45,47,48], two in five studies [15,33,38,42,43], three in one study [10] and four in only two studies [11,26]. Thus, only 20 studies [7,8,10,11,15,16,18,26,28,29,33,35,37–39,42,43,45,47,48] were observed to have assessed at least one attitude.

A total of 16 studies [7,8,10,11,15,18,26,33,35–38,42,43,45,47,48] assessed complacency as a misprescription-related factor, with a direct relationship being reported in 14 [7,8,10,11,15,18,26,35,38,42,43,45,47,48] and no relationship in two [33,37]. Fear was assessed and found to show a direct relationship with misprescription in seven studies [10,11,16,26,28,42,43]. The remaining attitudes, such as ignorance, indifference and responsibility of other professionals, were assessed by fewer than seven studies (see Table 4).

Patients' characteristics

Twenty [6–12,16,20–25,28,31,36,42–45] studies assessed patients' age, with a direct relationship being found in seven [6,7,10,11,16,31,36], a inverse relationship in three [12,42,45] and no relationship in 10 [20–25,28,43,44,46].

In terms of frequency of assessment in the studies selected, the following patient-related factors were symptoms and signs present at the time of prescription, with signs being assessed in 13 [7,8,15,18,20–22,28,31,35,36,40,47] and symptoms in 10 cases [7,10,16,18,21,28,36,43,44,48]. Most of these studies observed a direct relationship with one or more symptoms [7,10,16,36] or signs [8,16,20–22,35,36,40,47] evaluated (fever, pathological murmur and productive cough).

The remaining factors studied, which included race [12,18,19,35,36,45,48], co-morbidities [7,12,20,28,45], socio-economic level [8,15,18,26,45,48], patients' gender [21,36,45] and type of insurance [11,17,19,31,36,43], were assessed by fewer than seven studies.

Factors related with health care organization

A total of 13 studies [6,9,13–15,17,33,37,44,45,50,51] assessed the relationship between health care burden (measured by reference to the volume of patients that passed through a doctor's practice on a work day) and misprescribing, with a direct relationship being observed in seven studies [6,9,13–15,45,50] and no relationship in six [17,33,37,44,46,51]. Other factors related with health care organization were studied by fewer than seven papers and included the following: location of the health care centre [6,31,38,45,51] (rural/urban), private or public care, the structure and organization of the medical practice, and type of health care centre (tertiary, district, university) (see Table 4).

Lastly, four studies [8,10,41,46] evaluated the pressure exerted by the pharmaceutical industry on prescribing, with a direct relationship being found in two [10,46], and no relationship in the other two [8,41].

Discussion

This is the first systematic review to address factors associated with the misprescribing of antibiotics in ambulatory care. The results of this review indicate that there is very little evidence to show which factors influence the quality of antibiotic prescription. On the one hand, the few studies conducted are very heterogeneous, and on the other, most of these studies display major methodological limitations that qualify the grade of evidence supporting their conclusions. Only complacency and, to a lesser extent, fear emerge as possible factors that affect the misprescription of antibiotics.

The methodological limitations range from failure to describe the type of study design to failure to indicate the unit of analysis or dependent variables used in selected studies. To identify factors that influence prescription quality, outcome variables should ideally be obtained from prescription indicators which apply a gold standard to real prescriptions. Such prescription data can be obtained by reviewing clinical histories or using computerized prescription records. Nevertheless, most of the studies use fictitious cases posed on a questionnaire in order to simulate prescribing, and then relate this with knowledge/attitudes measured in the same questionnaire. By using simulated prescription, one is assuming that the only factor influencing prescribing is doctors' knowledge, whereas in reality other studies which have analysed the prescription of medications report that other factors, such as pressure exerted by the patient, health care system or pharmaceutical industry, also have an influence [6,10,16,27,45,47,48,52]. What this therefore means is that, with simulated prescribing, no factor other than knowledge could ever be detected. In our review, only five studies [18,19,37,42,43,50] used questionnaires and reviews of clinical histories or prescriptions to link attitudes to real prescribing. Yet, none of them made an overall assessment of the

socio-demographic characteristics, knowledge, attitudes and setting-related factors that might influence the prescription of antibiotics.

In the course of our review, we located 19 studies [7,53–70] that exclusively used qualitative methodology. Only two of the studies included [33,48], however, referred to the use of qualitative methodology as a preliminary stage for identifying factors related with the prescription of antibiotics. We feel that this methodology could be of great interest as an instrument for exploring and identifying the kind of prescriber-related knowledge and attitudes which could not be identified by researchers a priori. The results of these studies could serve as a basis for subsequently designing purpose-made questionnaires that prove more comprehensive than those used in the studies surveyed [71].

The identification of prescription-related factors may be very important for designing interventions aimed at improving the prescribing of antibiotics. There are many studies [52,72–78] which assess the efficacy or effectiveness of different interventions undertaken to improve the prescription of antibiotics, with widely varying results. The scant efficacy of these measures may, in great part, be due to the complexity of the factors that influence the prescribing of antibiotics, many of which are either unknown or not quantified, as can be seen from our review. Some authors indicate that the success of interventions among health care professionals is based on the prior detection of the gaps and shortcomings that are to be targeted [2,79]. Hence, the reason why intervention studies [52,72–78] designed to improve antibiotic prescription quality have not had more favourable results may conceivably be due to a failure to identify gaps in health care professionals' knowledge and attitudes.

Despite the methodological limitations found, our review appears to show that, save for years of clinical practice (which may be linked to education and training), doctors' socio-demographic and personal factors do not exert much influence. Insofar as attitudes are concerned, it is complacency vis-à-vis the patient, and to a lesser extent, fear that are associated with the prescription of antibiotics. This is a major shortcoming which could be remedied by educational interventions, based on ample evidence to show that patients generally seem to expect less medication than is perceived by doctors. With respect to health care organization, observation in half the studies that assessed this aspect seems to indicate that heavier health care burdens are associated with greater prescription of antibiotics, possibly because of the shorter time available for making differential diagnoses of other (e.g. viral) diseases. Lastly, it is noteworthy that only three studies assessed the role of industry, when a number of studies have reported an relationship with the quantity prescribed [10,46,67,80–83].

We were unable to find a theoretical framework which would model the possible factors that influence the prescribing of antibiotics and the interrelationships among such factors. To render interpretation of the results of this review easier, we endeavoured to classify certain attitudes or factors expressed in the questionnaires, by using a theoretical frameworks applied in pharmacoepidemiology, that is, the mixed theoretical model (which is a combination of knowledge, attitudes and practices, and the satisfaction of needs) [84,85]. This model would enable both the extrinsic (patients, industry, health care system) and intrinsic factors (knowledge and attitudes) to be explained. To model attitudes, we made use of the model that explains the determinants of ADR underreporting by reference to Inman's seven deadly sins [86]. On numerous occasions, the results of a given study had to be allocated to one of the attitudes or factors of the models, a task that entailed some difficulty. Although our allocation of factors may possibly not coincide with that of other authors, we feel that this in no way alters the principal conclusions of this review.

There is little evidence on the factors that influence antibiotic prescribing, a finding that may go some way to explain why the different interventions implemented in this field have not been effective. Only attitudes such as complacency and fear display some relationship. Using previous theoretical frameworks applied to other related spheres [86–88], measuring instruments (questionnaire, databases) could be designed, which would enable the potential factors that intervene in prescribing to be simultaneously measured and then related with indicators of antibiotic prescription quality (drawn up on the basis of real data). From these data, we could design studies that enable the attitudes associated with antibiotic's prescriptions by primary care doctors. This would allow for gaps to be identified, something that would be extremely useful for designing more effective interventions to improve antibiotic-prescribing quality, which could, in turn, serve to reduce the prevalence of bacterial resistance to certain antibiotics in the longer term.

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