Social, Cultural and Personal Determinants of Antibiotic Prescribing for Upper Respiratory Tract Infections in West European Primary Care: A Systematic Review and In-Depth Interview Study

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Abstract

Background. Antibiotics are vital for healthcare, however, rising antibiotic resistance is posing a serious threat. This can be partly attributed to inappropriate prescribing. A significant portion of antibiotics are prescribed in primary care, particularly for upper respiratory tract infections (URTIs). This means that URTIs are prone to Potentially Inappropriate Prescribing (PIP). Therefore, this study explores the determinants that play a role in the decision-making process among general practitioners (GPs) and patients regarding antibiotic prescribing for URTIs in Western Europe.

Methodology. A literature review was performed to identify determinants that play a role in the decision-making processes among GPs and patients regarding antibiotic prescribing for upper respiratory infections. The text of each included paper was firstly literally extracted. All results were then analysed again to extract a meaning beyond their literal sense to enable a more nuanced comparison of the results. To gain further insight, qualitative research has been conducted in the form of in-depth interviews. Interviews were conducted with three patients and two GPs from the Netherlands. During the interviews all questions were asked in the context of URTIs. Questions were asked about their experiences with antibiotics, their thoughts on antibiotics, and in the case of GPs, also about their approach to prescribing antibiotics. Data was analysed using Atlas.ti to identify possible other determinants.

Results. An electronic search performed in March 2023, using databases PubMed and Scopus, resulted in 200 studies. After screenings, 13 studies met the inclusion criteria and were included in the review. Three determinants were found in the literature and confirmed by the in-depth interviews (IDIs): 'Expectations', 'view on recovery', 'Relationship between patient and GP'. The determinants 'Patient characteristics (age)', 'guideline non-adherence', 'time pressure', Quick availability of diagnostic tests' and 'patient education' were also found to play a role in the decision-making process of the GPs in either the literature or the IDIs. The determinants found in the literature and the IDIs did not always align, indicating a potential gap in the literature.

Conclusion. This study identified determinants that play a role the decision-making process in antibiotic prescribing in primary care. By identifying these determinants, recommendations can be made about further research, exploration of other infections such as urinary tract infections and policy changes. They underscore the importance of considering social, cultural, and personal factors when it comes to writing interventions for antibiotic prescribing in URTIs. However, a recurring problem is time constraint, which is a difficult to solve in the current health climate and may decrease the effectiveness of potential solutions.

Table of content

Introduction

Infectious diseases have affected humanity since ancient times [1]. Due to the discovery of antibiotics in the 20th century, bacterial infections were since then, in most cases, no longer deadly. The effect of the discovery of antibiotics was tremendous: Before the commercialisation of antibiotics, infectious diseases caused around 25% of the mortality in the United Kingdom (UK). After commercialisation, this number shrunk to less than 1% [2]. Antibiotics are a type of medication that manage bacterial infections in humans by targeting the bacteria. This is unlike most other medical treatments that target the patient itself. Since the discovery of the first kind of antibiotic penicillin, many more kinds of antibiotics have been discovered.

The 1940s to the 1960s are called the golden era of antibiotic research. However, since then, there has been a steep decline in the discovery of new antibiotics [3]. Consequently, the available antibiotics have been used often, leading to resistance in many bacteria. This is called antibiotic resistance and belongs under the umbrella term antimicrobial resistance (AMR). The resistance to antibiotics by bacteria is caused by changes within the bacterium in response to the interaction with the antibiotics. These changes cause the bacterium to be able to resist the effects of the antibiotic, which leads to antibiotic resistance [4]. Microorganisms such as bacteria are easily transferred between individuals, which means that resistant bacteria are also easily transferred between individuals. As a consequence, the number of individuals who are infected with resistant bacteria and can therefore not be treated with antibiotics is rising rapidly [1].

The danger of antibiotic resistance

Antibiotic resistance is very dangerous for humankind because it can negatively influence the health of an individual significantly, both directly and indirectly [5]. A direct consequence of antibiotic resistance is that it becomes increasingly difficult to treat bacterial infections, leading to more extended hospital stays, higher healthcare costs, disabilities, and death. Antibiotic resistance also indirectly influences health by influencing the success of medical treatments. Certain treatments require immunosuppression, such as chemotherapy. As a result of antibiotic resistance, these treatments will be less successful, which can significantly decrease someone's health status or even lead to death [6]. The increase of antibiotic resistance in multiple bacteria has developed into a global crisis. Currently, most bacterial infections can still be treated using the available antibiotics or a mixture of them. However, the number of clinical cases where treatment fails due to resistance is increasing. In recent years, there have been no significant discoveries in antibiotics. This means that when the current antibiotics on the market cannot treat bacterial infections anymore, there are no alternative treatments available, and people will die of diseases that used to be treatable [7].

It can be stated that antibiotic resistance affects the public health significantly. The European Centre for Disease Prevention and Control (ECDC) is a European agency that works closely together with the European Commission and the national governments of European Union (EU) member states. It studies and provides support on public health issues, such as transmittable diseases. In November 2022, a report was published with updated estimates about the effects of antibiotic resistance within the EU and what has changed compared to previous estimates. In the EU in 2016-2020, the estimated number of infections and attributable deaths due to antibiotic-resistant bacteria increased significantly. In 2020 a slight decrease was seen, which can be attributed to measures taken in light of the COVID-19 pandemic. However, estimates for the years after 2020 show that the burden due to antibiotic resistance will continue to increase [8]. Within the EU, there are agreements on managing different medications, such as antibiotics. Even though it seems inevitable to view antibiotic resistance as an unavoidable side effect of prescribing antibiotics, inappropriate use of antibiotics is a significant

contributor to the emergence of resistance. Once a strain of bacteria has developed resistance, it cannot be reversed. Therefore, in order to tackle the problem of antibiotic resistance worldwide, it is vital to prevent inappropriate antibiotic prescribing [9].

Primary care

Most antibiotics are prescribed in primary care. It is estimated that in the Netherlands, 80% of antibiotics are prescribed by the general practitioner (GP); most often, these antibiotics are prescribed to treat respiratory or urinary tract infections [10]. Many studies have shown that antibiotics are often prescribed even though guidelines do not state that antibiotics should be prescribed [11]. Inappropriate antibiotic prescribing by the GP is relatively common in upper respiratory tract infections (URTIs) [12].

Upper respiratory tract infections

URTIs are infections that can be caused by various viruses and bacteria. Infections of the upper respiratory tract affect the major airways, the larynx, the pharynx, the sinuses and the nose. These infections can cause different illnesses, such as sinusitis, pharyngitis, epiglottitis and tracheobronchitis. Whatever the cause of the infection, symptoms of a URTI are often similar. Because of this similarity, it is challenging for a GP to define the cause of the infection. URTIs are known to be self-limiting [13]. Self-limiting is a term used to describe an illness that patients will recover from without seeking treatment [14]. This means that prescribing antibiotics is often inappropriate. Secondly, as stated before, not only bacteria but also viruses can cause URTIs. It is difficult for a GP to determine which of the two causes the infection. As antibiotics cannot treat viral infections, prescribing antibiotics if a virus causes the URTI is always inappropriate. In the case of a URTI in the Netherlands, in 40% of the cases, antibiotics were prescribed even though there was no indication of prescribing antibiotics based on the guidelines. In other words, URTIs are prone to Potentially Inappropriate Prescribing (PIP) of antibiotics [15]. There are several reasons why prescribing an antibiotic can be inappropriate. The three most common causes of inappropriate antibiotic prescribing are prescribing antibiotics when it is not necessary or when it is only slightly beneficial, choosing a suboptimal antibiotic, and lastly, not or delayed prescribing of antibiotics when they should be prescribed [11]. Some studies have been conducted on determinants in prescribing antibiotics among GPs, but these often take a broad perspective and do not specifically focus on a particular infection or condition. Therefore, this thesis is a valuable addition to the available information because it specifically examines a group of infections where PIP occurs [16]. Western Europe is an interesting area for antibiotic prescribing behaviour because all countries have very similar protocols on when antibiotics should be prescribed. When comparing the primary healthcare values of these different countries, they are quite similar [17].

A lot is still unknown as to why PIP occurs. Therefore, this study explores the determinants that play a role in the decision-making processes among GPs and patients regarding antibiotic prescribing for URTIs. Therefore, this thesis aims to answer the research question: Which determinants play a role in the decision-making processes in primary care regarding antibiotic prescribing for upper respiratory tract infections in West European countries?

Methods

A systematic review and in-depth interviews were conducted to gain insight into the determinants that play a role in the decision-making processes among GPs and patients regarding antibiotic prescribing for URTIs.

Systematic Review

The systematic review was focused on identifying determinants in the West European countries Belgium, Germany, Ireland, the Netherlands and the UK in healthcare decision-making processes among GPs and patients regarding antibiotic prescribing for URTIs.

Eligibility criteria

This review was restricted by multiple inclusion criteria to ensure a homogenous sample of studies. These inclusion criteria were:

1. The study was conducted in Western Europe. In this systematic review, the definition of Western Europe is restricted to Belgium, France, Germany, Ireland, Luxembourg, the Netherlands, and the UK. In this thesis, a country is deemed Western European if it is recognised as such by the united nations (UN) and is also a member of the EU. The UK is not a part of the EU, yet it was so during a large part of the studied period (2016 or later) and was therefore also included.
2. The study focused on infections that fell under the umbrella term URTI, such as sinusitis, pharyngitis, epiglottitis, laryngitis.
3. The study focused on antibiotic prescribing. Meaning that the paper was excluded if the paper's primary focus was on the biological component of antibiotics.
4. The study focused on primary care.
5. The study was published in the English language.
6. The study used primary data.
7. The study was published in 2016 or later, since guidelines were revised in 2016.

To the best of the author's knowledge, no other reviews have been published on antibiotic prescription by GPs for URTIs in the Western European context.

Information sources and search strategy

The first step of the search strategy was to determine the keywords used to collect the papers for the systematic review. This literature search was performed in March 2023. For this review, five groups of keywords were used, namely 'Countries', 'Upper respiratory tract infection', 'Antibiotics', 'Primary care', and 'prescribing'. The complete search strategy can be viewed in Table 1.

Group	Keywords
Countries	German* OR Dutch OR Netherlands OR Holland OR “West*-Europe*” OR Ireland OR Irish OR “United Kingdom” OR UK OR England OR English OR Scotland* OR Scottish OR Wales OR Belgium OR Fleming OR Flanders OR Belgian OR Luxembourg OR Luxembourgish OR Luxembourgian OR France OR French OR Benelux
Upper respiratory tract infection	“urti” OR "Upper respiratory tract infection" OR "sinus infection" OR sinusitis OR pharyngitis OR epiglottitis OR laryngitis OR laryngotracheitis OR tonsillitis OR "upper respiratory infection" OR "URI" OR "respiratory tract illness"
Antibiotics	“abx” OR antibiotic* OR antimicrobial* OR “amr” OR “ABR”
Primary care	"primary care" OR GP OR "General practi*" OR "clinical practice*" OR g.p. OR "family practi*" OR "primary health care" OR "family doctor*" OR "family physician*" OR “primary patient care”
Prescribing	Underprescri* OR overprescri* OR over-prescri* OR prescri* OR treat* OR therap* OR use OR administ* OR dispens*

Table 1. The search strategy used in the systematic review.

Study selection and data collection process

These keywords were then run through the databases PubMed and Scopus using title, abstract, and keywords. These databases were chosen because PubMed has its primary focus on (bio)medical papers, which is similar to the focus of this systematic review. Scopus is a much broader database that covers most scientific fields and would therefore provide a broader spectrum of papers that could be beneficial to this review. All papers collected through the search of these two databases were run through the software program Covidence, and all duplicates were automatically removed. Using Covidence, all papers were screened based on the title and abstract by the writer of this thesis. A second reviewer screened 20% of the papers based on the title and abstract on the eligibility criteria to determine if the overlap between the two reviewers was significant. After this, the remaining papers were reviewed fully by the first reviewer. If there was no agreement between the two reviewers on whether the paper should be included, a third reviewer was included, and disagreements were resolved through discussion. The reviewer’s agreement was evaluated using Cohen’s Kappa. A higher value indicates a stronger agreement between the reviewers. Generally, a Cohen’s Kappa between 0.61 and 0.80 is considered as substantial agreement [18], [19]. The goal for agreement in this study was a Cohen’s Kappa of 0.70 or higher. The Cohen’s Kappa of this review was calculated to be 0.80. Of all the papers that were included in the systematic review data was extracted using Microsoft Excel.

Data extraction

The data extraction was conducted in two phases. In the initial step, the entire content of each paper was systematically reviewed, including the results and discussion sections. With this method, it was attempted to report a comprehensive overview. The literal text from the papers was extracted, with a focus on important components including the participant characteristics, research design and outcomes. The aim of using literal text was to show the data objectively without imposing any outside perspective. The data from the first phase was recorded in an Excel spreadsheet. The data was extracted for different categories, and the spreadsheet’s columns were grouped accordingly. There were three main categories, with each multiple sub-categories, of which a few examples will be provided. The first category was ‘general information about the paper’ with sub-categories such as

'Title', 'Publication year' and 'Location'. The second category was 'Information about the study' with sub-categories such as 'study design', 'Sex' and 'Age'. The third category was 'Outcomes' with sub-categories such as 'Determinants' and 'Limitations'. The entire table can be found in Appendix A. This Excel file served as the basis for the next step of the analysis.

A second round of analysis was conducted for the purpose of synthesizing the findings. At this point, the retrieved data was analysed to extract meaning from the text beyond its literal sense, this enabled a more nuanced comparison of the results of the papers [19]. This way, it was possible to find trends, contradictions, and underlying themes. This was a required step to compare the findings of the different papers included in the systematic review.

Data items

On the 7th of April 2023, the electronic search resulted in 200 studies. 56 studies were retrieved from PubMed, and 144 studies were retrieved from Scopus. After removing the duplicates, 151 studies remained for the title and abstract screening. After the first screening, 45 studies were eligible for screening the full text. 32 studies did not meet the inclusion criteria for the following reasons: wrong intervention (18), wrong study design (6), wrong comparator (5), and wrong setting (3). Therefore, 13 studies met the inclusion criteria and were included in this review. A flowchart of the data selection process is visualised in Figure 1.

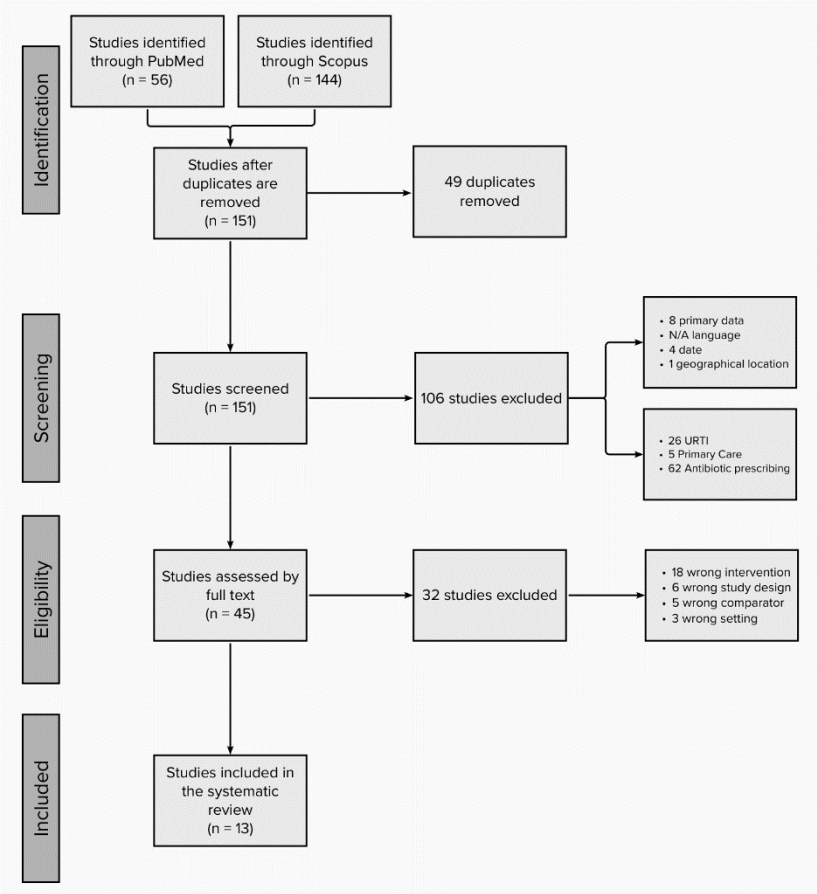

Figure 1. Flowchart of the systematic review.

Interview

Ethics

Ethical approval for the study was granted by the BMS Ethical Committee / Domain Humanities & Social Sciences (request number: 230885) on the 1st of June 2023.

Participants & Recruitment

For the IDIs, three female patients and two male GPs were interviewed. Convenient sampling was used for the recruitment of participants for the IDIs. Patient recruitment was carried out through verbal communication, participants were approached directly personally and provided with information about the study. The GPs were recruited through verbal communication and email communication. The inclusion criteria for patients consisted of:

1. Being an adult (18+ years old).
2. Having received a prescription for antibiotics within the last 12 months for a URTI.

For GPs, the inclusion criteria were:

1. Practising as a GP in the Netherlands.
2. Having prescribed antibiotics for a URTI within the past 12 months.

Informed consent

Prior to each interview's initiation, all participants were required to provide written consent indicating their willingness to take part in the study (Appendix B). Informed consent forms were presented in Dutch to ensure comprehension. All participants were informed that their participation in the interviews was entirely voluntary, and they had the option to withdraw at any time without providing a reason. Participants did not receive compensation for their involvement in the study. Participation was entirely voluntary, and individuals were not incentivized with monetary rewards.

Materials & Procedure

Individuals were asked if they would like to participate in interviews for the thesis. They were provided with an information letter via email or in person to explain the study's purpose and expectations. If participants agreed to join, a suitable interview date was scheduled. They were given the option to conduct the interview either in person or online. All participants opted for in-person interviews. Before commencing each interview, a clear explanation was provided regarding the interview's goals and the measures in place to safeguard their privacy.

All patients were interviewed at their own homes. Of the GPs, one GP was interviewed at their home and one in the practice. Before the start of each interview, participants were asked to provide written consent, confirming their willingness to participate in the study. One researcher conducted all interviews. The patient interview covered the following topics: personal background, knowledge of antibiotics, adherence to treatment, treatment preferences, expectations and doubts of antibiotics and factors influencing antibiotic choice. An overview of the specific questions can be found in appendix C. The GP interview covered the following topics; GP background and experience, timing of antibiotic prescriptions, factors influencing antibiotics prescribing, patient-induced pressure to prescribe antibiotics, perceived pros and cons and their impact on prescribing, influence of the trust bonds with patients and prescribing, variations in prescribing behaviour among GPs, perceptions of responsibility for antibiotic stewardship and the impact of patient medical knowledge on GP prescribing decisions. An overview of the specific questions can be found in appendix D. All interviews were audio recorded, and records will be retained in a secure p-drive owned by the University of

Twente, until the end of the bigger project “What to do with the flu” (CHARE-GD-II). The transcripts of the interviews will be stored for 10 years in the P-drive and recordings will be destroyed.

Data-analysis

First, all interviews were transcribed verbatim. For the data analysis, ATLAS.ti software was employed. The analysis process involved coding all the interviews. Initially, specific codes were assigned to all responses. In the subsequent step, patient and GP interviews were processed separately. All patient interviews and codes were visualised, and an effort was made to associate as many of these codes with those previously identified in the systematic review. New codes were generated for novel determinants. Ultimately, these codes for all interviews were consolidated. A similar approach was applied in the case of GPs. Their data went through a parallel process of coding and categorisation.

The analysis of both patient and GP data was conducted visually, allowing for a comprehensive understanding of the patterns and insights that emerged from the coded responses.

Results

Systematic Review

The 13 included studies (see Table 2) were performed in the UK (6), the Netherlands (2), Ireland (1), Germany (2), Belgium (1), and one study that used data from the UK and Germany. Most focused on all patient age-groups, three focused on all ages except babies and young children, one focused on adults and three focused only on children. On average, the papers found two determinants, adding up to a total of five different determinants. These are described below. In Table 2, the variable ‘N’ is used to indicate the sample size for each of the included studies. The interpretation of ‘N’ can differ based on the research setting; all variations of ‘N’ are listed in one row despite these variations to preserve a clear overview. The same goes for ‘Ratio male/female’, some studies include one or multiple ratios, but not all of them so there is also some variation in this row.

Author	Country	Design & Setting	N	Ratio male/ female	Age	Determinants
Borek A.J., et al.	UK	Mixed-methods study	19 GPs	12/7	All ages	Relationship between patient and GP, Expectations
Colliers A., et al.	Belgium	Retrospective cohort study	111.600 visits	N/A	All ages	Relationship between patient and GP, Guideline non-adherence
Debets V.E.C., et al.	The Netherlands	Retrospective cohort study	4.825.980 prescriptions	N/A	All ages	Patient characteristics
Eggermont D., et al.	The Netherlands	Retrospect study	22.412 visits	Patients: N/A GPs: 5.956/5.329	Mean: 46	Patient characteristics, View on recovery

Table 2. Initial overview of the studies found in the systematic review (continues on the next page).

Gunnarsson R., et al.	Germany, UK	Retrospect study	680 surveys	N/A	All ages	Guideline non-adherence
Hueber S., et al.	Germany	Retrospect study	3.324 primary care practices	N/A	>15	Expectations
Kern W.V., et al.	Germany	Case-control study	7.250 participants	N/A	≤ 6	Patient characteristics, Expectations
Maguire F., et al.	Ireland	Cross-sectional study	1.007 patients	N/A	<6	Relationship between patient and GP, Expectations
Nowakowska M., et al.	UK	Retrospect study	1.151.105 antibiotic prescriptions	N/A	>3	Patient characteristics, View on recovery
Pouwels K.B., et al.	UK	Retrospect study	128.566 consultations	Only female	>14	View on recovery
Smieszek T., et al.	UK	Retrospect study	845.282 consultations	N/A	All ages	View on recovery
Smith D.R.M., et al.	UK	Retrospect study	4.570.000 consultations	1.645.200/2.924.800	All ages	Patient characteristics, View on recovery
Williams M.R., et al.	UK	Retrospect study	3.304 patients	1.673/1.631	< 5 Mean: 3	Patient characteristics

Table 2. Initial overview of the studies found in the systematic review (continued).

Expectations

In the systematic review, four papers have found expectations to be a determinant in antibiotic prescribing. These studies were conducted in the Germany, Ireland and the UK. All papers state that the GP can feel pressured by the patient to prescribe antibiotics [20]–[23]. One paper suggested that GPs can be divided into two categories namely, high prescribers and low prescribers. As the name suggests, high prescribers are GPs who prescribe more antibiotics than their low-prescriber colleagues. A reason for this could be that these high-prescribing GPs often work in large practices and see a lot of patients, so they might have a higher workload. The study showed that these high-prescribing GPs are more likely to identify URTI symptoms as being bacterial and therefore are more willing to prescribe antibiotics to treat the symptoms. In the paper, they also suggest that the fact that these GPs are seen as high prescribers might work as a self-fulfilling prophecy. Patients might come to these GPs specifically because they expect them to prescribe antibiotics, consequently pressuring the GP into prescribing antibiotics. Alternatively, the GP might assume that the patient seeks help from them specifically because of their reputation. Therefore, presuming that the patient wants antibiotics and therefore prescribes antibiotics [21].

Of the four papers, one of the papers found that 11% of the patients seeking help for a URTI expect that they will receive antibiotics [22]. As stated before all four papers showed that this expectation

might pressure the GP into prescribing antibiotics [20]–[23]. However, in two papers it was found that this pressure by the patient might be interpreted incorrectly. Most of the patients who go into the consultation with the expectation that they will receive antibiotics stated that if the GP were not in favour of prescribing antibiotics, they would trust their GP and accept that they will not receive antibiotics. Apart from expectations that might be misinterpreted by the GP, the two papers suggest that antibiotic information-seeking might be interpreted by the GP as pressuring, while this is not the intent of the patient [22], [23]. One paper looked at children especially and they found that GPs often mistakenly interpret parental concern as a pressure into prescribing antibiotics [23].

Patient Characteristics

Six of the articles included mention certain determinants concerning the characteristics of a patient having an impact on antibiotics prescribing, namely age and gender. These studies are conducted in Germany, the Netherlands and the UK [12], [22], [24]–[27].

Four papers have investigated patients' age regarding antibiotic prescribing [12], [22], [24], [27]. Two of them focused on age differences among adults. Both found a positive correlation between age and the chance of receiving an antibiotic prescription for a URTI. This correlation is very weak for young adults; however, the correlation becomes stronger in older adults [12], [22]. The other two papers looked into prescribing practices for children [24], [27]. One paper compared children (<18 years) and adults (>18). They found that children (<18 years) were prescribed more antibiotics (13.1%) compared to adults (7.8%). The other paper discussing children had its focus on young children (<5 years). Results showed a strong positive correlation between the chance of receiving antibiotic prescribing and age [27]. According to all four papers, a possible explanation for the fact that comparatively more children and older adults receive antibiotics could be that these age categories are more often found in risk groups, (such as co-morbidities in elder adults) [12], [22], [24], [27]. It is also suggested that the increase in prescribing that comes with the increase in age in children might be due to the fact that it is easier to diagnose older children and therefore there is a higher confidence in the diagnosis and the necessity for antibiotics [27].

Three papers have investigated patients' gender regarding antibiotic prescribing, however, none of the papers found any statistical significance [25]–[27]. It is generally known and accepted that the gender of the patient a GP consultation [25]. These studies have looked at the gender of a patient, specifically in URTI cases where antibiotics might be prescribed. Two studies looked at the correlation between gender and age. Both papers found no indication that gender plays a part in antibiotic prescribing in children. One paper found a link between gender and age in adults. Adult women received more antibiotics compared to men (69%). However, the proportion of consultations made by women was also higher. Therefore, they suggested that differences in behaviour can explain this gender gap. They concluded that women might be seeking help from a GP more, and therefore they receive more antibiotics [26]. One paper found a small correlation between the gender of the patient and the gender of the GP. A male GP showed no difference in prescribing whether the patient was female or male [27]. When comparing male and female GPs, overall female GPs prescribe less than their male colleagues. Especially the combination of a female GP and a female patient is associated with less antibiotic prescribing. However, all the results of this study were not significant [25].

View on recovery

The next determinant that will be discussed is the view on recovery. Five studies have found this determinant. The studies were conducted in the Netherlands and the UK [12], [25], [26], [28]. A GP might question the chances of the body recovering on its own if the patient has co-morbidities but sometimes it also has to do with the duration of the symptoms [11], [12], [25], [26], [28]. Four studies included in this systematic review have reported on co-morbidities [11], [12], [25], [26]. As stated

before, the causes of URTIs can be very diverse. Because it can be caused by a variety of bacteria or viruses, there are no strict guidelines on what type of treatment should be used to treat certain symptoms. Therefore, URTIs are often classified as non-protocolled diagnoses, meaning that these diagnoses give GPs different options for treatment and that antibiotics are not by default the best treatment option [25]. All four studies found that when GPs have multiple treatment options during non-protocolled URTI consultations, co-morbidity is marked as a significant predictor for receiving antibiotics [11], [12], [25], [26]. Two of the studies looked specifically at whether the prescribing was appropriate, and they found that inappropriate prescribing was more likely for patients with co-morbidities. This connection was found for all URTIs [12], [28]. Three studies found that the behaviour found in patients with a co-morbidity might play a role in the chance of receiving an antibiotic prescription. Patients with co-morbidities might be more insecure about their chances of increasing their health without antibiotics, causing GPs to feel more obligated to prescribe antibiotics [12], [25], [26]. One study suggests that GPs are more likely to prescribe antibiotics to sicker patients, such as patients with co-morbidity. They suggest that the GP is more likely to prescribe antibiotics in the case of co-morbidities for two reasons. Firstly, it might be that the GP is afraid of health decline due to underlying co-morbidities and therefore is more likely to prescribe antibiotics. A second reason is that patients with co-morbidities are more likely to have had microbiological tests done before and those results might cause GPs to be more in favour of prescribing antibiotics [12].

Relationship between patient and GP

The fourth determinant found is the relationship between patient and GP. Out-of-hours (OOH) prescribing means that primary care is provided to the patient outside of the regular working hours of a GP. During OOH, the patient consults a GP who is not their regular GP. A patient can also seek help from another GP other than their regular GP when their regular GP is not available. In this systematic review, the term locum will be used to describe a licensed GP working in a temporary position, often for multiple organisations, covering short-term absences or vacancies, therefore a GP without a well-established relationship with the patient [20]. Four papers reported not being a patient's regular GP as a determinant for antibiotic prescribing [20], [23], [24], [29]. All four studies found that not going to the regular GP increases the chance of receiving an antibiotic prescription. These studies were conducted in Belgium, Ireland, The Netherlands, and the UK. Only one paper looked at children in a setting where the GP is not familiar with the patient [23], the other three papers only studied adult patients [20], [24], [29]. In all four papers, a higher chance of receiving an antibiotic prescription was found when the GP was not familiar with the patient. Two papers indicated that the reason for this increased prescribing is due to the lack of a personal relationship with the patient [20], [29]. This is the case in both OOH and locums [20]. It is suggested that this temporary role makes it more difficult for the locum to for example determine whether the symptoms are indeed as they are described by the patient. This leads to much uncertainty [20], [29]. Especially because the chances are slimmer that there will be a follow-up appointment between the locum and the patient, locums are more likely to prescribe antibiotics [20], [29]. One of the papers found that in the case of OOH, the workload is especially high, meaning they have less time to use diagnostic tools or talk through the symptoms well enough, which leads to more inappropriate prescribing [29]. In the case of prescribing by locums, one paper gave multiple behavioural reasons as to why the prescribing rates are higher in locums. Multiple locums were interviewed, and results showed that because these GPs are only temporarily active in the organisation, they might feel less accountable for the prescribing rates of the organisation as a whole because they feel less invested or concerned [20]. Two papers gave reasons that can put this finding of higher prescribing chances during OOH into perspective [20], [24]. These studies propose that the severity of the symptoms should be taken into consideration when investigating the role of OOH in antibiotic prescribing. Most URTIs fell under the lowest urgency levels, which meant that

patients were advised to wait until office hours to come in for a consultation. This means that during OOH, a GP sees relatively more patients with more severe or acute symptoms, which will lead to a higher percentage of antibiotic prescribing [20].

Guideline non-adherence

GPs have guidelines that they have to follow when it comes to prescribing antibiotics. However, often the guidelines are not followed because as stated before, antibiotic prescribing is in a lot of cases labelled as inappropriate. Non-adherence to the guidelines was found as the last determinant in this systematic review. Guidelines are not always strict rules and there is room for interpretation. However, there are some cases where the rules are clear, and the GP still chooses to not follow the appropriate guidelines. Two papers have found possible explanations as to why a GP might choose to deviate from the guidelines. These studies were conducted in Belgium, Germany and the UK [29], [30]. One paper found that GPs might not follow a guideline because they simply do not understand the guideline, so there is a lack of knowledge. Some GPs stated that this knowledge gap is due to the workload. A second reason is that they do not agree with the guidelines, there has been no research as to why they would not agree [29]. The second paper came up with a reason as to why a GP might not agree, namely that this is due to the age of the GP and more specifically the period in which they were in medical school. For example, older GPs are more likely to do a blood test to determine the cause of the symptoms because this was a requirement in the past even though guidelines today say otherwise. In most cases, they deviated from the guidelines because they did not agree with the new guidelines, so they were aware of the change in guidelines. It was their personal preference to use another diagnostic method [30].

Interviews

Participant characteristics

Three female Dutch patients were interviewed. Their ages ranged from 21 to 60 years. Notably, one of the participants had a medical background, as she worked as a nurse in a hospital, possessing professional knowledge related to antibiotics. All the interviewed patients had received prescriptions for antibiotics to treat URTIs by their GPs within the past 12 months.

Additionally, two Dutch male GPs participated. One GP is retired and occasionally practised until the middle of 2023. The other GP is actively practising. Both were active in the region of Twente in the Netherlands and have prescribed antibiotics to treat URTIs in the previous 12 months.

The IDIs conducted have resulted in multiple determinants, namely ‘expectations’, ‘View on recovery’, ‘Relationship between patient and GP’, ‘Quick availability of diagnostic tests’, and ‘Time pressure’.

The patients’ perspective

Expectations

The first determinant that came forward was expectations. All patients described that they first try to let their body recover on its own or with other medication and that when they do seek help from the GP, they expect the GP to come up with a solution that they have not tried themselves yet. All patients mentioned that they typically attempt self-treatment with these medications before turning to their GP for assistance. One of the patients expressed it as, *"I only seek a GP's help when my symptoms become truly bothersome, and I'm not confident that my body can recover on its own."* One patient expressed that having knowledge about antibiotics makes her more mindful when deciding whether to use them: *“The benefits [of antibiotics] are, of course, that if you have an infection that your body cannot clear up on its own, you have a much faster chance of healing. The downside is that you run the risk of becoming resistant. For instance, in your later years, you may not have as many antibiotics available. So that is why you should not do it if it is not necessary.”* All patients describe how they

expected the GP to prescribe antibiotics upon their consultation. However, two patients have experienced that this wish was not fulfilled by the GP. The reaction of the patient to this outcome differs. After expressing their expectations, one patient said that by discussing with the GP they concluded that antibiotics were not the correct solution at the time. One patient mentions: *"After discussing, my GP could convince me that antibiotic prescribing would not be appropriate at that time, and it was better to wait, and I was okay with that."* One patient described they felt unheard when the expectations were not met because the patient knows their own body best and therefore knows if antibiotics are appropriate. Another patient mentions: *"I felt like I had to convince the GP that I was not doing okay. He tried to send me off with some tips I had already tried and later he only wanted to describe antibiotics if he could do a blood test. But I know my own body very well and I have had respiratory tract infections multiple times. I knew what it was, so it felt unnecessary to do all that."*

One of the patients that was interviewed was a nurse working in a hospital. She described how her knowledge of antibiotics not only shapes her perspectives but also influences her interactions with her GP. She believes that because her GP is aware of her expertise, the GP might be more cautious when prescribing antibiotics, suspecting that the patient knows how to describe symptoms to obtain antibiotics, even if the presented symptoms do not align with an actual need for them. This viewpoint is emphasized by the patient as follows: *"I do feel that the GP trusts me, but at the same time, I also have the impression that the GP might be a bit more cautious because they know that I am aware of what trigger words I should use that essentially compel the GP to take action. So, I do have the impression that they might be more reserved to prescribe antibiotics because they know that I am aware of what I should say to get what I want."* If antibiotics were prescribed, all patients state that they follow the instructions strictly. One patient mentioned that they trust their GP and therefore follow the instructions, one patient stated that they follow the instructions because they fear antibiotic resistance otherwise.

View on recovery

One patient deals with a co-morbidity, namely diabetes type 1. They stated they follow the instructions closely because they are afraid of becoming more ill *"Because I have diabetes, I always finish it [the antibiotic course] because if I do not, the infection might not go away, and I might have to take it again."* Because this co-morbidity influences the immune system, the patient feels that antibiotics are often a better option because letting the body recover on its own poses an extra risk that the patient is not willing to take. The patient stated: *"Yes, I think that when I look at my age, you should try other things as well, and I would rather not go straight for antibiotics. Maybe I would like to try letting my body resolve it on its own first. But if that poses a higher risk for me because I have diabetes, then I choose to not let my body go through that and resolve it with antibiotics."* The patient describes that they believe the GP's decision is influenced by her co-morbidity as well. *"I do feel that the doctor prescribes antibiotics more quickly for me. I have never asked, so I am not sure if it is really the case. But there have been times when I thought to myself whether this is necessary or if I should try something else first, like letting it run its course and see if my body can resolve it [the infection] on its own."*

Relationship between patient and GP

All patients state that they accept the treatment given by the GP and trust the GP in their judgment on whether antibiotics should be prescribed. One patient describes how she has not always agreed with the GP but will trust their judgment in the end because she does believe there are many alternatives to antibiotics: *"Sometimes you might think you cannot do anything else [antibiotics] against such an infection, while there are actually quite a few other options."*

Educating patients

All patients stated that GPs must inform patients about the benefits and drawbacks of antibiotics because patients might lack this knowledge. This viewpoint is emphasized by a patient as followed*: "I believe that education is especially important, particularly for the general public who are not in the field [medical] and may not have much knowledge about it [antibiotics] or be aware of other options. I think it should primarily be the responsibility of the GP who treats the person. Other treatments may be a bit slower, and it may not always be feasible, but where it is possible, you might prefer to explore alternative options."* Additionally, one patient suggests that the government of the Public Health Service (GGD) could also serve as a trustworthy source for patients to consider when making decisions about whether to use antibiotics. This is highlighted by the patient quoting the following: *"The government or the GGD can provide clearer information about the risks associated with taking antibiotics."*

One patient states that due to her co-morbidity, she might require different information than other patients. Finding clear information on the internet is difficult because the complexity of the disease led her to question whether different infections, antibiotics and diabetes types require tailored approaches. Her questions are emphasized by the following quotes: *"I do not know if I can [let her body recover without antibiotics] because I have diabetes; I have not gathered enough information on that yet"* and *"I sometimes found it a bit challenging to navigate. But perhaps it is because it varies depending on the type of infection, the antibiotic, and maybe even the type of diabetes."* The patient reveals how she would like to be more informed by the GP about the risks and recognizes that it is important to seek this information: *"What I want to do next time with the GP is inquire about the risks because I often receive antibiotic prescriptions, and in my perception, it happens quite frequently."*

The GPs' perspective

Expectations

The first determinant found in the GP IDIs was expectations. Both GPs state that they see patients who come to the consult and expect antibiotics, however, the number of patients who come in with those expectations decreases. The GPs give two reasons as to why this number decreases, namely the generation and educational level. One of the GPs states that there is a difference in generations. In the past antibiotics were prescribed more often and therefore the older generations expect it more often. *"A portion of the patients does expect antibiotics, but this expectation has certainly decreased over the years. Antibiotics were commonly prescribed for many years, so that expectation still exists. I believe there is a difference among generations. In my experience, the younger generation has a much lower expectation of receiving antibiotics."* Both GPs mention that the educational level of the patient also influences the expectations. One of the GPs states that if a patient is not capable of understanding the risks of antibiotics or does not understand why antibiotics are not the way to treat a certain URTI it is difficult to change their expectations. *"You need to be able to communicate effectively with a patient. However, the patient also needs to have the ability to comprehend. This can be a challenge at times because if they don't understand, it becomes much more difficult to explain things thoroughly."* One of the GPs sees many high educated patients. They believe that the level of education might influence the expectations of the patient. A GP states that these high educated patients are often high demanding and are more persistent, they suggest that this might be because these patients are under pressure at work. *"What I sometimes find challenging in our practice is that it involves many highly educated patients, they tend to be demanding when it comes to wanting antibiotics. They are busy and, so to speak, would prefer it if the antibiotics had been prescribed yesterday. They have little patience and quickly resort to various remedies, which often results in a demand for antibiotics."* Another GP adds that especially if they believe that if the patient is expecting antibiotics, especially if they believe that it is an easy fix or they can easily obtain them, they might encounter a heightened sense of

restraint from the GP. The GP emphasizes that a thorough medical assessment is needed before antibiotics are considered. *“Just like people who request antibiotics over the phone but do not want to come in. If you deem it so important to get antibiotics, then you should come in person so I can perform a medical assessment. I never handle such matters over the phone."*

A medical determinant that has a significant influence on behavioural determinants mentioned before such as expectations of the patient is a relatively new tool called the C-reactive protein (CRP) test. With a fingerstick, the number of a reactive proteins can be determined within a minute. This number indicates whether the symptoms are caused by a viral or bacterial agent. *"Especially before the implementation of the CRP test, if people returned frequently with requests for antibiotics or insisted on prescribing antibiotics, you would consider prescribing antibiotics quicker.”* Concluding, the expectation of a patient is a determinant for antibiotic prescribing.

View on recovery

Co-morbidity

The second determinant that was found during the IDIs was the view on recovery. Both GPs state that if there is reason to believe that the body will have more difficulty to clear the infection, they are more likely to prescribe antibiotics. Both GPs mention that either co-morbidities that cause the immune system to be compromised or patients taking certain medicines that compromise the immune system are a determinant in whether they will be prescribed antibiotics. A GP mentions: *"If the patient has specific conditions, it becomes a different story. For instance, if someone has a weakened immune system or certain diseases or medications, it becomes a more complex situation where you need to pay closer attention, provide clearer instructions, and may also consider prescribing antibiotics earlier."* Another GP gives a similar reasoning, namely: *"Patients sometimes have a risk profile where their immune system is compromised. For example, individuals on specific medications or with certain illnesses. This indicates the vulnerability of a patient. If a patient scores higher on that risk profile, it is more likely to prompt an earlier consideration of antibiotics."*

Age

One GP states that age can also be a determinant in some cases. Especially age in combination with the severity of the infection. They explain*: "You want to assess how vulnerable someone is. In the case of a young child or an elderly person, different risk factors may come into play. In those situations, you tend to be more inclined to prescribe antibiotics more readily because you know that complications might arise otherwise."*

Relationship between patient and GP

Both GPs state that the trust between the patient and the GP is a very important determinant for prescribing antibiotics. If a patient comes in with the expectation of receiving antibiotics, the trust bond between the GP and the patient also influences the prescribing behaviour of the GP. The first reason why a trust bond is a determinant in prescribing antibiotics is given by one of the GPs, they state that if there is a trust bond, it will be easier to convince a patient that antibiotics are not the solution. On the other hand, a lack of trust bond can result in more antibiotic prescribing. They explain: *"If you have known someone for a long time, and you say, 'It is not necessary,' it is done, and they trust you. If you do not know them, you kind of have to strike a deal to maintain good contact with the patient. You are more inclined to agree to prescribe antibiotics to gain their trust in the future. Ideally, with someone you know well, you do not have to.”* So, the GP states that the lack of a trust bond with the patient can, in some cases, result in more antibiotic prescribing. Another GP’s view on a trust bond between patients partly overlaps with the first GP as they both state that a well-formed trust bond between the GP and the patient often results in no antibiotic prescribing. However, they state that a trust bond between the patient and GP can also result in him being more lenient. On the other hand,

the lack of a trust bond can result in less prescribing, which is the opposite of the statement of the first GP. Another GP mentions: *"I find that if you know the patient well, they are more likely to accept your recommendations. But it goes both ways, as when you know someone well and they have been sick for a while or are extremely busy with work, you might sometimes think, I will just prescribe an antibiotic. However, if a patient does not trust you or you do not know them, and they keep nagging and insisting on receiving antibiotics, there are times when I think, 'That is enough from you,' and I am very persistent to not prescribe an antibiotic."*

Quick availability of diagnostic tests

The medical device CRP test has influenced the amount of prescribing drastically. Both GPs state that this tool has helped massively in convincing patients that antibiotics are not necessary, especially if a patient is not convinced by the GP telling the patient that antibiotics are not effective in their case, which could indicate a lack of trust. One of the GPs mentions *"Otherwise healthy individuals can also overcome a bacterial infection. However, in the case of respiratory symptoms, it is often caused by a virus, and the result of the CRP test can be presented as supporting evidence."* Another GP states that they have seen a large decline in prescribing due to the CRP test. *"Nowadays, we have the C-reactive protein meter. It is an excellent indicator that we did not have before. In the past, much was based on the clinical picture, but with this epidemiological figure, we now know that in many cases, it is a viral infection. This often provides an additional argument to determine how ill someone is and how we prescribe."*

Time pressure

Both interviewed GPs described time pressure as a determinant of whether antibiotics are prescribed or not. One of the GPs stated that creating a bond with a patient is very important because, as stated before, patients are more likely to take the advice of the GP. However, this takes time, which there is not a lot of. *"Well, time is the most crucial factor. You must attempt to establish a partnership with your patient. However, you have only short moments each time, so this often requires a lot of time."* Another gave one reason as to why time pressure influences prescribing, namely that they feel that time pressure results in less time to examine and especially advise the patient. There is no time to explain why antibiotics might not be the best solution. This time pressure is seen during office-hour care, but the time pressure is even more extreme in OOH because it is extremely busy, especially at the weekends. *"I am less satisfied with that. In such cases, I feel like this is not the kind of medicine I prefer, but more of a quick-fix medical approach [prescribing antibiotics]. What you really want is to examine the patient thoroughly, providing them with proper time, attention, and sound advice. Time constraints often make this difficult, and sometimes I prescribe antibiotics when I might not have done so had there been more time."*

OOH prescribing

One of the GPs states that time pressure is especially seen in OOH care. The time pressure in combination with the types of patients can result in more antibiotic prescribing. *"At the emergency room, it is always extremely busy. Working there is not enjoyable, and in reality, hardly anyone enjoys it. The waiting room is crowded, and not all patients in there are pleasant. There is often aggression and frustration because they sometimes have to wait for an hour. As a result, as a GP, you are already at a disadvantage. So, you occasionally consider a different approach than you normally would. You do not always want to engage in a discussion. Moreover, there is little time to explain things because the entire waiting room is still full."*

An overview of the theme's found in the literature and interviews can be found in Table 3. Here the overlap can be seen between the determinants found in the literature and the interviews.

Theme	Description	Interviews	Articles
Expectations	What expectations bout antibiotic prescribing do the patients have when they see a GP.	GPs and patients	[20]–[23]
Patient characteristics	The personal characteristics of the patient apart from health, influencing antibiotic prescribing.	GPs	[12], [22], [24]–[27]
View on recovery	The chance that the patient will recover on its own according to the GP.	GPs	[11], [12], [25], [26], [28]
Relationship between patient & GP	Whether there is a trust bond between the patient and the GP and what importance this has for the patient and the GP.	GPs and patients	N/A
Educating patients	Which parties are responsible for educating patients.	Patients	N/A
Guideline non-adherence	In what cases the GP deviates from the guidelines.	N/A	[29], [30]
Quick availability of diagnostic tests	Are diagnostic tests available and what is the influence of them for the GP and the patient.	GPs	N/A
Time pressure	Limited time during a consultation, which may put pressure on the GP and consequently impact the consultations or decision-making process.	GPs	[29]
OOH prescribing	Primary care is provided to the patient outside of the regular working hours of a GP and/or the patient consults a GP that is not their regular GP.	GPs	[20], [23], [24], [29]

Table 3. Overview of the literature and the interviews.

Discussion

The research question for this thesis is "Which determinants play a role in the decision-making processes in primary care regarding antibiotic prescribing for upper respiratory tract infections in West European countries?" This question can now be answered. In the decision-making process in primary care the following determinants were found in literature and confirmed by the interviews; 'Expectations', 'view on recovery' and 'Relationship between the patient and GP'. It is noteworthy to mention that the explanation as to why these are determinants in prescribing antibiotics differ between the literature and the interview findings in some determinants. Apart from these determinants, some determinants were only found in literature, namely; 'patient characteristics (age)' and 'guideline non-adherence'. Two determinants were only found in the interviews of the GPs, namely 'time pressure' and 'Quick availability of diagnostic tests', and one only in the patient IDIs, namely 'patient education'.

In the literature, there were five determinants found in antibiotic prescribing for URTIs. Patient expectations is a determinant that was found in literature [20]–[23] and was extensively discussed during the interviews, demonstrating its impact. According to the literature, a portion of the patients expect to receive antibiotics [20]–[23]. This is confirmed by the interviews with the GPs where they recounted different situations in which patients expected an antibiotic prescription for URTIs. However, as the literature also suggests, despite expecting antibiotics, most patients would trust their

GP if they advised against it [22], [23]. This observation is also validated by the patient interviews. In the interviews, GPs also highlight that, in instances where a trust bond is established between the GP and the patient, the patient is generally receptive to not receiving antibiotics, even if their initial expectation was different. Expectations seem to go hand in hand with the trust bond between the GP and the patient. In order to increase the trust bond there are multiple initiatives. Since 2013, the Netherlands have guidelines on shared decision making (SDM) with the goal to increase the trust bond in all sectors of healthcare. SDM is increasing in all sectors of health care. In this approach clinicians and patients work together to come up with a solution to a medical problem. So, in practice, there are already many initiatives in order to increase the bond. However, there seem to be other factors at play. The findings of the results seem to imply that time constraints are playing a role in antibiotic prescribing. In the interviews, GPs have stated that one of the reasons they do not give thorough explanations is time constraints. Secondly, even though patients in the interviews have stated to be open to other solutions apart from antibiotics, it is important to remember that this may not be the case for all patients. Alternative approaches, like educational campaigns, might be able to help people who are not receptive to altering their viewpoint on antibiotics. However, studies on changing social behaviour have found that to create community awareness, multiple stakeholders must be actively involved. In practice, this means that all parties should be involved which is time consuming, expensive, and complex [31]. Time constraint is currently a big problem within primary care. Campaigns might act as a temporary fix for the issue that GPs do not always have enough time to explain all important aspects about antibiotics during a consultation, however it will probably not be enough to significantly change the behaviour of the patient [31].

The second discussed determinant was patient characteristics, which included age and gender. The analysis revealed that age is identified in both literature and the GP interviews as a determinant [12], [22], [24], [27]. However, the level of impact of the determinant was deemed to have some variance. In the literature, age is hardly cited as a factor influencing prescribing behaviour in primary or secondary care outside of antibiotic prescribing. In articles where age is mentioned, it does not appear to be the primary determinant. Most often, it is linked to other determinants such as co-morbidities [32]. During the IDIs, GPs stated that a patient's age might play a role in the GPs view on their health status. This implies that it is not necessarily age itself that influences prescribing but rather the overall health status. Therefore, it can be suggested that age acts as a confounding variable [32]. This might imply that currently, in practice the policies do not have a sufficient emphasis on the understanding of the underlying morbidities because they are focusing on the age. In the literature, gender was also identified as a determinant [25]–[27], however the interviews with the GPs did not confirm this finding. The lack of indication for gender as a determinant in the interviews, together with the fact that the literature only showed non-significant results, suggests there is a need for a cautious interpretation of the literature. Therefore, it is not advisable to conclude gender as a determinant in this context.

The view on recovery is mentioned in both the literature and the interviews. Especially the consideration of co-morbidities was mentioned [11], [12], [25]. The view on recovery plays a part in antibiotic prescribing behaviour, for example in the case of co-morbidity [33]. In contrast to age, co-morbidities are directly related to the view on the recovery according to the GP. In this systematic review, how co-morbidities play a part in antibiotic prescribing exactly is not touched upon much. In other facets of treatment and care, this is more studied. Some prior studies explored the relationship between comorbidity and the rate of recovery, mainly in the context of injuries combined with infections. They showed that a comorbidity increased the time patients were in recovery significantly [34]. A study conducted in secondary care explored the impact of comorbidities on treatment decisions. They concluded that because co-morbidities are decreasing the health status, both patients and doctors are more risk aversive. Meaning that they are more likely to prescribe a certain treatment

or refer them to a specialist for further evaluation [35]. Since this is the case for secondary care, it may be the case that this also goes for primary care. In secondary care, they try to address this problem by developing protocols. However, a drawback emerges here. Especially in the case of co-morbidity or other special circumstances that influence health, there are often complex situations, making protocols often suboptimal. Therefore, a highly personalised plan is preferred [36]. However, as highlighted in the interviews, time constraints pose a challenge. This raises the question how feasible the advice to make an even more personal plan with each patient is. Currently, it might not be a realistic solution.

A well-established relationship between the patient and the GP emerged as a determinant in both the literature study and the IDIs [20], [23], [24], [29]. However, the provided literature differs from the insights gained by the interviews. The literature suggests that a lack of follow-up or the lack of feeling responsible, most often in OOH settings, might factor into increased antibiotic prescribing [20], [23], [24], [29]. However, the GPs during the IDIs expressed a strong sense of responsibility in prescribing antibiotics. Therefore, challenging the notion that locums might be less cautious. In the interviews, aggression during OOH came forward as a reason to prescribe medication. An investigation by Dutch newspaper Trouw found that in 2019, 29 of the 50 urgent care centres in the Netherlands dealt with aggression frequently [37]. A study conducted in 2010 studied the effects of aggression and pressure by patients on prescribing behaviour in secondary care. Their results showed that in almost half of the cases this aggression led to the patient being prescribed the medication they requested [38]. This study did not differentiate between different kinds of prescription medication and took place in secondary care, however it can be suggested that this occurs in primary care as well and that this plays a role in antibiotic prescribing.

In the literature, two papers mention that OOH and locum GPs both lead to a higher likelihood of prescribing antibiotics for a URTI due to less familiarity with the patients [20], [29]. It is notable that the concept of a trust bond is not extensively addressed in the literature, however the trust bond is highlighted often in the interviews. Patients repeatedly mention its importance and for the GPs, the trust bond seems to be a substantial determinant not only for antibiotic prescribing but also across their entire professional practice. This discrepancy might be a valuable observation because it suggests that the relationship between the patient and the GP might not be adequately explored or emphasised in the existing literature on antibiotic prescribing in primary care. This relationship, which is referred to as the trust bond in this thesis, may have a significant impact not only directly on antibiotic prescribing but also indirectly on the other determinants found during the systematic review.

Lack of time was found in both the literature as the IDIs to be a reason for different prescribing behaviours during OOH compared to office hours. However, time constraints are not limited to OOH but are also seen during office hours [39]. A study conducted in the Netherlands concluded that GPs with a higher workload adhere less to certain guidelines. Guidelines that require relatively much time are adhered to significantly less than guidelines who save time [40]. There is insufficient information available on the time required for following antibiotic guidelines compared to other treatments. However, if antibiotic guidelines require relatively much time, this could potentially play a part in the decision making.

The last determinant that will be discussed is guideline non-adherence. The determinant guideline non-adherence can be found mainly in the literature. In the literature, results show that there is inappropriate prescribing, which means guidelines are not followed properly. As stated before, the time it takes to execute guidelines correctly could be of playing a part in antibiotic prescribing. Another reason as to why guidelines are not followed correctly can be partly explained by the fact that, in general, guidelines are often quite broad so there is room for interpretation [41]. A systematic review

on adherence to chronic obstructive pulmonary disease (COPD) medication guidelines showed significant variability within primary care [41]. These results seem to hint at the potential for the guidelines being too broad. It could be that this is also the case for guidelines on URTI diagnoses and antibiotic prescribing. However, in the interviews with the GPs, the GPs are quite clear. They state that URTIs are most often a viral infection and therefore antibiotics are not on their list of possible treatment options. Based on the interviews, it can be suggested that when GPs deviate from the guidelines, it is driven by other reasons. Overall, it seemed that both GPs take the decision to prescribe antibiotics seriously and do not think it should be made hastily. It seems evident that the intention is to adhere to the existing guidelines. The three determinants mentioned above delve into the three most prevalent factors that were identified during the literature search that potentially clarify part of the reasoning behind antibiotic prescriptions. Taken together, the results suggest that there seems to be a different justification for antibiotic prescriptions that has nothing to do with the GP's opinions or sentiments of the guidelines.

Recommendations

The systematic review in combination with the IDIs revealed various determinants influencing antibiotic prescribing for URTIs. Based on these, several recommendations for further research are formulated.

It might be possible that multiple determinants found in this thesis are not limited to URTIs. Therefore, this thesis advocates for a broader application of these insights beyond URTIs. Looking ahead, future studies should consider delving deeper into these determinants. Expanding the scope of the research to a broader spectrum, including different medical conditions and infections such as urinary tract infections (UTIs), skin infections or gastrointestinal infections, will enrich our understanding of how antibiotic prescribing is influenced in different contexts. This thesis might be a guide for future research and policy decisions aimed at optimising antibiotic prescribing for URTIs and other medical scenarios. In the IDIs, it became apparent that GPs found that some infections lead to more challenges than URTIs do. Particularly when considering the emergence of antibiotic resistance. Therefore, a plausible next step in research could involve revisiting the study conducted in this thesis, perhaps with a focus on UTIs. This is because both GPs emphasise the severity of UTIs. One of the GPs notes: *"In the context of upper respiratory tract infections, resistance is less common, but a particularly notorious example is a urinary tract infection. The high prevalence of urinary tract infections poses a significant challenge."* Another GP reaffirms this perspective, stating: *"When discussing this, I find that the approach to respiratory tract infections in the Netherlands is proceeding well, possibly even better than surrounding countries. […] However, in the realm of urinary tract infections, I see room for improvement. There are significant opportunities for further progress in that area."*

Secondly, in the discussion, it is stated that it is crucial to dive further into the relationship between the GP and the patient. Future research should also explore how a trust bond between the GP and the patient influences how patients follow their treatment plans and how this influences a GP's decision to prescribe antibiotics. In the interviews, it was observed that a well-established trust bond between the GP and the patient can lead to the GP being more lenient with the patient when it comes to prescribing antibiotics. It can be suggested that this leniency is motivated by an understanding of the patient's unique situation. So, from the GP's perspective, there is a genuine motive to provide optimal care. Future research can delve into factors contributing to the leniency and provide nuanced insights into how the prescribing behaviour of a GP can be adapted based on an established trust bond. The lack of literature found on the trust bond compared to the interviews suggests that the relationship between the patient and the GP might not be adequately explored or emphasised in the existing literature on antibiotics. Therefore, this thesis also advocates to focus future research on how the trust

bond influences antibiotic prescribing directly but also if there is an indirect influence of this trust bond on other determinants.

In the patient interviews it becomes clear that patients would like more information about antibiotics and seem genuinely open to it. In the interviews with the GPs, it also emerges that they are keen to provide information and explanations, however, there simply is not always time due to time constraints. Therefore, a third recommendation is to explore how more and better information about antibiotic prescribing for URTIs could be provided through alternative means.

Fourthly, in the literature, there is no consideration given to caregivers of small children or older individuals. [42]. A large study conducted in the United States found that interactions with a caregiver lead to challenges for both the patient and the GP [43]. In this study, a substantial impact of caregivers on prescribing behaviour is seen, it would be interesting to examine how this applies to antibiotics for URTIs or, more broadly, to other infections.

Lastly, in this thesis, the focus has been on Western Europe. It is generally known that in Southern Europe, there are different norms when it comes to antibiotics [44]. For example, antibiotics for URTIs are readily prescribed there, and you can even get them over the counter without a prescription [45]. GP 2 mentions this in the interview: *"People often look at countries around us, and that is not without reason. It happens all around us. There are actually much larger problems, if you've been to Greece, you can easily obtain antibiotics. People come back from vacation with a bag full of misery [antibiotics]. In comparison, we are already doing very well in the Netherlands in terms of prescribing antibiotics.'* It could be interesting for future research to explore why there are such variations within Europe. Perhaps this is due to cultural differences [46], however, a study should be conducted to find out which determinants play a role.

Strengths and Limitations

The following section will go into the strengths and limitations of this thesis.

The first limitation of this systematic review is that the search of papers was limited to only two databases, namely PubMed and Scopus. It is possible that some relevant studies have been missed because they were not in one of the databases used. This could lead to an incomplete overview of all determinants known in the literature. However, even though the systematic review was limited to two databases, the two databases were chosen deliberately to capture the broadest possible range of potentially relevant articles. PubMed contains a wealth of medically specific articles, while Scopus has a much broader scope. This approach was taken to maximise the coverage of relevant articles. Secondly, efforts were made to minimise bias by having a subset of articles independently assessed by two separate researchers. A limitation of the IDIs is the fact that the sample size is very small. IDIs are in its essence subjective which makes it difficult to be able to generalise. The limited number of participants further challenges the ability to generalise the findings to a broader population. Furthermore, the small sample size limits the statistical power greatly. However, the interviews did provide valuable insights into the determinants of the patients. Therefore, these interviews could serve as a foundation for conducting a more generalisable study. Lastly, this study is limited due to a language bias. All interviews were exclusively conducted with participants holding the Dutch nationality and only English papers were included. Considering that the thesis focuses on Western Europe, this creates a problem when attempting to compare the outcomes. The narrow focus limits the ability to generalise the results of the IDIs and excluding papers other than English potentially limited the depth of the review [47]. The decision not to extend beyond Dutch and English was made due to time constraints and language proficiency limitations.

An important strength of the overall research is that the research followed a step-by-step process, starting with a systematic review and later delving into qualitative research. This enabled a thorough exploration of the determinants and also validated the systematic review findings in the specific context of the Netherlands. This careful approach strengthens the reliability of the results. Both the systematic review and IDIs give a first insight into the found determinants. The study could be repeated in different parts of the Netherlands and West-Europe to increase the generalisability. Secondly, the interviews were conducted in an environment where respondents felt comfortable being honest. This approach discouraged socially desirable answers, adding authenticity to the gathered insights. A third strength of the IDIs is that the interview questions themselves were designed with sensitivity in mind, therefore also minimising the likelihood of participants feeling uncomfortable. This approach aimed to encourage open and honest responses from the participants.

Conclusion

An important takeaway from this thesis is the identification of several determinants play a role in the prescribing of antibiotics for URTIs among GPs. The thesis revealed a complex interplay of determinants when it comes to prescribing antibiotics for URTIs, such as patient expectations, trust bond between the patient and the GP, expectations and challenges that come into play during OOH care.

Importantly, the thesis highlights differences between the existing literature and the actual primary care practice. This urges one to be cautious when interpreting established determinants. A key message of this thesis is therefore that it is important to understand that antibiotic prescribing decisions go beyond the determinants established in the literature. Trust bonds were found to be an important determinant in antibiotic prescribing for URTIs, however, this determinant does not seem to have been adequately investigated in the existing literature. Furthermore, there seems to be a connection between the expectations of a patient and the amount of trust between the patient and the GP. In order to fully understand the complexity of prescribing antibiotics it is important to look at the dynamics between the patient and the GP that come into play, apart from other determinants. Factors outside of the patient and the GP also appear to have an impact on the prescribing behaviour of the GP, particularly time pressure. Resolving this issue is challenging in the current healthcare climate, however it is a notable factor contributing to the inappropriate prescribing problem. This thesis shows the importance of considering social, cultural, and personal factors when it comes to writing interventions on antibiotic prescribing in URTIs.

This explorative study is a first step in this research direction, and it suggests areas for future research and exploration.

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Appendices

Appendix A

General information about the paper	Authors
	Title
	Publication year
	Journal
	DOI
	Quality rating
	Funding source
	Study location
Information about the study	Study design
	Study duration
	Final N
	Sex
	Race/ethnicity
	Age
	Type of antibiotics
	Factors controlled for
	Definitions
Outcomes	Conclusion
	Determinants
	Out of office prescribing (YES/NO)
	% of incorrect prescribing
	Limitations
	Solutions

Appendix B

Determinanten in het besluitvormingsproces van huisartsen met betrekking tot het voorschrijven van antibiotica voor URTI's in West-Europa

Toestemming om deel te nemen aan onderzoek

- Ik, ..., ga vrijwillig akkoord om deel te nemen aan dit onderzoek.

- Ik begrijp dat zelfs als ik ermee instem om nu deel te nemen, ik me op elk moment kan terugtrekken of kan weigeren om een vraag te beantwoorden zonder enige consequenties van welke aard dan ook.

- Ik begrijp dat ik de toestemming voor het gebruik van gegevens uit het interview binnen twee weken na het interview kan intrekken, in welk geval het materiaal wordt verwijderd.

- Het doel en de aard van het onderzoek heb ik mondeling uitgelegd gekregen en ik heb de gelegenheid gehad om vragen te stellen over het onderzoek.

- Ik begrijp dat deelname één kwalitatief gesprek van ongeveer 30 minuten inhoudt.

- Ik begrijp dat ik niet direct baat heb bij deelname aan dit onderzoek.

- Ik ga ermee akkoord dat mijn interview wordt opgenomen.

- Ik begrijp dat alle informatie die ik voor dit onderzoek verstrek, vertrouwelijk zal worden behandeld.

- Ik begrijp dat in elk rapport over de resultaten van dit onderzoek mijn identiteit anoniem zal blijven. Dit zal gebeuren door mijn naam niet op te nemen en details van mijn interview te verhullen die mijn identiteit of de identiteit van mensen over wie ik spreek kunnen onthullen.

- Ik begrijp dat verkapte fragmenten uit mijn interview geciteerd kunnen worden in:

    - Thesis Charlotte Batenburg
    - Project "What to do with the flu"

- Ik heb begrepen dat ondertekende toestemmingsformulieren en originele audio-opnames worden bewaard in een beveiligde p-drive van de Universiteit Twente, tot het einde van het grotere project "What to do with the flu" (CHARE-GD-II). De transcripties van de interviews worden 10 jaar bewaard in de p-drive en opnames worden vernietigd.

- Ik begrijp dat ik onder de legalisatie van de vrijheid van informatie te allen tijde recht heb op toegang tot de informatie die ik heb verstrekt terwijl deze in opslag is zoals hierboven gespecificeerd.

- Ik begrijp dat het mij vrij staat om contact op te nemen met een van de mensen die betrokken zijn bij het onderzoek om verdere opheldering en informatie te vragen.
    - Charlotte Batenburg: c.batenburg@student.utwente.nl
    - Nienke Beerlage-de Jong: n.beerlage-dejong@utwente.nl

Handtekening van onderzoeksdeelnemer *Datum*

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Handtekening van de onderzoeker
Ik geloof dat de deelnemer geïnformeerde toestemming geeft om deel te nemen aan het onderzoek

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Appendix C

CHARE GD II **Interview patienten**

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IDI nummer: …… **Nederland/Duitsland**
Datum: …… **Interviewer:** ……

- **Voorstellen**
- **Kort uitleg van het doel van de studie:**
- Ik ben momenteel bezig met mijn scriptie voor Gezondheidswetenschappen, waarin ik me richt op het onderwerp antibiotica. Eerder heb ik Neuro- en Gedragswetenschappen gestudeerd aan de Universiteit van Groningen, en momenteel volg ik mijn master aan de Universiteit van Twente. Voor mijn scriptie ben ik van plan huisartsen en patiënten te interviewen. De vragen zullen gericht zijn op uw ervaringen en meningen met betrekking tot antibiotica. Deze vragen zijn niet bijzonder persoonlijk, maar als er iets is wat u liever niet wilt beantwoorden, hoeft dat uiteraard niet. Uw medewerking zou zeer waardevol zijn voor mijn onderzoek.
- **Geschatte tijd voor het interview:** +/-60 minuten.
- **Recht op deelname aan en terugtrekking uit het onderzoek:** Uw deelname aan dit onderzoek is vrijwillig. U kunt zich op elk moment terugtrekken uit het onderzoek. Ook bent u vrij om vragen over te slaan die u liever niet wilt beantwoorden.
- **Gebruik van bandrecorder:** Om het interview goed te kunnen vastleggen, stel ik voor om een recorder te gebruiken, mits u hier geen probleem mee heeft. Vind u het erg als ik een recorder gebruik? (kijk of de persoon het hier mee eens is)
- **Plan om de identiteit van de deelnemer te beschermen:** De informatie die we hier vandaag bespreken blijft anoniem. Uw naam wordt uit de gegevens verwijderd en niemand kan uw naam koppelen aan wat er wordt gezegd. Behalve het onderzoeksteam heeft toegang tot de data. Deze gegevens worden gepubliceerd en gedeeld met de wetenschappelijke gemeenschap, maar uw naam komt in geen van de publicaties voor.
- **Basis regels:** Er zijn geen goede of foute antwoorden. Ik waardeer ieder idee, mening en ervaring.
- Heeft u nog vragen?
- **Consent:** Onderteken het formulier “informed consent”.
- De interviewer zet de digitale recorder aan en begint met het interview.

Introductie vragen

1. **kunt u wat vertellen over uzelf?**

Probe: Naam, geslacht, leeftijd, opleiding, werk, etniciteit, woonplaats.

2. **Bent u bekend met antibiotica?**

Probe: Wat was de reden waarom u antibiotica heeft gebruikt?
Heeft u de behandeling uitgevoerd zoals u is uitgelegd door de huisarts of apotheek, waarom wel of niet?
Wanneer kan antibiotica gebruikt worden?
Is antibiotica effectiever dan andere medicatie, waarom wel of niet?

Hoofdvragen

3. **Bij het behandelen van hoge luchtweg infecties (bijvoorbeeld: verkoudheid, keelpijn, hoesten, middenoorontsteking en bijholteontsteking), heeft antibiotica of 'gewoon uitzieken' uw voorkeur, en waarom?**

Probe: Gaat u weleens teleurgesteld weg bij de huisarts omdat u niet de antibiotica kuur kreeg die u had gewild?
In hoeverre probeert u de huisarts over te halen om antibiotica voor te schrijven bij het behandelen van hoge luchtweg infecties?

4. **Heeft u weleens getwijfeld of u de voorgeschreven antibiotica wel moest gebruiken, waarom wel of niet?**

Probe: Welke informatie mbt antibiotica vindt u belangrijk om te krijgen tijdens het bezoek aan de huisarts en krijgt u die informatie?

5. **Wat zijn de voor en nadelen van antibioticagebruik bij het behandelen van hoge luchtweg infecties?**

Probe: Bent u bekend met de term antibioticaresistentie en wat kunt u hierover vertellen?
Wat zijn de gevolgen voor u of anderen?

6. **Wat beïnvloedt uw keuze om antibiotica te gebruiken om hoge luchtweg infecties te behandelen?**

Probe: Is uw omgeving terughoudend in het gebruik van antibiotica, waarom wel of niet?
Heeft u informatie over antibiotica opgezocht en via welke bronnen?
Was de informatie duidelijk?

Slotvragen

7. **Wat kan gedaan worden om risico op antibioticaresistentie te verlagen of voorkomen?**

Probe: Wie (de regering, huisartsenvereniging, de patiënten) moet actie nemen en wat voor interventies kunnen uitgevoerd worden?

Appendix D

CHARE GD II Interview huisartsen

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IDI nummer: …… **Nederland/Duitsland**
Datum: …… **Interviewer:** ……

- **Voorstellen**
- **Kort uitleg van het doel van de studie:** Ik ben momenteel bezig met mijn scriptie voor Gezondheidswetenschappen, waarin ik me richt op het onderwerp antibiotica. Eerder heb ik Neuro- en Gedragswetenschappen gestudeerd aan de Universiteit van Groningen, en momenteel volg ik mijn master aan de Universiteit van Twente. Voor mijn scriptie ben ik van plan huisartsen en patiënten te interviewen. De vragen zullen gericht zijn op uw ervaringen en meningen met betrekking tot antibiotica. Deze vragen zijn niet bijzonder persoonlijk, maar als er iets is wat u liever niet wilt beantwoorden, hoeft dat uiteraard niet. Uw medewerking zou zeer waardevol zijn voor mijn onderzoek.
- **Geschatte tijd voor het interview:** +/-30 minuten.
- **Recht op deelname aan en terugtrekking uit het onderzoek:** Uw deelname aan dit onderzoek is vrijwillig. U kunt zich op elk moment terugtrekken uit het onderzoek. Ook bent u vrij om vragen over te slaan die u liever niet wilt beantwoorden.
- **Gebruik van bandrecorder:** Om het interview goed te kunnen vastleggen, stel ik voor om een recorder te gebruiken, mits u hier geen probleem mee heeft. Vind u het erg als ik een recorder gebruik? (kijk of de persoon het hier mee eens is).
- **Plan om de identiteit van de deelnemer te beschermen:** De informatie die we hier vandaag bespreken blijft anoniem. Uw naam wordt uit de gegevens verwijderd en niemand kan uw naam koppelen aan wat er wordt gezegd. Behalve het onderzoeksteam heeft toegang tot de data. Deze gegevens worden gepubliceerd en gedeeld met de wetenschappelijke gemeenschap, maar uw naam komt in geen van de publicaties voor.
- **Basis regels:** Er zijn geen goede of foute antwoorden. Ik waardeer ieder idee, mening en ervaring.
- Heeft u nog vragen?
- **Consent:** Onderteken het formulier “informed consent”.
- De interviewer zet de digitale recorder aan en begint met het interview.

Introductie vragen

1. **kunt u wat vertellen over uzelf?**

Probe: geslacht, leeftijd, waar heeft u de opleiding gedaan, werkervaring, werkplek (groot/klein praktijk)

2. **Wat kunt u vertellen over antibiotica resistentie?**

Probe: Komt u dit vaak tegen?
Hoe vaak denk u aan dit probleem?

Hoofdvragen

3. **Beschrijf de behandelingsprocudure bij een patient met symptomen van hogeluchtweg infectie.**

Probe: Welke behandelingsopties biedt u uw patienten?
Wat voor richtlijnen houd u aan en wijkt u daar wel eens vanaf?
In welke mate is de patient betrokken bij de keuze?

Wordt antibiotica veel gevraagd of verwacht vanuit de patient met hogeluchtweg infecties en is die verwachting terecht?

4. **Wanneer biedt u antibiotica aan?**

Probe: Op basis van wat (microbiologische test) kom u tot het besluit om antibiotica aan te bieden?
Waarom denk u dat artsen antibiotica voorschrijven bij hogeluchtweg infectie?
Op basis van welke factoren (bijvoorbeeld: leeftijd, soort URTI, co-morbidities, etniciteit) schrijft u sneller antibiotica voor?
Is er een druk om antibiotica voor te schrijven door de pharmaceutische industrie?

5. **Wat zijn de voor en nadelen?**

Probe: Hoe neemt u deze voor en nadelen mee in het besluiten over de behandeling van hogeluchtweg infecties?

6. **Als u kijkt naar collegas in het buitenland bijvoorbeeld duitsland, zijn er veel verschillen in de behandeling van hogeluchtweg infecties, waarom wel of niet?**

Probe: Hebben deze verschillen invloed op uw besluitsvorming?

Slotvragen

7. **Wat kan gedaan worden om risico op antibiotica resistentie te verlagen of verkomen?**

Probe: Wie (de regering, huisartsenvereniging, de patienten) moet actie nemen en wat voor interventies kunnen uitgevoerd worden?