Improving antimicrobial prescription in primary care: a multi-dimensional approach to antimicrobial resistance

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Chapter 3

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.

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 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 (i.e., 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 (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 (e.g., 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 for quantitative studies and the Critical Appraisal Skills Programme (CASP) for qualitative studies (22, 23).

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 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 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 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). 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 while a third study found no association with practice size (29,31,35). 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 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 with a possible cause being that they are less familiar with guidelines and rely more on their clinical experience (29,31,34). 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.

Tables

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)

Legend:

*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

¶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

#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

Figure 1. Study Selection

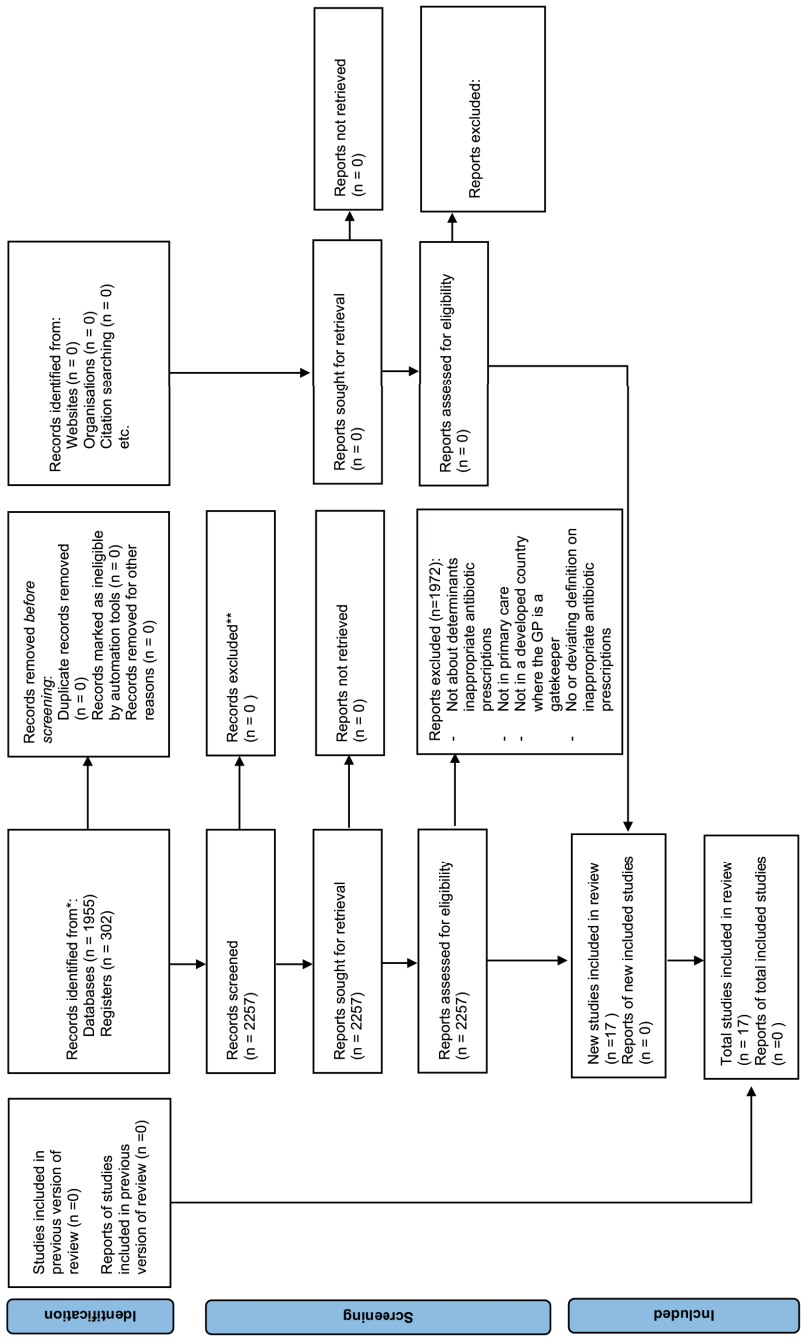
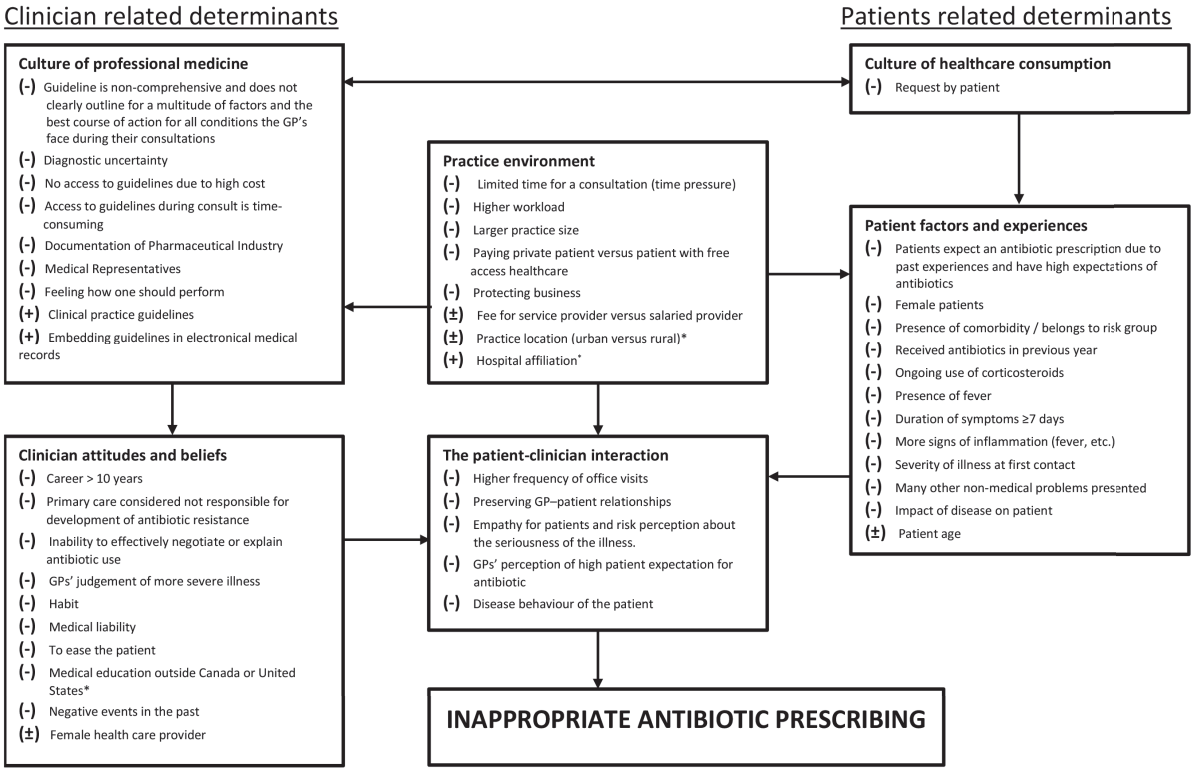


Figure 2. Framework for determinants of inappropriate antibiotic prescribing in primary care in developed countries



Legend:

Determinants associated with more inappropriate antibiotic prescribing

± Determinants with conflicting results on inappropriate antibiotic prescribing

+ Determinants associated with less inappropriate antibiotic prescribing

* Determinants found for only one country

References

1. Worldwide country situation analysis: response to antimicrobial resistance 2015 [World Health Organisation report]. Available from: https://www.who.int/drugresistance/documents/situationanalysis/en/ accessed May 2019.
2. Bell BG, Schellevis F, Stobberingh E, et al. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. BMC infectious diseases 2014;14:13. doi: 10.1186/1471-2334-14-13 [published Online First: 2014/01/11]
3. Antimicrobial consumption ECDC website2020 [European Centre for Disease Prevention and Control report]. Available from: https://ecdc.europa.eu/en/antimicrobial-consumption/surveillance-and-disease-data/database accessed December 2020.
4. National Institute for Public health and the Enivronment (RIVM), SWAB. Nethmap 2021. Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands in 2020 [Available from: https://swab.nl/nl/nethmap.
5. NHG_workgroup. Acute coughing 2011 [Dutch Society of General Practitioners guideline]. Available from: https://richtlijnen.nhg.org/standaarden/acuut-hoesten accessed June 2020.
6. NHG_workgroup. Dutch Society of General Practitioners guideline: Bacterial Skin infections 2019 [Available from: https://richtlijnen.nhg.org/standaarden/bacteriele-huidinfecties.
7. NHG_workgroup. Dutch Society of General Practitioners guideline: Acute rhinosinusitis 2014 [Available from: https://richtlijnen.nhg.org/standaarden/acute-rhinosinusitis2020.
8. NHG_workgroup. Dutch Society of General Practitioners guideline: Urinary tract infections 2020 [Available from: https://richtlijnen.nhg.org/standaarden/urineweginfecties2020.
9. National Institute for Health Care and Excellence (NICE): Self-limiting respiratory tract and ear infections – antibiotic prescribing overview [cited 2020. Available from: https://pathways.nice.org.uk/pathways/self-limiting-respiratory-tract-and-ear-infections-antibiotic-prescribing#path=view%3A/pathways/self-limiting-respiratory-tract-and-ear-infections-antibiotic-prescribing/self-limiting-respiratory-tract-and-ear-infections-antibiotic-prescribing-overview.xml&content=view-index accessed June 2020.
10. National Institute for Health Care and Excellence (NICE): Urinary tract infections overview [Available from: https://pathways.nice.org.uk/pathways/urinary-tract-infections accessed June 2020.
11. Bianco A, Papadopoli R, Mascaro V, et al. Antibiotic prescriptions to adults with acute respiratory tract infections by Italian general practitioners. Infect Drug Resist 2018;11:2199-205. doi: 10.2147/IDR.S170349 [doi];idr-11-2199 [pii]
12. Jorgensen LC, Friis CS, Cordoba CG, et al. Antibiotic prescribing in patients with acute rhinosinusitis is not in agreement with European recommendations. Scand J Prim Health Care 2013;31(2):101-05. doi: 10.3109/02813432.2013.788270 [doi]
13. Hek K, van Esch TEM, Lambooij A, et al. Guideline Adherence in Antibiotic Prescribing to Patients with Respiratory Diseases in Primary Care: Prevalence and Practice Variation. Antibiotics (Basel, Switzerland) 2020;9(9) doi: 10.3390/antibiotics9090571 [published Online First: 2020/09/10]
14. Howarth T, Brunette R, Davies T, et al. Antibiotic use for Australian Aboriginal children in three remote Northern Territory communities. PloS one 2020;15(4) doi: http://dx.doi.org/10.1371/journal.pone.0231798
15. Debets VE, Verheij TJ, van der Velden AW. Antibiotic prescribing during office hours and out-of-hours: a comparison of quality and quantity in primary care in the Netherlands. The British journal of general practice : the journal of the Royal College of General Practitioners 2017;67(656):e178-e86. doi: 67/656/e178 [pii];10.3399/bjgp17X689641 [doi]
16. Peñalva G, Fernández-Urrusuno R, Turmo JM, et al. Long-term impact of an educational antimicrobial stewardship programme in primary care on infections caused by extended-spectrum β-lactamase-producing Escherichia coli in the community: an interrupted time-series analysis. The Lancet Infectious diseases 2020;20(2):199-207. doi: 10.1016/s1473-3099(19)30573-0 [published Online First: 2019/11/27]
17. Morgan DJ, Leppin AL, Smith CD, et al. A Practical Framework for Understanding and Reducing Medical Overuse: Conceptualizing Overuse Through the Patient-Clinician Interaction. Journal of hospital medicine 2017;12(5):346-51. doi: 10.12788/jhm.2738 [published Online First: 2017/05/02]

18. Flottorp SA, Oxman AD, Krause J, et al. A checklist for identifying determinants of practice: a systematic review and synthesis of frameworks and taxonomies of factors that prevent or enable improvements in healthcare professional practice. Implementation science : IS 2013;8:35. doi: 10.1186/1748-5908-8-35 [published Online First: 2013/03/26]

19. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ (Clinical research ed) 2021;372:n71. doi: 10.1136/bmj.n71

20. nations U. World economic situation and prospect 2015 [

21. OECD Health System characteristics Survey 2019 [Organisation for Economic Co-operation and Development report]. Available from: http://www.oecd.org/ accessed May 2019.

22. National Heart Lung and Blood Institute: Study quality assesment tools [Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools accessed May 2019.

23. CASP Chekclist [Available from: https://casp-uk.net/casp-tools-checklists/ accessed 07-05-2019 2019.

24. Akkerman AE, Kuyvenhoven MM, Van der Wouden JC, et al. Determinants of antibiotic overprescribing in respiratory tract infections in general practice. The Journal of antimicrobial chemotherapy 2005;56(5):930-36. doi: dki283 [pii];10.1093/jac/dki283 [doi]

25. Damoiseaux RA, de Melker RA, Ausems MJ, et al. Reasons for non-guideline-based antibiotic prescriptions for acute otitis media in The Netherlands. Family practice 1999;16(1):50-53.

26. Dekker ARJ, Verheij TJM, van der Velden AW. Inappropriate antibiotic prescription for respiratory tract indications: most prominent in adult patients. Family practice 2015;32(4):401-07. doi: 10.1093/fampra/cmv019

27. Eggermont D, Smit MAM, Kwestroo GA, et al. The influence of gender concordance between general practitioner and patient on antibiotic prescribing for sore throat symptoms: a retrospective study. BMC family practice 2018;19(1):175. doi: 10.1186/s12875-018-0859-6 [published Online First: 2018/11/19]

28. Pouwels KB, Dolk FCK, Smith DRM, et al. Actual versus 'ideal' antibiotic prescribing for common conditions in English primary care. Journal of Antimicrobial Chemotherapy 2018;73(Supplement 2):ii19-ii26.

29. Singer A, Fanella S, Kosowan L, et al. Informing antimicrobial stewardship: factors associated with inappropriate antimicrobial prescribing in primary care. Family practice 2018;35(4):455-60. doi: 10.1093/fampra/cmx118 [published Online First: 2017/12/14]

30. Akkerman AE, Kuyvenhoven MM, Van der Wouden JC, et al. Analysis of under- and overprescribing of antibiotics in acute otitis media in general practice. The Journal of antimicrobial chemotherapy 2005;56(3):569-74. doi: dki257 [pii];10.1093/jac/dki257 [doi]

31. Cadieux G, Tamblyn R, Dauphinee D, et al. Predictors of inappropriate antibiotic prescribing among primary care physicians. CMAJ 2007;177(8):877-83. doi: 177/8/877 [pii];10.1503/cmaj.070151 [doi]

32. Fletcher-Lartey S, Yee M, Gaarslev C, et al. Why do general practitioners prescribe antibiotics for upper respiratory tract infections to meet patient expectations: a mixed methods study. BMJ open 2016;6(10):e012244. doi: 10.1136/bmjopen-2016-012244 [published Online First: 2016/11/01]

33. O'Doherty J, Leader LFW, O'Regan A, et al. Over prescribing of antibiotics for acute respiratory tract infections; a qualitative study to explore Irish general practitioners' perspectives. BMC family practice 2019;20(1):27. doi: 10.1186/s12875-019-0917-8 [doi];10.1186/s12875-019-0917-8 [pii]

34. Silverman M, Povitz M, Sontrop JM, et al. Antibiotic Prescribing for Nonbacterial Acute Upper Respiratory Infections in Elderly Persons. Ann Intern Med 2017;166(11):765-74. doi: 2625386 [pii];10.7326/M16-1131 [doi]

35. Singer A, Kosowan L, Katz A, et al. Prescribing and testing by primary care providers to assess adherence to the Choosing Wisely Canada recommendations: a retrospective cohort study. CMAJ Open 2018;6(4):E603-E10. doi: 6/4/E603 [pii];10.9778/cmajo.20180053 [doi]

36. van Esch TEM, Brabers AEM, Hek K, et al. Does shared decision-making reduce antibiotic prescribing in primary care? The Journal of antimicrobial chemotherapy 2018;73(11):3199-205. doi: 10.1093/jac/dky321 [published Online First: 2018/08/31]

37. Malo S, Poblador-Plou B, Prados-Torres A, et al. Poor congruence with guidelines in the use of antibiotics for acute bronchitis: a descriptive study based on electronic health records. Family practice 2016;33(5):471-75. doi: cmw037 [pii];10.1093/fampra/cmw037 [doi]

38. Biezen R, Roberts C, Buising K, et al. How do general practitioners access guidelines and utilise electronic medical records to make clinical decisions on antibiotic use? Results from an Australian qualitative study. BMJ open 2019;9(8):e028329. doi: 10.1136/bmjopen-2018-028329 [published Online First: 2019/08/07]

39. Fernández-Álvarez I, Zapata-Cachafeiro M, Vázquez-Lago J, et al. Pharmaceutical companies information and antibiotic prescription patterns: A follow-up study in Spanish primary care. PloS one 2019;14(8):e0221326. doi: 10.1371/journal.pone.0221326 [published Online First: 2019/08/23]

40. Nowakowska M, van Staa T, Molter A, et al. Antibiotic choice in UK general practice: rates and drivers of potentially inappropriate antibiotic prescribing. The Journal of antimicrobial chemotherapy 2019 doi: 10.1093/jac/dkz345 [published Online First: 2019/08/21]

41. Kochling A, Loffler C, Reinsch S, et al. Reduction of antibiotic prescriptions for acute respiratory tract infections in primary care: a systematic review. Implementation science : IS 2018;13(1):47. doi: 10.1186/s13012-018-0732-y [published Online First: 2018/03/21]

42. Survey of Healthcare Workers' Knowledge, Attitudes and Behaviours on Antibiotics, Antibiotic Use and Antibiotic Resistance in the EU/EEA 2019 [European Centre for Disease Prevention and Control Report]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/survey-of-healthcare-workersknowledge-attitudes-behaviours-on-antibiotics.pdf accessed September 2020.

43. One health 2022 [World Health Organization report]. Available from: https://www.who.int/news-room/questions-and-answers/item/one-health.

44. Cals JW, Schot MJ, de Jong SA, et al. Point-of-care C-reactive protein testing and antibiotic prescribing for respiratory tract infections: a randomized controlled trial. Annals of family medicine 2010;8(2):124-33. doi: 10.1370/afm.1090 [published Online First: 2010/03/10]

45. Bjerrum L, Munck A, Gahrn-Hansen B, et al. Health Alliance for prudent antibiotic prescribing in patients with respiratory tract infections (HAPPY AUDIT) -impact of a non-randomised multifaceted intervention programme. BMC family practice 2011;12:52. doi: 10.1186/1471-2296-12-52 [published Online First: 2011/06/22]

46. Cals JW, Butler CC, Hopstaken RM, et al. Effect of point of care testing for C reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. BMJ (Clinical research ed) 2009;338:b1374. doi: 10.1136/bmj.b1374 [published Online First: 2009/05/07]

47. Gonzales R, Anderer T, McCulloch CE, et al. A cluster randomized trial of decision support strategies for reducing antibiotic use in acute bronchitis. JAMA Intern Med 2013;173(4):267-73. doi: 10.1001/jamainternmed.2013.1589 [published Online First: 2013/01/16]

48. Little P, Hobbs FD, Moore M, et al. Clinical score and rapid antigen detection test to guide antibiotic use for sore throats: randomised controlled trial of PRISM (primary care streptococcal management). BMJ (Clinical research ed) 2013;347:f5806. doi: 10.1136/bmj.f5806 [published Online First: 2013/10/12]

49. Touboul-Lundgren P, Jensen S, Drai J, et al. Identification of cultural determinants of antibiotic use cited in primary care in Europe: a mixed research synthesis study of integrated design "Culture is all around us". BMC Public Health 2015;15(1):908. doi: 10.1186/s12889-015-2254-8

50. Borg MA. National cultural dimensions as drivers of inappropriate ambulatory care consumption of antibiotics in Europe and their relevance to awareness campaigns. The Journal of antimicrobial chemotherapy 2012;67(3):763-7. doi: 10.1093/jac/dkr541 [published Online First: 2011/12/28]

51. Hofstede G. Compare countries tool 2020 [cited 2020 October]. Hofstede Insights]. Available from: https://www.hofstede-insights.com/product/compare-countries/.

52. Blommaert A, Marais C, Hens N, et al. Determinants of between-country differences in ambulatory antibiotic use and antibiotic resistance in Europe: a longitudinal observational study. The Journal of antimicrobial chemotherapy 2014;69(2):535-47. doi: dkt377 [pii];10.1093/jac/dkt377 [doi]

53. Cals JW, de Bock L, Beckers PJ, et al. Enhanced communication skills and C-reactive protein point-of-care testing for respiratory tract infection: 3.5-year follow-up of a cluster randomized trial. Annals of family medicine 2013;11(2):157-64. doi: 10.1370/afm.1477 [published Online First: 2013/03/20]

54. Andreeva E, Melbye H. Usefulness of C-reactive protein testing in acute cough/respiratory tract infection: an open cluster-randomized clinical trial with C-reactive protein testing in the intervention group. BMC family practice 2014;15:80. doi: 10.1186/1471-2296-15-80 [published Online First: 2014/06/03]

55. Little P, Stuart B, Francis N, et al. Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial. Lancet 2013;382(9899):1175-82. doi: 10.1016/s0140-6736(13)60994-0 [published Online First: 2013/08/07]

56. Little P, Stuart B, Francis N, et al. Antibiotic Prescribing for Acute Respiratory Tract Infections 12 Months After Communication and CRP Training: A Randomized Trial. Annals of family medicine 2019;17(2):125-32. doi: 10.1370/afm.2356 [published Online First: 2019/03/13]

57. Llor C, Bjerrum L, Munck A, et al. Access to point-of-care tests reduces the prescription of antibiotics among antibiotic-requesting subjects with respiratory tract infections. Respir Care 2014;59(12):1918-23. doi: 10.4187/respcare.03275 [published Online First: 2014/12/04]

58. Fernández Urrusuno R, Flores Dorado M, Vilches Arenas A, et al. Improving the appropriateness of antimicrobial use in primary care after implementation of a local antimicrobial guide in both levels of care. Eur J Clin Pharmacol 2014;70(8):1011-20. doi: 10.1007/s00228-014-1704-z [published Online First: 2014/06/04]

59. Francis NA, Butler CC, Hood K, et al. Effect of using an interactive booklet about childhood respiratory tract infections in primary care consultations on reconsulting and antibiotic prescribing: a cluster randomised controlled trial. BMJ (Clinical research ed) 2009;339:b2885. doi: 10.1136/bmj.b2885 [published Online First: 2009/07/31]

60. Macfarlane J, Holmes W, Gard P, et al. Reducing antibiotic use for acute bronchitis in primary care: blinded, randomised controlled trial of patient information leaflet. BMJ (Clinical research ed) 2002;324(7329):91-4. doi: 10.1136/bmj.324.7329.91 [published Online First: 2002/01/12]

61. Småbrekke L, Berild D, Giaever A, et al. Educational intervention for parents and healthcare providers leads to reduced antibiotic use in acute otitis media. Scand J Infect Dis 2002;34(9):657-9. doi: 10.1080/00365540210147651 [published Online First: 2002/10/11]

62. Lambert MF, Masters GA, Brent SL. Can mass media campaigns change antimicrobial prescribing? A regional evaluation study. The Journal of antimicrobial chemotherapy 2007;59(3):537-43. doi: 10.1093/jac/dkl511 [published Online First: 2007/02/07]

63. Little P, Gould C, Williamson I, et al. Pragmatic randomised controlled trial of two prescribing strategies for childhood acute otitis media. BMJ (Clinical research ed) 2001;322(7282):336-42. doi: 10.1136/bmj.322.7282.336 [published Online First: 2001/02/13]

64. Mas-Dalmau G, Villanueva López C, Gorrotxategi Gorrotxategi P, et al. Delayed Antibiotic Prescription for Children With Respiratory Infections: A Randomized Trial. Pediatrics 2021;147(3) doi: 10.1542/peds.2020-1323 [published Online First: 2021/02/13]

65. McNulty C, Hawking M, Lecky D, et al. Effects of primary care antimicrobial stewardship outreach on antibiotic use by general practice staff: pragmatic randomized controlled trial of the TARGET antibiotics workshop. Journal of Antimicrobial Chemotherapy 2018;73(5):1423-32. doi: 10.1093/jac/dky004

66. Butler CC, Simpson SA, Dunstan F, et al. Effectiveness of multifaceted educational programme to reduce antibiotic dispensing in primary care: practice based randomised controlled trial. BMJ (Clinical research ed) 2012;344:d8173. doi: 10.1136/bmj.d8173 [published Online First: 2012/02/04]

67. Dyrkorn R, Gjelstad S, Espnes KA, et al. Peer academic detailing on use of antibiotics in acute respiratory tract infections. A controlled study in an urban Norwegian out-of-hours service. Scand J Prim Health Care 2016;34(2):180-5. doi: 10.3109/02813432.2016.1163035 [published Online First: 2016/04/08]

68. Persell SD, Doctor JN, Friedberg MW, et al. Behavioral interventions to reduce inappropriate antibiotic prescribing: a randomized pilot trial. BMC infectious diseases 2016;16:373. doi: 10.1186/s12879-016-1715-8 [published Online First: 2016/08/09]

69. Briel M, Langewitz W, Tschudi P, et al. Communication training and antibiotic use in acute respiratory tract infections. A cluster randomised controlled trial in general practice. Swiss Med Wkly 2006;136(15-16):241-7. [published Online First: 2006/05/19]

70. Welschen I, Kuyvenhoven MM, Hoes AW, et al. Effectiveness of a multiple intervention to reduce antibiotic prescribing for respiratory tract symptoms in primary care: randomised controlled trial. BMJ (Clinical research ed) 2004;329(7463):431. doi: 10.1136/bmj.38182.591238.EB [published Online First: 2004/08/07]

71. Gjelstad S, Høye S, Straand J, et al. Improving antibiotic prescribing in acute respiratory tract infections: cluster randomised trial from Norwegian general practice (prescription peer academic detailing (Rx-PAD) study). BMJ (Clinical research ed) 2013;347:f4403. doi: 10.1136/bmj.f4403 [published Online First: 2013/07/31]

Supplements

Supplement 1. Original study protocol

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Constructing a framework for the eterminants of inappropriate antibiotic prescription in primary care: a systematic review

Martijn Sijbom, Frederike Büchner, Nicholas Saadah, Mark de Boer, Mattijs Numans

Citation

Martijn Sijbom, Frederike Büchner, Nicholas Saadah, Mark de Boer, Mattijs Numans. Constructing a framework for the eterminants of inappropriate antibiotic prescription in primary care: a systematic review. PROSPERO 2023 CRD42023396225 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023396225

Review question

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.

Searches

PubMed, Embase, Web of Science and the Cochrane Library

Types of study to be included

There are no restriction on the types of studies.

Condition or domain being studied

Primary care and inappropriate prescription of antibiotics

Participants/population

General population, 18 years and older

Intervention(s), exposure(s)

Inappropriate prescription of antibiotics

Comparator(s)/control

Not relevant

Main outcome(s)

Determinants which influence inappropriate antibiotic prescription presented in a framework

Additional outcome(s)

Framework for primary care on inappropriate prescription of antibiotics

Data extraction (selection and coding)

2 reviewers (MS and FB) independently review the titles, index terms and abstracts of the identified references and rated each abstract as potentially relevant or not. Discrepancies are resolved by consensus and if necessary discussed with a third researcher (MdB). Potentially relevant abstracts are assessed full-text for eligibility by 2 reviewers and selected for inclusion in the review if they fulfill the inclusion criteria.

The data will be extracted from the included studies by using a standardized form. This form will be used for the assessment of the quality and evidence synthesis. The data will include: study setting, study population, participant demographics, definition of inappropriate antibiotic use, determinants which influence inappropriate use, study methodology, information for assessment of the risk of bias.

Risk of bias (quality) assessment

The study quality assessment tool of the National Heart and Lung institute will be used to asses the bias. If the risk of bias is (very) high, articles can be excluded.

Strategy for data synthesis

Determinants are placed in a framework by a reviewer (MS) to be able to provide a comprehensive overview of all determinants and their interactions. Discrepancies on the determinants on the framework are resolved by discussion with all authors . We use a practical framework setup as described by Morgan et al. 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' is 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.

Determinants are eligible to be added to the framework if they were found in at least one quantitative study or repeatedly in two or more qualitative studies. The determinants are 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 is noted in the framework with a plus or minus sign. The identified determinants are categorized and attributed to the framework domains specified (17). Determinants specific to one country, as well as those on which studies reported conflicting results, are included to create a complete framework appropriate to various settings. Determinants on which studies returned conflicting results are noted in the framework with a plus or minus sign (+/-).

Analysis of subgroups or subsets

None

Contact details for further information

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Organisational affiliation of the review

LUMC

Review team members and their organisational affiliations

Dr Martijn Sijbom. LUMC
Dr Frederike Büchner. LUMC
Dr Nicholas Saadah. LUMC
Professor Mark de Boer. LUMC
Professor Mattijs Numans. LUMC

Type and method of review

Narrative synthesis, Synthesis of qualitative studies, Systematic review

Anticipated or actual start date

01 February 2019

Anticipated completion date

30 December 2023

Funding sources/sponsors

LUMC

Conflicts of interest

Language

English

Country

Netherlands

Stage of review [1 change]

Review Completed not published

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Anti-Bacterial Agents; Antimicrobial Stewardship; Humans; Inappropriate Prescribing; Prescriptions

Date of registration in PROSPERO

12 February 2023

Date of first submission

01 February 2023

Stage of review at time of this submission [1 change]

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Revision note

Submitting for publication

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

12 February 2023
12 February 2023
22 February 2023

Supplement 2. Search strategies

PubMed

((("prescribing"[ti] OR "prescription"[ti] OR "prescriptions"[ti] OR prescri*[ti]) AND ("Anti-Bacterial Agents"[majr] OR "anti-bacterial agents"[ti] OR "anti-bacterial agent"[ti] OR "antibacterial agents"[ti] OR "antibacterial agent"[ti] OR "antibacterials"[ti] OR "antibiotic"[ti] OR "antibiotics"[ti] OR antibiotic*[ti] OR "anti-biotic"[ti] OR "anti-biotics"[ti] OR anti biotic*[ti]) AND ("Primary Health Care"[majr] OR "General Practice"[majr] OR "General Practitioners"[majr] OR "Family Practice"[majr] OR "Physicians, Family"[majr] OR "Primary Health Care"[ti] OR "General Practice"[ti] OR "General Practitioners"[ti] OR "Family Practice"[ti] OR "Family Physicians"[ti] OR "Primary HealthCare"[ti] OR "Primary Care"[ti] OR "General Practitioner"[ti] OR "Family Physician"[ti]) AND ("prescription behavior"[tw] OR "prescribing behavior"[tw] OR "prescription behaviors"[tw] OR "prescribing behaviors"[tw] OR "prescription behaviour"[tw] OR "prescribing behaviour"[tw] OR "prescription behaviours"[tw] OR "prescribing behaviours"[tw] OR "reduced prescription"[tw] OR "reduced prescribing"[tw] OR "prescription rates"[tw] OR "prescription rate"[tw])) **OR** (("inappropriate antibiotic"[tw] OR "inappropriate antibiotics"[tw] OR (("Inappropriate Prescribing"[Mesh] OR "inappropriate prescribing"[tw] OR "inappropriate prescription"[tw] OR "inappropriate prescriptions"[tw] OR inappropriate prescri*[tw] OR "over prescribing"[tw] OR over prescri*[tw] OR "overprescribing"[tw] OR overprescri*[tw] OR "unnecessary prescribing"[tw] OR "unnecessary prescription"[tw] OR "unnecessary prescriptions"[tw] OR "inappropriate"[tw] OR inappropriat*[tw] OR "misprescription"[tw] OR "misprescriptions"[tw] OR misprescri*[tw] OR "mis prescription"[tw] OR mis prescription*[tw] OR "determinant"[tw] OR "determinants"[tw]) AND ("Anti-Bacterial Agents"[Mesh] OR "Anti-Bacterial Agents"[Pharmacological Action] OR "anti-bacterial agents"[tw] OR "anti-bacterial agent"[tw] OR "antibacterial agents"[tw] OR "antibacterial agent"[tw] OR "antibacterials"[tw] OR "antibiotic"[tw] OR "antibiotics"[tw] OR antibiotic*[tw] OR "anti-biotic"[tw] OR "anti-biotics"[tw] OR anti biotic*[tw]))) AND ("Primary Health Care"[Mesh] OR "General Practice"[Mesh] OR "General Practitioners"[Mesh] OR "Family Practice"[Mesh] OR "Physicians, Family"[Mesh] OR "Primary Health Care"[tw] OR "General Practice"[tw] OR "General Practitioners"[tw] OR "Family Practice"[tw] OR "Family Physicians"[tw] OR "Primary HealthCare"[tw] OR "Primary Care"[tw] OR "General Practitioner"[tw] OR "Family Physician"[tw]))**)**

Embase (OVID-version)

((("prescribing".ti OR "prescription".ti OR "prescriptions".ti OR prescri*.ti) AND (exp *"Antibiotic Agent"/ OR "anti-bacterial agents".ti OR "anti-bacterial agent".ti OR "antibacterial agents".ti OR "antibacterial agent".ti OR "antibacterials".ti OR "antibiotic".ti OR "antibiotics".ti OR antibiotic*.ti OR "anti-biotic".ti OR "anti-biotics".ti OR anti biotic*.ti) AND (exp *"Primary Health Care"/ OR *"General Practitioner"/ OR *"General Practice"/ OR "Primary Health Care".ti OR "General Practice".ti OR "General Practitioners".ti OR "Family Practice".ti OR "Family Physicians".ti OR "Primary HealthCare".ti OR "Primary Care".ti OR "General Practitioner".ti OR "Family Physician".ti) AND ("prescription behavior".mp OR "prescribing behavior".mp OR "prescription behaviors".mp OR "prescribing behaviors".mp OR "prescription behaviour".mp OR "prescribing behaviour".mp OR "prescription behaviours".mp OR "prescribing behaviours".mp OR "reduced prescription".mp OR "reduced prescribing".mp OR "prescription rates".mp OR "prescription rate".mp)) **OR** (("inappropriate antibiotic".mp OR "inappropriate antibiotics".mp OR ((exp "inappropriate prescribing"/ OR "inappropriate prescribing".mp OR "inappropriate prescription".mp OR "inappropriate prescriptions".mp OR inappropriate prescri*.mp OR "over prescribing".mp OR over prescri*.mp OR "overprescribing".mp OR overprescri*.mp OR "unnecessary prescribing".mp OR "unnecessary prescription".mp OR "unnecessary prescriptions".mp OR "inappropriate".mp OR inappropriat*.mp OR "misprescription".mp OR "misprescriptions".mp OR misprescri*.mp OR "mis prescription".mp OR mis prescription*.mp OR "determinant".mp OR "determinants".mp) AND (exp "Antibiotic Agent"/ OR "anti-bacterial agents".mp OR "anti-bacterial agent".mp OR "antibacterial agents".mp OR "antibacterial agent".mp OR "antibacterials".mp OR "antibiotic".mp OR "antibiotics".mp OR antibiotic*.mp OR "anti-biotic".mp OR "anti-biotics".mp

OR anti biotic*.mp))) AND (exp "Primary Health Care"/ OR "General Practitioner"/ OR "General Practice"/ OR "Primary Health Care".mp OR "General Practice".mp OR "General Practitioners".mp OR "Family Practice".mp OR "Family Physicians".mp OR "Primary HealthCare".mp OR "Primary Care".mp OR "General Practitioner".mp OR "Family Physician".mp))**)**

Web of Science

((ti=("prescribing" OR "prescription" OR "prescriptions" OR prescri*) AND ti=("Antibiotic Agent" OR "anti-bacterial agents" OR "anti-bacterial agent" OR "antibacterial agents" OR "antibacterial agent" OR "antibacterials" OR "antibiotic" OR "antibiotics" OR antibiotic* OR "anti-biotic" OR "anti-biotics" OR "anti biotic*") AND ti=("Primary Health Care" OR "General Practitioner" OR "General Practice" OR "Primary Health Care" OR "General Practice" OR "General Practitioners" OR "Family Practice" OR "Family Physicians" OR "Primary HealthCare" OR "Primary Care" OR "General Practitioner" OR "Family Physician") AND ts=("prescription behavior" OR "prescribing behavior" OR "prescription behaviors" OR "prescribing behaviors" OR "prescription behaviour" OR "prescribing behaviour" OR "prescription behaviours" OR "prescribing behaviours" OR "reduced prescription" OR "reduced prescribing" OR "prescription rates" OR "prescription rate")) **OR** ((ts=("inappropriate antibiotic" OR "inappropriate antibiotics") OR (ts=("inappropriate prescribing" OR "inappropriate prescribing" OR "inappropriate prescription" OR "inappropriate prescriptions" OR inappropriate prescri* OR "over prescribing" OR over prescri* OR "overprescribing" OR overprescri* OR "unnecessary prescribing" OR "unnecessary prescription" OR "unnecessary prescriptions" OR "inappropriate" OR inappropriat* OR "misprescription" OR "misprescriptions" OR misprescri* OR "mis prescription" OR "mis prescription*" OR "determinant" OR "determinants") AND ts=("Antibiotic Agent" OR "anti-bacterial agents" OR "anti-bacterial agent" OR "antibacterial agents" OR "antibacterial agent" OR "antibacterials" OR "antibiotic" OR "antibiotics" OR antibiotic* OR "anti-biotic" OR "anti-biotics" OR "anti biotic*"))) AND ti=("Primary Health Care" OR "General Practitioner" OR "General Practice" OR "Primary Health Care" OR "General Practice" OR "General Practitioners" OR "Family Practice" OR "Family Physicians" OR "Primary HealthCare" OR "Primary Care" OR "General Practitioner" OR "Family Physician")) **OR** ((ts=("inappropriate antibiotic" OR "inappropriate antibiotics") OR (ti=("inappropriate prescribing" OR "inappropriate prescribing" OR "inappropriate prescription" OR "inappropriate prescriptions" OR inappropriate prescri* OR "over prescribing" OR over prescri* OR "overprescribing" OR overprescri* OR "unnecessary prescribing" OR "unnecessary prescription" OR "unnecessary prescriptions" OR "inappropriate" OR inappropriat* OR "misprescription" OR "misprescriptions" OR misprescri* OR "mis prescription" OR "mis prescription*" OR "determinant" OR "determinants") AND ts=("Antibiotic Agent" OR "anti-bacterial agents" OR "anti-bacterial agent" OR "antibacterial agents" OR "antibacterial agent" OR "antibacterials" OR "antibiotic" OR "antibiotics" OR antibiotic* OR "anti-biotic" OR "anti-biotics" OR "anti biotic*"))) AND ts=("Primary Health Care" OR "General Practitioner" OR "General Practice" OR "Primary Health Care" OR "General Practice" OR "General Practitioners" OR "Family Practice" OR "Family Physicians" OR "Primary HealthCare" OR "Primary Care" OR "General Practitioner" OR "Family Physician"))**)**

Cochrane

((("prescribing" OR "prescription" OR "prescriptions" OR prescri*):ti AND ("Antibiotic Agent" OR "anti-bacterial agents" OR "anti-bacterial agent" OR "antibacterial agents" OR "antibacterial agent" OR "antibacterials" OR "antibiotic" OR "antibiotics" OR antibiotic* OR "anti-biotic" OR "anti-biotics" OR "anti biotic*"):ti AND ("Primary Health Care" OR "General Practitioner" OR "General Practice" OR "Primary Health Care" OR "General Practice" OR "General Practitioners" OR "Family Practice" OR "Family Physicians" OR "Primary HealthCare" OR "Primary Care" OR "General Practitioner" OR "Family Physician"):ti AND ("prescription behavior" OR "prescribing behavior" OR "prescription behaviors" OR "prescribing behaviors" OR "prescription behaviour" OR "prescribing behaviour" OR "prescription behaviours" OR "prescribing behaviours" OR "reduced prescription" OR "reduced prescribing" OR "prescription rates" OR "prescription rate"):ti,ab,kw) **OR** ((("inappropriate antibiotic" OR "inappropriate antibiotics") OR (("inappropriate

prescribing" OR "inappropriate prescribing" OR "inappropriate prescription" OR "inappropriate prescriptions" OR inappropriate prescri* OR "over prescribing" OR over prescri* OR "overprescribing" OR overprescri* OR "unnecessary prescribing" OR "unnecessary prescription" OR "unnecessary prescriptions" OR "inappropriate" OR inappropriat* OR "misprescription" OR "misprescriptions" OR misprescri* OR "mis prescription" OR "mis prescription*" OR "determinant" OR "determinants") AND ("Antibiotic Agent" OR "anti-bacterial agents" OR "anti-bacterial agent" OR "antibacterial agents" OR "antibacterial agent" OR "antibacterials" OR "antibiotic" OR "antibiotics" OR antibiotic* OR "anti-biotic" OR "anti-biotics" OR "anti biotic*"))) AND ("Primary Health Care" OR "General Practitioner" OR "General Practice" OR "Primary Health Care" OR "General Practice" OR "General Practitioners" OR "Family Practice" OR "Family Physicians" OR "Primary HealthCare" OR "Primary Care" OR "General Practitioner" OR "Family Physician")):ti,ab,kw**)**

Supplement 3. Prisma Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1,7
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 5,6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 7
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplement 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7,8
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 8
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 7
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	NA
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7, 8
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	NA

Section and Topic	Item #	Checklist item	Location where item is reported
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 7, 8
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 8, 9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 8, 9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 8,9
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 8
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 8
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 10, figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	NA
Study characteristics	17	Cite each included study and present its characteristics.	Supplement 6
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplement 7 and 8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Supplement 6

Section and Topic	Item #	Checklist item	Location where item is reported
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 11
	23b	Discuss any limitations of the evidence included in the review.	Page 14
	23c	Discuss any limitations of the review processes used.	Page 14
	23d	Discuss implications of the results for practice, policy, and future research.	Page 14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 3, 7
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 3, 7
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 18
Competing interests	26	Declare any competing interests of review authors.	Page 18
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supplement 6

Supplement 4. List of developed countries according to the United Nations (20)

- Australia
- Austria
- Belgium
- Britain
- Bulgaria
- Canada
- Croatia
- Cyprus
- Czech Republic
- Denmark
- Estonia
- Finland
- France
- Germany
- Greece
- Hungary
- Iceland
- Ireland
- Italy
- Japan
- Latvia
- Lithuania
- Luxembourg
- Malta
- New Zealand
- Norway
- Poland
- Portugal
- Romania
- Slovakia
- Slovenia
- Spain
- Sweden
- Switzerland
- The Netherlands
- United States

20. United Nations: Country classification 2014 [Available from: https://www.un.org/en/development/desa/policy/wesp/wesp_current/2014wesp_country_classification.pdf accessed May 2019.

Supplement 5. Countries with a health care system where the general practitioner act as a gatekeeper (21)

- Australia
- Canada
- Chile
- Costa Rica
- Denmark
- Estonia
- Finland
- Ireland
- Italy
- Latvia
- Lithuania
- Netherlands
- New Zealand
- Norway
- Poland
- Slovenia
- Spain
- Sweden
- United Kingdom

21. OECD Health System characteristics Survey 2019 [Organisation for Economic Co-operation and Development report]. Available from: http://www.oecd.org/ accessed May 2019.

Supplement 6a: Characteristics included studies

Study authors Publication year	Study design	Geographical location	Research period	Study population	Definition of inappropriate antibiotic prescription	Number of patients/ practices/general practitioners
Akkerman 2005	Prospective cohort study	Netherlands	2003	RTI	Not according to the guidelines	146 GP's/1469 consultations
Akkerman 2005	Prospective cohort study	Netherlands	2003	Acute otitis media	Not according to the guidelines	146 GP's/458 consultations
Biezen 2019	Focus-groups	Australia	2018	GPs	Not according to the guidelines	26 GPs
Cadieux 2007	Retrospective cohort study	Canada	1990-1998	Viral RTI, bacterial RTI and UTI	Antibiotic prescription for a viral infection	104,230 episodes viral infection/ 852 physicians
Damoiseaux 1999	Observational study with semi-structured interviews	Netherlands	1994-1995	Acute otitis media	Not according to the guidelines	22 GP's/362 patients
Dekker 2015	Observational study	Netherlands	2008-2010	RTI	Antibiotic prescription not according to the guidelines	2739 consultations/48 practices
Eggermont 2018	Retrospective cross-sectional	Netherlands	2013	Sore throat symptoms (ICPC R21, R22, R72, R74, R76, R77)	Not indicated by the international guidelines	11,285 consultations/ 25 GP's
Fernandez-Alvarez 2019	Questionnaire	Spain	2010	GPS	Not according to indicators	2100 GPs
Fletcher-Lartey 2016	Cross-sectional survey and semi-structured survey	Australia	2014	GP's	Not indicated	584 GP's filled in survey (response rate 23.7%), 32 GP's interviewed
Malo 2016	Retrospective cross-sectional	Spain	2011	acute bronchitis (ICPC code R78)	Not according to the guidelines	36955 episodes of acute bronchitis

Study authors Publication year	Study design	Geographical location	Research period	Study population	Definition of inappropriate antibiotic prescription	Number of patients/ practices/general practitioners
Nowakowska 2019	Observational study	United Kingdom	2010-2014	sinusitis	Not according to the guidelines	1,151,105 antibiotic prescriptions
				otitis externa		
				otitis media		
				upper respiratory tract infection (URTI) (including unspecified URTI, tracheitis, laryngitis, sore throat and tonsillitis)		
				lower respiratory tract infection (LRTI) (including bronchitis, unspecified chest infection and unspecified LRTI)		
				urinary tract infection (UTI)		
O'Doherty 2019	Explorative qualitive design	Ireland		Acute RTI	Antibiotic prescription for acute RTI	13 GP's
Pouwels 2018	Retrospective cohort	United Kingdom	2013-2015	Acute cough	Not indicated by the guidelines and above the range of a quality indicator	3.7 mil patients, 2,046,095 consultations
				Acute bronchitis		
				Asthma exacerbations		
				COPD exacerbations		
				Acute sore throat		
				Acute rhinosinusitis		
				AOM		
				Upper RTI		
				Lower RTI		
				Influenza-like illness		
				UTI		
				Impetigo		
				Acne		
				Gastroenteritis.		

Study authors Publication year	Study design	Geographical location	Research period	Study population	Definition of inappropriate antibiotic prescription	Number of patients/ practices/general practitioners
Silverman 2017	Retrospective database cohort	Canada	2012	Patients > 65 years with nonbacterial acute upper RTI.	Antibiotic prescription for a non-bacterial acute upper RTI	185,014 patients and visits/ 8990 primary care physicians
				Acute nasopharyngitis (common cold)		
				Acute bronchitis		
				Acute sinusitis		
				Acute laryngitis/tracheitis		
Singer 2018	Retrospective cohort	Canada		Acute mild-to-moderate sinusitis (ICD-9 461)	Antibiotic prescription for a viral infection as indicated in the disease group	16,742 patients (15,6%)/ 239 GP's
				Upper respiratory tract infection (ICD-9 465)		
				Bronchitis (ICD-9 466)		
				Acute rhinitis (ICD-9 460)		
				Acute laryngitis and tracheitis (ICD-9 464)		
				Nasopharyngitis (ICD-9 477)		
				Influenza (ICD-9 487/488)		
Singer 2018	Retrospective cohort	Canada	1999-2016	All antibiotic prescriptions	Not according to the guidelines	32 clinics/196,923 patients

Study authors Publication year	Study design	Geographical location	Research period	Study population	Definition of inappropriate antibiotic prescription	Number of patients/ practices/general practitioners
van Esch 2018	Retrospective cohort	Netherlands	2016	Acute cough ICPC codes, 31% of the patients; Acute cough (R05) Whooping cough (R71) Laryngitis/tracheitis (R77) Acute bronchitis/bronchiolitis (R78) Acute rhinosinusitis ICPC codes, 34% of the patients Sinus symptom/complaint (R09) Upper respiratory infection acute (R74) Acute/ chronic sinusitis (R75) Urinary tract infection ICPC codes, 36% of the patients. Dysuria/painful urination (U01) Urinary frequency/urgency, (U02) Cystitis/urinary tract infection (U71)	Antibiotic prescription not indicated by the guideline.	8192 adults (15 practices)

GPs: General Practitioner
ICPC: International Classification Primary Care
ICPC R21: Throat symptoms
ICPC R22: Tonsils symptoms
ICPC R72: Strep throat
ICPC R74: Acute Upper Respiratory Infection
ICPC R76: Acute tonsillitis
ICPC R77: Laryngitis/tracheitis
RTI: Respiratory Tract Infection
UTI: Urinary Tract Infection

Supplement 6b: Determinants and their domains from included studies

Study authors Publication year	Determinants of inappropriate antibiotic prescription		
	Negative impact	**No impact**	**Positive impact**
Akkerman 2005	More signs of inflammation (fever etc)	Patient age	
	GP's judgement of more severe illness		
	GP's perception of high patient expectation for antibiotic		
Akkerman 2005	Age of patient younger than 24 months		
	GP's judgement of more severe illness		
	GP's perception of high patient expectation for antibiotic		
Biezen 2019	Patients expect an antibiotic due to past experience and have high expectations of antibiotics		Imbedding guidelines in an EMR
	No access to guidelines due to high cost		
	Access to guidelines during consult is time-consuming		
Cadieux 2007	Medical education outside Canada or United States		
	More years in practice		
	Higher practice volume		
Damoiseaux 1999	Severity of illness at first contact		
	Co-morbidity		
	Young age (less than 2 years)		
	Belongs to risk group		
	Disease behaviour of the patient		
	Request by patient		
	GP's perception of high patient expectation for antibiotic		
	Many other non-medical problems presented		
	Impact of disease on patient		
	Habit		
	To ease the patient		
	Negative events in the past		
	Feeling how one should perform		

Framework					
Culture of healthcare consumption	**Patient factors and experiences**	**Culture of professional medicine**	**Clinician attitudes and beliefs**	**Practice environment**	**The patient-clinician interaction**
	More signs of inflammation (fever etc)		GP's judgement of more severe illness		GP's perception of high patient expectation for antibiotic
	Age of patient younger than 24 months		GP's judgement of more severe illness		GP's perception of high patient expectation for antibiotic
		No access to guidelines due to high cost			Patients expect an antibiotic due to past experience and have high expectations of antibiotics
		Access to guidelines during consult is time-consuming			
		Medical education outside Canada or United States		More years in practice	
				Higher practice volume	
	Severity of illness at first contact	Feeling how one should perform	Habit		Disease behaviour of the patient
			To ease the patient		Request by patient
	Co-morbidity		Negative events in the past		GP's perception of high patient expectation for antibiotic
	Young age (less than 2 years)				
	Belongs to risk group				
	Many other non-medical problems presented				
	Impact of disease on patient				

Study authors Publication year	Determinants of inappropriate antibiotic prescription		
	Negative impact	**No impact**	**Positive impact**
Dekker 2015	GP's perception of high patient expectation for antibiotic	Reduced general health	
	Presence of fever		
	GP's judgement of more severe illness		
	Age > 18 years		
	Duration of symptoms ≥ 7 days		
	Presence of comorbidity		
	Female gender		
Eggermont 2018	Comorbidity OR 1.21 (95% CI:1.01-1.32)	Concordance OR 0.92 (95% CI: 0.82-1.02)	
		Gender GP OR 0.83 (95% CI: 0.58-1.08)	
		Gender patient OR 0.96 (95% CI: 0.85-1.06)	
		Age patient OR 1.00 (95% CI: 0.99-1.00)	
Fernandez-Alvarez 2019	Documentation of Pharmaceutical Industry OR 2.09 (95% CI: 1.70–2.87)	Pharmaceutical Industry Training 1.45 OR (95% CI: 0.93–1.15)	Clinical Practice Guidelines OR 1.25 (95% CI: 1.02–1.54)
	Medical Representatives OR 2.50 (95% CI: 1.63–3.66)	Previous clinical experience OR 1.27 (95% CI: 0.77–2.12)	
		Other specialists OR 1.03 (95% CI: 0.93–1.23)	

Framework					
Culture of healthcare consumption	**Patient factors and experiences**	**Culture of professional medicine**	**Clinician attitudes and beliefs**	**Practice environment**	**The patient-clinician interaction**
	Presence of fever		GP's judgement of more severe illness		GP's perception of high patient expectation for antibiotic
	Age >18 years				
	Duration of symptoms ≥7 days				
	Presence of comorbidity				
	Comorbidity				
		Documentation of Pharmaceutical Industry			
		Medical Representatives			

Study authors Publication year	Determinants of inappropriate antibiotic prescription		
	Negative impact	**No impact**	**Positive impact**
Fletcher-Lartey 2016	Patients expect an antibiotic prescription	Age of GP	
	Time pressure	Years worked as a GP	
	Diagnostic uncertainty	Gender	
	Medical liability	Location of practice and socioeconomic profile of practice population	
	Primary care considered not responsible for development of antibiotic resistance		
	Preserving GP–patient relationships		
	Protecting business		
	Inability to effectively negotiate or explain antibiotic use		
	Empathy for patients and risk perception about the seriousness of the illness		
Malo 2016	Increasing age		Female patient
	Co-morbidity		
	Ongoing use of corticosteroids		
Nowakowska 2019	Comorbidity	Socioeconomic deprivation	
	Received antibiotics in previous year		
O'Doherty 2019	Guideline is non-comprehensive and does not clearly outline for a multitude of factors and the best course of action for all conditions the GP's face during their consultations		
	Paying private patient versus patient with free access healthcare		
	Patients expect an antibiotic due to past experience and have high expectations of antibiotics		
	Limited time for an consultation		
Pouwels 2018	Comorbidity	Weekday of consultation	

Framework					
Culture of healthcare consumption	**Patient factors and experiences**	**Culture of professional medicine**	**Clinician attitudes and beliefs**	**Practice environment**	**The patient-clinician interaction**
Patients expect an antibiotic prescription		Medical liability	Diagnostic uncertainty	Time pressure	Preserving GP–patient relationships
			Primary care considered not responsible for development of antibiotic resistance		Protecting business,
			Inability to effectively negotiate or explain antibiotic use		Empathy for patients and risk perception about the seriousness of the illness
	Co-morbidity				
	increasing age				
	ongoing use of corticosteroids				
	Comorbidity				
	Received antibiotics in previous year				
A paying private patient versus patient with free access healthcare		Guideline is non-comprehensive and does not clearly outline for a multitude of factors such as cough, sinus pain and the best course of action for all conditions the GP's face during their consultations		Limited time for an consultation	Patients expect an antibiotic due to past experience and have high expectations of antibiotics
	Comorbidity				

Study authors Publication year	Determinants of inappropriate antibiotic prescription		
	Negative impact	**No impact**	**Positive impact**
Silverman 2017	Received antibiotics in previous year	Payment model (fee for service, capitation)	Female physician
	11-24 year career versus < 11 year career		Hospital affiliation (Canada)
	>25 year career versus < 11 year career		
	Medical education outside Canada or United States		
	Workload > 150 days/year		
	25-44 patients/day versus < 25 patients/day		
	> 45 patients/day versus < 25 patients/day		
Singer 2018	Female versus male patient OR 1.22 (95% CI: 1.15-1.30)	Practice location (urban versus Rural)	
	Age patient < 60 year versus > 60 year OR 1.19 (95% CI: 1.02–1.38)	Practice size (< 1055 patients versus > 1055 patients)	
	Comorbidity 3 or more versus 0 OR 2.02 (95% CI:1.90–2.14)	Provider age (= 43 year versus > 43 year)	
	Comorbidity 1 or 2 versus 0 OR 1.34 (95% CI: 1.28–1.39)	Provider sex (male versus Female)	
	Fee for service provider versus salaried provider OR 4.35 95% CI: (3.31–5.72)	No. Of encounters per week (< 53 versus ≥ 53)	
	Frequency of office visits (per 2 visit increase to the same primary care provider) OR 1.48 (95% CI: 1.30-1.69)		
Singer 2018	Patient age (per 10 year increase) OR 1.13 (95% CI: 1.03-1.24)	Female patients	
	Number of comorbid conditions OR 1.11 (95% CI: 1.07-1.17)	Country of graduation (other than Canada)	
	Office visit frequency 1.12 (95% CI: 1.08-1.22)	Higher prescriber age (per 10 years increase)	
	Rural practice location OR 1.47 (95% CI: 1.17-1.84)		
	Larger practice size OR 2.26 (95% CI: 1.76-3.16)		
Van Esch 2018		Shared decision making	

CI: Confidence interval
EMR: Electronic Medical Record
OR: Odds ratio

Framework					
Culture of healthcare consumption	**Patient factors and experiences**	**Culture of professional medicine**	**Clinician attitudes and beliefs**	**Practice environment**	**The patient-clinician interaction**
	Received antibiotics in previous year		11-24 year career versus < 11 year career	Workload > 150 days/year	
			>25 year career versus < 11 year career	25-44 patients/ day versus < 25 patients/day	
			Medical education outside Canada or United States	> 45 patients/ day versus < 25 patients/day	
Fee for service provider versus salaried provider	Female				Frequency of office visits (per 2 visit increase to the same primary care provider)
	Age patient < 60				
	Comorbidity 3 or more versus 0				
	Female patients			Rural practice location	
	Number of comorbid conditions			Larger practice size	
	Office visit frequency				

Supplement 7. Quality assessment of cross-sectional studies

Study	Akkerman 2005a	Akkerman 2005b	Cadieux 2007	Dekker 2015	Eggermont 2018	van Esch 2018	Malo 2016	Nowakowska 2019	Pouwels 2018	Silverman 2017	Singer 2018	Singer 2018
1.Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Ye	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the participation rate of eligible persons at least 50%?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5. Was a sample size justification, power description, or variance and effect estimates provided?	No	No	No	No	No	No	No	No	No	No	No	No
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	NA	NA	NA	NA	NA	NA	NA	Yes	NA	NA	NA	NA
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Study	Akkerman 2005a	Akkerman 2005b	Cadieux 2007	Dekker 2015	Eggermont 2018	van Esch 2018	Malo 2016	Nowakowska 2019	Pouwels 2018	Silverman 2017	Singer 2018	Singer 2018
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
10. Was the exposure(s) assessed more than once over time?	No	No	No	No	No	No	No	No	No	No	No	No
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Were the outcome assessors blinded to the exposure status of participants?	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
13. Was loss to follow-up after baseline 20% or less?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Conclusion	LB	LB	LB	LB	LB	LB	LB	LB	LB	LB	LB	LB

LB: Low risk of bias
NA: Not applicable
NS: Not stated

Supplement 8. Quality assessment of qualitative studies

Study	Biezen 2019	Damoiseaux 1999	Fletcher-Laherty 2016	O'Doherty 2018
Was there a clear statement of the aims of the research?	Yes	Yes	Yes	Yes
Is a qualitative methodology appropriate?	Yes	Yes	Yes	Yes
Was the research design appropriate to address the aims of the research?	Yes	Yes	Yes	Yes
Was the recruitment strategy appropriate to the aims of the research?	Yes	Yes	Yes	Yes
Was the data collected in a way that addressed the research issue?	Yes	Yes	Yes	Yes
Has the relationship between researcher and participants been adequately considered?	Yes	Yes	Yes	Yes
Have ethical issues been taken into consideration?	Not applicable	Not applicable	Not applicable	Not applicable
Was the data analysis sufficiently rigorous?	Yes	Yes	Yes	Yes
Is there a clear statement of findings?	Yes	Yes	Yes	Yes