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Determinants of inappropriate antibiotic prescription in primary care in developed countries with general practitioners as gatekeepers: a systematic review and construction of a framework

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ABSTRACT

Objectives This study aimed to identify determinants of inappropriate antibiotic prescription in primary care in developed countries and to construct a framework with the determinants to help understand which actions can best be targeted to counteract development of antimicrobial resistance (AMR).

Design A systematic review of peer-reviewed studies reporting determinants of inappropriate antibiotic prescription published through 9 September 2021 in PubMed, Embase, Web of Science and the Cochrane Library was performed.

Setting All studies focusing on primary care in developed countries where general practitioners (GPs) act as gatekeepers for referral to medical specialists and hospital care were included.

Results Seventeen studies fulfilled the inclusion criteria and were used for the analysis which identified 45 determinants of inappropriate antibiotic prescription. Important determinants for inappropriate antibiotic prescription were comorbidity, primary care not considered to be responsible for development of AMR and GP perception of patient desire for antibiotics. A framework was constructed with the determinants and provides a broad overview of several domains. The framework can be used to identify several reasons for inappropriate antibiotic prescription in a specific primary care setting and from there, choose the most suitable intervention(s) and assist in implementing them for combatting AMR.

Conclusions The type of infection, comorbidity and the GPs perception of a patient's desire for antibiotics are consistently identified as factors driving inappropriate antibiotic prescription in primary care. A framework with determinants of inappropriate antibiotic prescription may be useful after validation for effective implementation of interventions for decreasing these inappropriate prescriptions.

PROSPERO registration number CRD42023396225.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study focuses specifically on antibiotic prescription in primary care while most studies on this topic focus on hospital care.
⇒ The scope of the review was somewhat limited by only selecting studies on primary care in developed countries where general practitioners act as gatekeepers.
⇒ The framework provides a broad overview of both determinants of—and knowledge gaps regarding antibiotic prescription habits.
⇒ The information conveyed in this paper can be used for designing initiatives to improve prudent antibiotic prescription in primary care, and thereby reduce the development of antimicrobial resistance.
⇒ The proposed framework needs validation before it can be implemented.

INTRODUCTION

Antimicrobial resistance (AMR) is increasing worldwide and represents a major threat to global healthcare.[1] The major driver of the rise in AMR is the use, frequently inappropriate, of antibiotics.[2] Worldwide efforts are now underway to decrease unnecessary antibiotic prescribing and consequently reduce the development of AMR.[1] The most common prescribers of antibiotics in developed countries are general practitioners (GPs), accounting for between 80% and 90% of all antibiotic prescriptions.[3 4] As such, GPs play an important role in reducing AMR. However, there is currently insufficient insight into which potentially changeable determinants are associated with inappropriate antibiotic prescription in this setting.

GPs prescribe antibiotics for a variety of infectious diseases, ranging from respiratory tract infections (RTI) to cellulitis.[5–10] However between 44% and 98% of the antibiotic prescriptions for RTIs are classified as inappropriate.[11–14] The proportion of inappropriate antibiotic prescriptions for urinary tract infections is estimated at between 3% and 36.5%.[15 16] Antibiotic prescriptions are

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generally considered inappropriate when, according to the guidelines, no or other antimicrobials should be used. The high proportion of inappropriate antibiotic prescriptions combined with the large quantity of antibiotics prescribed by GPs suggest that efforts to improve antibiotic prescribing in primary care may have a substantial effect on the development of AMR.

Determinants across several domains affect the proportion of inappropriate antibiotic prescribing in primary care. These domains include patient–doctor interactions, the organisation of primary care, the national role of primary care and the nationwide healthcare system.[17 18] Reducing inappropriate antibiotic prescribing is therefore complex. To increase effectiveness, each domain should be taken into account in any intervention. However, it is still unclear which determinants play a role in each specific domain and how the different determinants may interact.

The aim of this review is to identify the determinants influencing inappropriate antibiotic prescribing by GPs, sort the determinants into a framework according to their domain and identify which determinants may be subject to antimicrobial stewardship interventions for reducing inappropriate antibiotic prescribing.

METHODS

Systematic review search strategy and study selection

A systematic review was conducted. Briefly, the search included studies describing determinants in primary care in developed countries through 9 September 2021. The protocol developed to conduct this study was registered in PROSPERO (online supplemental file 1). PubMed, Embase, Web of Science and the Cochrane Library databases were searched. The full electronic search strategy can be found in online supplemental file 2. We additionally searched grey literature (ie, abstracts of conferences, symposia and meetings) and relevant references found in initially identified studies found in Embase, Web of Science and the Cochrane Library. There were no language restrictions in the search. The reporting of our systematic review was based on the protocol specified by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (online supplemental file 3).[19]

Studies were, regardless of their design, selected for reviewing if they provided a definition of inappropriate antibiotic prescription according to the guidelines used in that study. Only studies performed in developed countries, as defined by the United Nations (UN), in which the GP plays a 'gatekeeper' role in the healthcare system, were included (online supplemental files 4; 5).[20 21] This gatekeeper role is defined by the UN as a compulsory GP referral to access most types of specialist care, except in case of emergency.[21] Studies had to report determinants that influence the inappropriate prescribing of antibiotics as an outcome. Studies on specific subgroups of patients (eg, those with specific comorbidities) or specific diseases (such as asthma or chronic obstructive pulmonary disease) were excluded as reasons for appropriate or inappropriate antibiotic prescriptions for these groups differ, while our aim was to develop a framework for the whole population. Two reviewers (MS and FLB) independently reviewed the titles, index terms and abstracts of the identified references and rated each abstract according to the inclusion and exclusion criteria. Full texts of potentially relevant abstracts were assessed for eligibility by two reviewers (MS and FLB). Discrepancies were resolved by consensus. If consensus could not be reached, a third reviewer (MGJdB or MEN) was consulted.

Data extraction and quality assessment

The determinants of inappropriate prescription of antibiotics were extracted from the included studies, along with the study design, geographical location, disease group, definition of inappropriate prescribing, study population and research period. ORs describing associations between determinants and inadequate prescription were extracted where provided. Study quality was assessed using the National Heart and Lung Institute (NHLI) study quality assessment tool[22] for quantitative studies and the Critical Appraisal Skills Programme (CASP)[23] for qualitative studies.

Framework

Determinants were placed in a framework by a reviewer (MS) which was thereafter reviewed by the research group and adapted based on consensus in the groups' discussion. We used a practical framework set-up as described by Morgan *et al*.[17] This framework is specifically designed for understanding and reducing medical overuse in primary care and takes all relevant domains of influence into account, including the culture of healthcare consumption, patient factors and experiences, the culture of professional medicine, clinician attitudes and beliefs, practice environments and patient–clinician interactions. The domain 'government' was left out of the framework as it was found to be redundant owing to our selection of studies from developed countries in which GPs play a gatekeeper role.

If the definition of determinants showed large similarity, we choose to combine the determinants to prevent overlap in our framework. Determinants were eligible to be added to the framework if they had a positive or negative impact on inappropriate antibiotic prescribing. The determinants were classified as having either a positive or negative influence on inappropriate antibiotic prescription according to the findings and description in their study. Subsequently, each determinant was noted in the framework with a plus or minus sign. The identified determinants were categorised and attributed to the framework domains specified by a method described by Morgan *et al*.[17] Determinants specific to one country, as well as those on which studies reported conflicting results, were included to create a complete framework appropriate to various settings. Determinants on which studies

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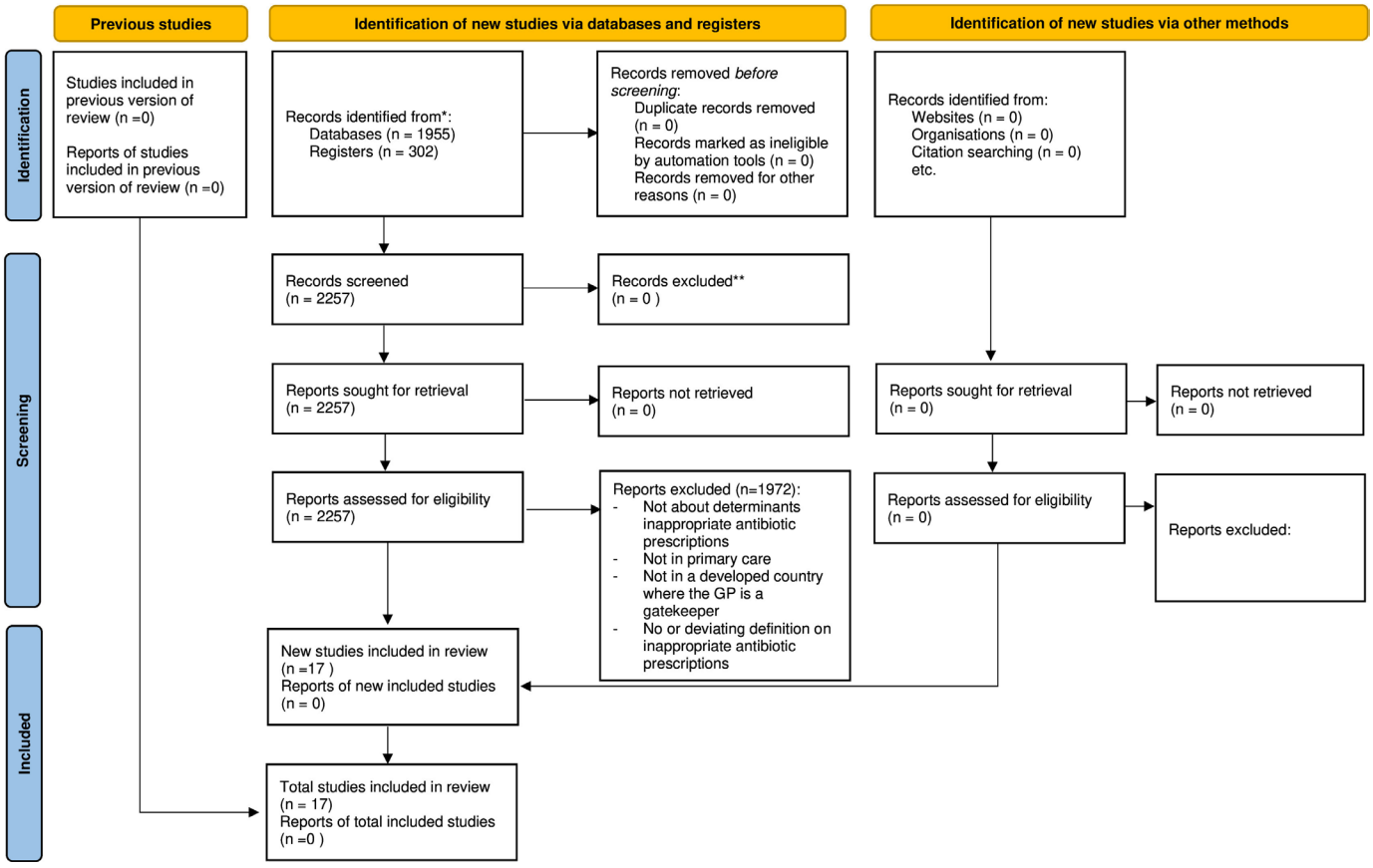

Figure 1 Flow diagram of study selection. GP, general practitioner.

returned conflicting results were noted in the framework with a plus or minus sign (±).

Patient and public involvement

Patients were not involved in designing the review, data collection, interpretation or write-up of this review.

RESULTS

The literature search identified 2257 studies. Following screening of titles and abstracts, 285 studies were retained for full-text review, of which 17 were ultimately included in the review as they specified determinants of inappropriate antibiotic prescription (figure 1).[24–40] Characteristics of the selected studies are presented in the online supplemental materials S6a and S6b. The studies were conducted in six countries: Australia, Canada, Ireland, The Netherlands, Spain and the UK. Four studies[25 32 33 38] had a qualitative design (one explorative qualitative design, one cross-sectional survey, one focus group and one questionnaire) while 13 studies had a quantitative design (all observational in nature). The methodologies of the included studies as assessed by the NHLI or CASP tool all had a low risk of bias. Quality assessment tables are presented in the online supplemental materials S7; S8.

Framework determinants of inappropriate prescriptions

In total, 54 determinants were identified from 17 studies. Seven determinants were directly not included in the framework as they showed no association with inappropriate antibiotic prescribing, either positive or negative (online supplemental materials S6b). Forty-five determinants were included and are presented in a framework (figure 2). There were five determinants with conflicting results from the included studies and three determinants with a positive impact on inappropriate antibiotic prescribing. Three determinants showed similarity and were combined with each other to one determinant.[34] Silverman *et al* compared careers of between 11 and 24 years with careers shorter than 11 years and careers longer than 25 years with careers less than 11 years.[34] These outcomes were combined to form one determinant, a career longer than 10 years.

DISCUSSION

We systematically reviewed the determinants of inappropriate antibiotic prescription in developed countries in which GPs act as the gatekeepers. Comorbidity and GPs' perceptions of a patient's expectation for antibiotics were consistently identified as main factors that drive inappropriate prescription of antibiotics in primary care. There were no restrictions on the design of the study for the inclusion as our aim was to include as many determinants as possible.

Determinants of inappropriate antibiotic prescription in primary care

Comorbidity was the most frequently found determinant of inappropriate antibiotic prescription.[25–27 29 35 37 40]

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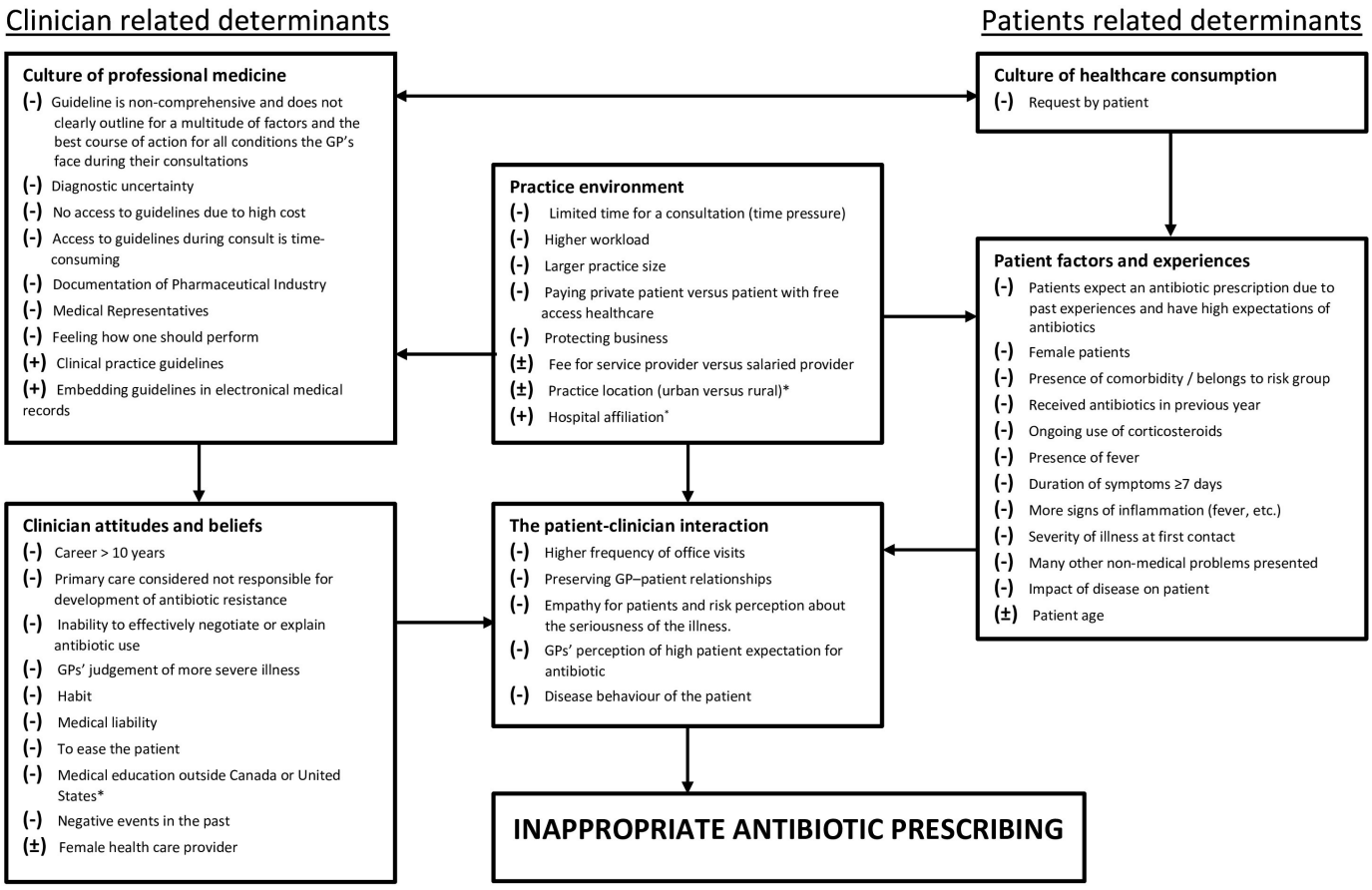

Figure 2 Framework for determinants of inappropriate antibiotic prescribing in primary care in developed countries. Determinants associated with more inappropriate antibiotic prescribing. ±Determinants with conflicting results on inappropriate antibiotic prescribing. *Determinants specific for a country. GPs, general practitioners.

However, it is not clear to what extent prescribing an antibiotic for a patient with one or more comorbidities is inappropriate. The guidelines for appropriate antibiotic use are largely based on studies of patients without comorbidities. Consideration of antibiotic prescription is also advised by guidelines in cases of comorbidity.[5 9] GPs may quickly choose to prescribe an antibiotic to be on the safe side with regard to complications, leading to more antibiotic prescriptions for patients presumably at risk for complications.

Another important determinant was the GPs perception of a patient's expectation of getting antibiotics.[24–26 30] GPs may assume the reason for a patient's visit is an antibiotic prescription, but may not verify this with the patient. Thus, more effort focused towards verifying the specific reason for the encounter may represent a typical primary care approach to further reducing inappropriate antibiotic prescriptions. Inability to effectively negotiate or explain antibiotic use also leads to more inappropriate prescriptions.[32] Both determinants illustrate the benefits of the availability of time to communicate with patients and efficient communication skills. This was confirmed by a recent review of communication training aimed at reduction of antibiotic prescriptions for RTIs.[41]

Remarkably, some GPs did not consider themselves responsible for antibiotic resistance.[32] In their opinion, their prescribing at an individual level did not contribute to AMR. Rather, they believe AMR is mainly driven by antibiotic prescriptions in hospitals or those in veterinary use. This notion was confirmed by a study performed by the European Centre for Disease Control.[42] In reality, up to 90% of antibiotic prescriptions find their origin in primary care.[3 4] Furthermore, according to the one health concept, antibiotic prescriptions from all sectors contribute to antibiotic selection pressure.[43] Additionally, more (inappropriate) antibiotic prescription is the cause of a vicious cycle of increasing AMR which leads to prescribing of second choice, mostly broad-spectrum antibiotics leading to increasing AMR. This points to the need for continuous education which emphasises that inappropriate antibiotic prescriptions give unnecessary antibiotic selection pressure and thus lead to more AMR.

There were conflicting results on some determinants. A study by Eggermont *et al* specifically designed to investigate gender differences in inappropriate antibiotic prescriptions failed to detect any such association with gender.[27] However, there were three studies reporting a gender association. Therefore, we included female gender as a determinant associated with more inappropriate antibiotic prescribing in our framework.[26 29 30]

Two studies found an association between larger practice size and inappropriate antibiotic prescription[29 31]

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Table 1 Overview determinants with examples of potential effective interventions

Determinants associated with inappropriate antibiotic prescribing	Examples of potential effective interventions
Culture of professional medicine	
Diagnostic uncertainty.	CRP POCT.*[44–46 53–57]
No access to guidelines due to high cost.	Free access to guidelines.[58]
Access to guidelines during consult is time-consuming.	CDSS.†[47 58]
Culture of healthcare consumption	
Request by patient.	Patient education.‡[45 59–61] Mass media campaign.§[62] Delayed antibiotic prescription.¶[44 63–65]
Clinician attitudes and beliefs	
Career >10 years.	Feedback on antibiotic prescribing.[45 65–68]
Primary care considered not responsible for development of antibiotic resistance.	
Habit.	
Inability to effectively negotiate or explain antibiotic use.	CST.**[53 66 69 70]
GPs' judgement of more severe illness.	CRP POCT.*[44–46 53–57]
Medical liability.	Physician education.††[45 67 70 71]
Delayed antibiotic prescription.¶[44 63–65]	Delayed antibiotic prescription.¶[44 63–65]
The patient–clinician interaction	
Preserving GP–patient relationships.	Delayed antibiotic prescription.¶[44 63–65]
Empathy for patients and risk perception about the seriousness of the illness.	Physician education.††[45 67 70 71]
GPs' perception of high patient expectation for antibiotic.	CST.**[53 66 69 70]
Disease behaviour of the patient.	Patient education.‡[45 59–61]
Patient factors and experiences patient	
Patients expect an antibiotic prescription due to past experiences and have high expectations of antibiotics. Received antibiotics in previous year.	Patient education.‡[45 59–61]
Presence of comorbidity/belongs to risk group. Ongoing use of corticosteroids. Presence of fever. Duration of symptoms ≥7 days. More signs of inflammation (fever, etc). Severity of illness at first contact.	Physician education.††[45 67 70 71]

*CRP POCT: C-reactive protein point-of-care testing for patients with a respiratory tract infection divers between uncomplicated and complicated respiratory tract infections and reduces antibiotic prescriptions.
†CDSS: Clinical decision support system is integrated in an electronic medical system. It gives direct access to guidelines and supports clinical decision-making.
‡Patient education: Patient can be educated through handout/leaflets and waiting room posters on the limited effect of antibiotics for a viral infection.
§Mass media campaign: Mass media campaign providing information on the appropriate use of antibiotic and reduces antibiotic prescriptions.
¶Delayed antibiotic prescription is prescribed directly at a consult but the patient is advised to use the antibiotic only when the symptoms persist or become more severe. It reduces antibiotic use by patients while maintaining patient satisfaction.
**CST: Communication skills training helps a physician to explain the limited effect of antibiotics to a patient and is effective in reducing antibiotic prescriptions.
††Physician education: Education of physicians about guidelines for infectious diseases, the limited effect of antibiotics for viral infections and which diagnostic tools can help to differ between a self-limiting infection and a more severe infectious diseases, such as a CRP POCT.
Feedback: Feedback on antibiotic prescribing provides insight in the number of antibiotic prescriptions by a physician and the impact on antibiotic resistance which stimulates a physician to reflect on his own antibiotic prescription habits.
GP, general practitioner.

while a third study found no association with practice size.[35] A higher daily patient load was associated with more inappropriate prescription of antibiotics in one study.[34] As practice size and patient load are generally related, a larger practice was included in the framework.

The determinant age of the patient was investigated by seven studies.[24–27 29 30 37] Two studies found that an age between 18 and 65 years was associated with increased inappropriate antibiotic prescription,[26 29] one study concluded increasing age to be associated with greater inappropriate antibiotic prescription[37] and two studies failed to find any such association.[24 27] Two studies focusing on otitis media found inappropriate antibiotic prescription more commonly occurred with children younger than 2 years of age as compared with children 2 years and older.[25 30] This was therefore included in the framework as a determinant with conflicting results.

The healthcare payment model was researched in several studies exploring various determinants, with some finding an association with inappropriate antibiotic prescription.[32–35] An explorative study in Ireland from O'Doherty *et al* reported a higher rate of inappropriate antibiotic prescriptions in self-paying or fee-for-service insured patients versus patients with free access

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to healthcare.[33] Likewise, a study in Canada found fee-for-service providers more commonly inappropriately prescribed antibiotics than salaried providers.[35] Another study from Canada failed to detect this association,[34] and likewise found no association between inappropriate antibiotic prescription and a healthcare capitation payment system. Protecting business was singled out as a reason for inappropriate antibiotic prescription in a cross-sectional survey study in Australia.[32]

Framework determinants of inappropriate antibiotic prescribing

As our aim was to construct a comprehensive framework as possible. The determinants practice location (rural vs urban), hospital affiliation and medical education outside the USA and Canada were put in the framework despite being specific to a country or setting.[29 31 34 35] Rural locations in Canada have a different context than rural locations in Europe and this determinant should be used in that context.[29] One study found that physicians trained outside Canada or USA prescribed more inappropriate antibiotics while working in Canada.[31] The constructed framework provides a broad overview of all determinants by domain and can be used, after validation, to design interventions intended to reduce inappropriate prescriptions in primary care. For example, the framework shows that clinical judgement differs between GPs due to different interpretations of the severity of the symptoms.[24 26 30] A career longer than 10 years was associated with more inappropriate antibiotic prescription,[29 31 34] with a possible cause being that they are less familiar with guidelines and rely more on their clinical experience. This illustrates that a more objective tool for judgement of severity is needed. A possible solution could be using C-reactive protein (CRP) and other point of care tests for patients with RTIs. CRP-guided treatment has been proven effective in reducing inappropriate antibiotic prescription for patients with RTIs.[44] More examples of effective interventions per determinant are presented in table 1. Only determinants associated with inappropriate antibiotic prescriptions that can be influenced by effective interventions were included (table 1). Studies on effective interventions for reducing antibiotic prescriptions in primary care show that multifaceted interventions thus covering more determinants seem to be more effective in reducing antibiotic prescribing.[44–48]

The focus and interpretation of the framework, and hence the needed interventions, differ by country. For example, patient expectations of an antibiotic may stem from local beliefs and attitudes and be more common in cultures placing an emphasis on masculinity as antibiotic prescription tends to be higher in such societies.[49] A priority in a masculine society is an early return to work and antibiotics are seen as an important facilitator therefore.[50] In societies in which this effect is smaller, illness is considered a legitimate reason for absence from work. Ireland, Spain and the UK have much higher masculinity scores than The Netherlands,[51] and antibiotic prescription rates are indeed higher in those three countries as compared with The Netherlands.[3] Interventions should focus on informing patients about the mild natural course of most infectious diseases and the low value of antibiotic use.

Strength and limitations

The strengths of our study include that our review summarises determinants covering many domains, thus providing a broad overview. Additionally, the Morgan *et al* framework was specifically designed to reduce overuse in primary care,[17] making it particularly useful when designing and/or implementing interventions to reduce inappropriate antibiotic prescription. Only studies from developed countries where GPs act as gatekeepers were included as both influence the level of appropriate antibiotic prescriptions in a country.[52] This choice reduced the number of eligible studies and may have concurrently reduced the number of detected determinants. Our framework has not been validated in this study, which is needed before it can be implemented. Another limitation was the lack of objective measure of the effect size due to the inclusion of qualitative studies. This makes it not possible to determine which determinants are more relevant.

CONCLUSIONS

The most important determinants of inappropriate antibiotic prescribing are comorbidity, diagnostic uncertainty, the GPs perception of a patient's wish for antibiotics, an inability to effectively negotiate or explain appropriate use of antibiotics and a direct request for an antibiotic by a patient. Although our framework needs validation before it can be used. It may provide a viable starting point for designing, implementing and conducting interventions aimed at evidence-based reduction of antibiotic prescriptions in primary care.

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