Why do physicians prescribe antibiotics? An in-depth understanding of psycho-socio-cultural factors related to antimicrobial prescribing

A mixed-method approach

Master Thesis
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Abstract

Background: To prevent the development of antibiotic resistant bacteria, antibiotic prescribing should be kept low. This study revealed an in-depth insight of psycho-socio-cultural factors related to antimicrobial prescribing according to physicians in primary, secondary, and tertiary care.

Methods: A mixed-method approach was used. A systematic review was conducted using the electronic databases PubMed and Scopus, from 01-01-2000 till the date of search, which was 08-03-2023. To evaluate study quality and risk-of-bias, several checklists were used. The 'Reporting of Observational Studies in Epidemiology' (STROBE) checklist was used as a quality assessment tool and the 'Newcastle-Ottawa Scale' (NOS) was used as a risk-of-bias tool for cohort and observational studies. For the cross-sectional studies the 'Appraisal tool for Cross-sectional Studies' (AXIS) checklist was used as a quality assessment and risk-of-bias tool. For qualitative studies the 'Consolidated Criteria for Reporting Qualitative Research' (COREQ) checklist was used as a quality assessment tool and the 'Joanna Briggs institute' (JBI) as a risk-of-bias tool. Because of the prevalently qualitative nature of the literature outcomes, a narrative summary was chosen as the synthesis method. To get in-depth insight of the found factors and to validate the found information of the systematic review, in-depth qualitative interviews took place. For the interviews semi-structured interview guides were used. Two clinical microbiologists and 12 physicians who prescribe antibiotics on a regular base were purposively selected out of primary, secondary, and tertiary care. Rather than developing concepts and theories, the focus was to gain an in-depth understanding of the physicians' perspective; for this reason, a deductive approach was used. To gain insight into possible other factors that did not emerge from the systematic review, an inductive question was asked at the end of the interviews. Thematic analysis with a combination of semantic and latent approach was used for the analysis.

Results: 8,370 articles were identified, 58 of which met the inclusion criteria and were reviewed. Eventually, 32 articles, which included 23 different countries, were included in the systematic review, resulting in three main themes: 1) personal, 2) psychological, and 3) organisational factors. Personal factors included: 1.1) work experience, 1.2) knowledge and 1.3) use of guidelines. Psychological factors included: 2.1) uncertainty avoidance, and 2.2) perceived patient and/or parental pressure. Organisational factors included: 3.1) diagnostic tests and results, ease to follow up, ease of referral, and costs, and 3.2) time and work pressure. These themes were used as the basis for the semi-structured interviews. Two clinical microbiologists and five physicians out of primary, secondary, and tertiary care agreed to participate and were interviewed by the author. The theme 2.3) psychological distance, was further in-depth explored in the interviews and the theme 2.4) other factors, emerged from the interviews. Other factors included good communication between health care professionals and personal preferences of physicians.

Conclusion: The study identified several psycho-socio-cultural factors that are related to antimicrobial prescribing. Cultural differences (in health systems) play a role in these factors. The most important factor of this is uncertainty avoidance. Prescribing physicians feel the least uncertainty when their decision is supported by microbiology laboratory results, but some microbiology tests can be burdensome for the patient, so this is not always the solution. The CRP test, however, provides a good solution. Work experience and knowledge are important factors that helped to reduce uncertainty. So, to reduce uncertainty, it is both important to better educate physicians about antimicrobials during their initial training and to maintain knowledge while working. In addition to reducing uncertainty, it is also important to teach physicians how to manage uncertainty. When physicians experience less uncertainty and cope with it better, physicians will also experience less patient and/or parental pressure, which in turn may contribute to reducing potentially inappropriate prescribing (PIP). Lastly, it is important to give physicians enough time per patient to reduce time and work pressure and therefore may reduce PIP.

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1. Introduction

As one of the top global public health threats, antimicrobial resistance (AMR) is listed by the World Health Organisation [1]. AMR occurs when microorganisms are exposed to antimicrobials and develop resistance to them [2]. The health impact of antibiotic-resistant infections in Europe is similar to that of influenza, tuberculosis, and HIV/AIDS combined [3]. Every year, more than 35,000 people in Europe die from AMR [3]. The United Nations expect this to reach 10 million deaths worldwide by 2050, which is more than the combined death rate from all kinds of cancer [4, 5].

One of the main reasons for the development of AMR is the use of antibiotics (ABs). Antibiotics are drugs that inhibit the growth or unbalance cell wall synthesis of bacteria that cause infections. Antibiotics can be divided into narrow- and broad-spectrum antibiotics. Narrow-spectrum antibiotics focus on a specific group of (unwanted) bacteria and broad-spectrum antibiotics focus on multiple groups of bacteria, which may include useful bacteria [6]. Using antibiotics only makes sense if the infection is caused by bacteria. Bacteria belong to the microorganisms and are known to multiply rapidly. Bacteria are useful for intestinal function and fending off other bacteria, viruses, and fungi, among other things, but unknown bacteria can also cause infections [6]. Infections can also arise from resistant bacteria [6]. Sometimes the immune system causes resistant bacteria to disappear from the body, but through inappropriate use of antibiotics, resistance can be irreversible. When the body cannot clear the infection itself or control the spread of infection, access to the right antibiotic is critical for individual patients. However, any antibiotic use promotes antibiotic resistance, particularly taking antibiotics when they are not the right treatment, such as when antibiotics are prescribed for a viral infection or an inflammation. For these reasons, antibiotics must be used only when necessary and appropriate [2, 6-9]. For antibiotics that are being prescribed inappropriately, over-prescribed, or misused, the term 'potentially inappropriate prescribing' (PIP) is used. PIP occurs when antibiotics are prescribed unnecessarily, or when the wrong dose or duration is prescribed, as well as when an antibiotic is needed but the wrong antibiotic is prescribed [10].

As a result of an infection with antimicrobial-resistant microorganisms, there is a higher risk of severe illness, higher mortality rates, and longer hospitalization. This results in higher healthcare costs [7], despite a lower quality of care. It is important to note that in antibiotic resistance, the bacteria are resistant to (one or more) antibiotics, not the person [3]. When a bacterium is resistant to a large number of antibiotics, it is called multidrug-resistant bacteria. These bacteria can only be treated with a few types of antibiotics [6, 11]. Even in people who have never used antibiotics, bacteria can be resistant. This is because (resistant) bacteria are transmissible from person to person, through sneezing and/or coughing or by shaking hands with each other, for example. Besides, person-to-person, (resistant) bacteria can also be transmitted through direct contact with animals, food, and the environment [12]. As a result, antibiotic resistance is not limited to country borders but is a global problem.

1.2 Antibiotics in the Netherlands

In the Netherlands, about 200 people die each year because of antibiotic resistance [6]. This is relatively low compared to other countries in Europe. One of the reasons for this is that people in the Netherlands, unlike in some other countries, only receive antibiotics on a physician prescription. Still, there are gains to be made regarding antibiotic use in the Netherlands as well [13]. The Dutch Working Party on Antibiotic Policy (SWAB) aims to optimize antibiotic use to reduce antibiotic costs and other negative effects and control resistance development. The SWAB does this by, among other things, establishing national guidelines for antibiotic use, surveillance of antibiotic use and antibiotic resistance, and promoting research in the field of antibiotics [14]. In addition, the Ministry of Health Welfare and Sport started the regional approach to antibiotic resistance (AMR) in 2016. An important part of this approach was the establishment of ten regional AMR care networks, which through collaboration aim to improve knowledge and skills in infection prevention and antibiotic resistance and prevent antibiotic spread at

the regional level [15]. This current research was initiated by the “Antibioticaresistentie Zorgnetwerk Noord Nederland (ABRZNN)”, a regional AMR health care network of experts and physicians who strive to improve antibiotic prescribing in the northern part of the Netherlands. To develop an effective improvement program, it is critical to analyse the factors that influence appropriate antibiotic use, as interventions can only lead to better medical behaviour if they are well-tailored to the problems, the target group, and the environment in which the change must occur [16]. A successful improvement intervention must therefore understand and address the determinants of antimicrobial prescribing behaviour.

Antibiotics can be prescribed in various healthcare settings, this can be in primary, secondary, and tertiary care. Approximately 80–90% of all antibiotic prescriptions in the Netherlands are written in primary care [7]. Some general practitioners (GPs) prescribe antibiotics up to six times more frequently per 1,000 patients than other GPs, which factors cause this difference is still unknown [17]. However, it is known that it can be related to empirical prescribing, which refers to that an antibiotic may be prescribed if the physician believes the infection is bacterial based on the patient's symptoms and the physicians experience, but without the physician using a diagnostic tool or using it only after the antibiotics have been prescribed, and thus it is likely that interpersonal differences and characteristics of patient and physician play a role in this [18, 19]. Such factors already known from the literature to play a likely role are risk aversion, uncertainty avoidance, and patient demand [17, 20, 21]. These factors may play a role, but little is known about how physicians themselves think about this, which is why the ABRZNN wanted to look at these factors from the perspective of the prescribing physician. It is expected that physicians who are risk-averse dislike taking risks and therefore, are probably more inclined to PIP. Uncertainty avoidance is the degree to which an individual tries to cope with anxiety by minimizing uncertainty, and therefore they are expected to be less prone to PIP [22]. Patients who ask for antibiotics are prescribed them more often than those who do not explicitly request them [20, 23, 24]. This makes antibiotic prescribing a relevant topic to investigate how the prescribing physicians perceive these patient pressures and how this affects the prescribing physician’s behaviour. Also, there needs to be a better understanding of the perspective of the prescribing physician regarding the balance between non-medical reasons and medical reasons for prescribing or not prescribing antibiotics, as physicians want the best care for the patient and are often unaware of incorrect prescribing [20, 25].

1.3 Research question

This study was about psycho-socio-cultural factors that influence antimicrobial prescribing, including the potential role of the experience of patient pressure and the potential impact of uncertainty avoidance and risk aversion. To find these factors a mixed-method approach was used. Because there is already a lot of information available about antimicrobial prescribing, a systematic review is done to get an overview of the best available evidence. To investigate the psycho-socio-cultural factors, the following research question is defined: “*Which psycho-socio-cultural factors are related to antimicrobial prescribing according to physicians?”.* To get in-depth insight of the found factors and to validate the found information of the systematic review, in-depth qualitative interviews took place with two clinical microbiologists and five physicians. The participants work in the North-Eastern region of the Netherlands. The outcomes of this study will be used in practice by “ABRZNN”, as a starting point for further research to improve antibiotic use.

2. Systematic review method

A mixed-method approach was used to answer the research question. In this first method section, the systematic review is described and in the second method section the interviews are described.

2.1 Eligibility criteria

2.1.2 Study design

To develop this systematic review protocol, guidance regarding Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) was used [26]. To minimalize the risk-of-bias in the included studies only studies that are primary data sources were included. There was no restriction on the type of study of primary data sources.

2.1.3 Study characteristics

Studies about the vision, knowledge, attitude, and/or behaviour of physicians were included. The definition retained as physician in this study is "One who prescribes antibiotics on a regular basis in first-, second- or third-line care." Other healthcare disciplines, such as nurses were excluded. All physicians were accepted regardless of their age, gender, or ethnicity. Only studies that were written in English or Dutch were included in the literature search. The time restriction that was used during the search was from 01-01-2000 till the date of the search, which was 08-03-2023. This relatively narrow time restriction was chosen because nowadays there is more shared decision making and patients now go to the physician with a different attitude/expectation than before, which may be related to PIP [24].

2.1.4 Settings

Because economic and cultural differences play a role in antibiotics, only studies that were conducted in Europe, including the Netherlands were included in the search [27]. Studies that were conducted in general practice, hospital or, inpatient settings were included. Other healthcare settings were excluded, such as studies that included healthcare professionals working in dentists, pharmaceutical or residential settings. For general practitioners, the definition of General practitioner [28] was used in this systematic review “A general practitioner is the medical specialist the patient goes to first when he or she has a complaint, illness or condition”. The definition that was used for inpatient settings was “Inpatient setting means an institution; licensed in the state in which it is located, which includes a short-term hospital, general, a chronic and convalescent nursing home, or a short-term hospital, special, hospice” [29]. For hospital setting the following definition was used “hospital, an institution that is built, staffed, and equipped for the diagnosis of disease; for the treatment, both medical and surgical, of the sick and the injured; and for their housing during this process” [30].

2.1.5 Other exclusion criteria

Articles were also excluded if they were only about:

- Medical reasons for prescribing antibiotics
- The patient’s perspective on antibiotic prescribing
- The prescription of drugs other than antibiotics
- Antibiotics for animals or agriculture
- Veterinarians prescribing antibiotics
- Telephonic prescriptions for antibiotics
- Out-of-office prescriptions of antibiotics
- Measuring the effect of an intervention
- Nurse prescribers of antibiotics

Articles were also excluded when they were from low quality or had a high risk-of-bias, see sections 2.4.2.1 and 2.7 for further explanation. For an overview of the inclusion and exclusion criteria, see appendix A.

2.2 Information sources

The systematic review was conducted in electronic databases. A uniform search strategy was developed and used in the different databases. The electronic databases that were used in this systematic review were PubMed (01-01-2000 to 08-03-2023) and Scopus (01-01-2000 to 08-03-2023). These databases were chosen because PubMed has references to medical scientific articles and Scopus is a more general database. Due to the time constrains, no authors were contacted when information was missing or unclear in a paper.

2.3 Search strategy

First, appropriate keywords were searched for each element, these keywords were placed in a table, see table A. Then synonyms for the keywords were searched for and added to the table. To ensure that the keywords and synonyms searched were complete, both an information specialist, as well as two clinical microbiologists assessed the search terms. The final keywords and synonyms resulted in the following search string: (((((antibiotic* OR antimicrobial* OR antibacterial OR antifungal OR "anti-bacterial" OR "anti-biotic*" OR "anti-microbial*" OR "anti-fungal")) AND (risk-avers* OR "uncertainty avoidan*" OR "inappropriate* withholding" OR prescrib* OR prescrip* OR treat*) AND (determinant* OR predictor* OR factor* OR influenc*) AND (Netherland* OR Dutch OR "the Netherlands" OR Europe))))

Table A
Keywords and synonyms for the search term

Antibiotics	antibiotic* OR antimicrobial* OR antibacterial OR antifungal OR "anti-bacterial" OR "anti-biotic*" OR "anti-microbial*" OR "anti-fungal"
Potentially inappropriate prescribing	risk-avers* OR "uncertainty avoidan*" OR "inappropriate* withholding" OR prescrib* OR prescrip* OR treat*
Netherlands	Netherland* OR Dutch OR "the Netherlands" OR Europe

2.4 Study records

2.4.2 Data management and selection process

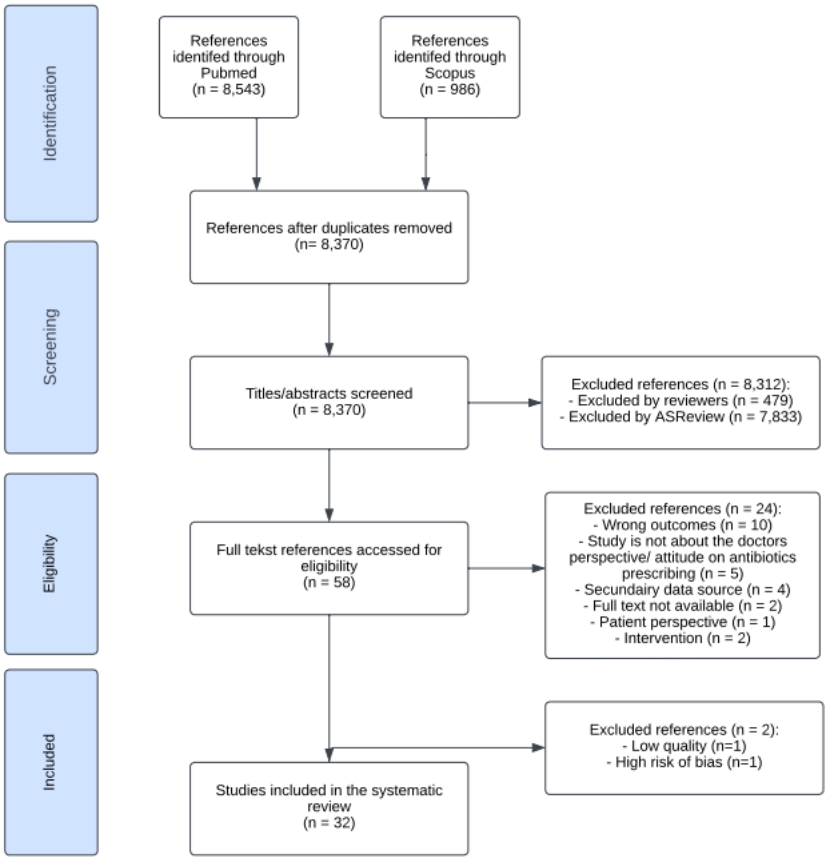
The search term resulted in 8,543 PubMed and 986 Scopus hits. Because of this large number of hits, it was decided not to make use of snowballing (identifying additional references from using reference lists from references). Also, because of this large number, it was decided to download the found references from the databases in the software ASReview LAB v1.2. ASReview LAB is a software that uses active learning to make reviewing much faster through artificial intelligence (AI). The first step of ASReview was to select the settings for the active learning model, the default settings were used because of their excellent performance [31]. Before the screening began, duplicates were removed through Covidence and an algorithm in ASReview. Based on prior knowledge on five papers for which it was indicated by two independent researchers if they were relevant and five papers indicated to be irrelevant by two independent researchers, ASReview ensures that potentially relevant articles are presented first, and potentially irrelevant articles presented last. To ensure that both reviewers trained the same active learning model, both reviewers selected the same articles as prior knowledge. The final decision on whether an article was relevant or not remained the reviewer's choice. ASReview LAB v1.2 was used for the first-stage screening.

In the first-stage screening of the systematic review titles and abstracts were screened using the inclusion and exclusion criteria by two independent reviewers (CL and NB). Since the probability of

potentially irrelevant articles increases the more articles one has screened, a stopping rule was formulated. In this review, the data-driven strategy was used and the stopping rule was when the reviewers excluded 100 articles in a row [31]. To demonstrate the reliability and the level of agreement between the two independent reviewers, Cohen's kappa was calculated [32]. 43 studies were approved by both reviewers without consultation. Differences of opinion between the two reviewers on the remaining articles were resolved by consultation and a mutual agreement was reached. Finally, 58 articles were marked as potentially relevant.

After this, the 58 potentially relevant references were transported to Covidence. Covidence is a tool that can help make the various steps of a systematic review, such as screening and data collection, more efficient [33]. Covidence was used to screen the full text of the collected studies. See figure A, for the PRISMA flowchart.

Figure A
PRISMA flowchart



2.4.2.1 Quality of the evidence

Each publication was evaluated based on a quality assessment checklist for the different study designs. The quality was assessed by one reviewer. For cohort and observational studies, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was used. The STROBE checklist is not primarily a tool for assessing the quality of a cohort study, but it can be used to determine whether a reference meets STROBE recommendations. The STROBE checklist was chosen because the completeness of the checklist allowed the quality of the reference to be assessed. The checklist consists of 22 items, which cover several domains such as (1) introduction, (2) methods, (3) results, (4) discussion, and (5) funding and sponsorship [34].

The quality of the cross-sectional studies is evaluated by using the Appraisal tool for Cross-Sectional Studies (AXIS) checklist. There was chosen for this tool because the tool focuses primarily on the presented methods and results, such as the representativeness of the sample, the reliability and

validity of the measurement instruments, and the description of possible confounders. By using this tool, systematic interpretation of cross-sectional studies can be simplified and quality judgments about the study can be made. The checklist consists of 20 questions, which cover several domains such as (1) introduction, (2) methods, (3) results, (4) discussion, and (5) other [35].

For qualitative studies, the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist was used. This checklist was selected because the checklist allows assessment of the transparency, accuracy, completeness, and credibility of the reference. The COREQ checklist consists of 32 questions, which cover several domains such as (1) research team and reflexivity, (2) study design, and (3) analysis and findings. When some information was not reported in the references N/A was noted in the checklist [36].

2.4.3 Data collection process

For the data extraction, the standard data extraction form of Covidence was personalized [37]. The personalized extraction form was pilot tested with four studies, based on which the form was modified to its final version. The data collection process was done by one researcher. The data abstraction form can be found in appendix B.

2.5 Data items

The data that were extracted were (1) General information (Study ID, title, abstract, lead author contact details, publishing data, and country in which the study is conducted), (2) Methods (aim of the study, study design and start and end date), (3) Participants (total number of participants invited, total number of participants participate, how many participants were excluded and why, in which setting took the study place, population description, inclusion criteria, exclusion criteria, method of recruitment of participants, method to conduct the interviews / questionnaires), (4) Analysis (which method is used for analysing), (5) Results (main outcomes, outcome table (determinant, target population, for which disease, relating to, significant effect, mean, confidence interval, percentage) and discussion outcomes), (6) Other (study funding sources, possible conflicts of interest and ethical approvement).

2.6 Outcomes and prioritization

The primary outcomes of the systematic review were factors that are related to antimicrobial prescribing, such as antibiotic prescribing, adherence to antimicrobial treatment guidelines, and the impact of psychological influences on prescribing practices. In addition, cultural differences were examined as secondary outcomes. This includes understanding the influence of cultural factors on antimicrobial prescribing practices, such as beliefs and behaviours related to antimicrobial use.

2.7 Risk-of-bias in individual studies

Different risk-of-bias checklists were used, because of the different study designs. The risk-of-bias checklists were assessed by one reviewer. For cohort and observational studies, the Newcastle-Ottawa Scale (NOS) was used. The NOS was used because the NOS can evaluate both methodological validity and reporting quality in combination with the STROBE checklist and was the best fit for the studies found. The NOS consists of 8 questions, which cover several domains such as (1) selection, (2) comparability, and (3) outcome [38]. For the cross-sectional studies, the AXIS checklist was used. The AXIS checklist can be used as a quality assessment tool as well as a risk-of-bias tool. There was chosen for the AXIS, because of the broad coverage of bias domains and simplicity of use [35, 39]. The Joanna Briggs Institute (JBI) checklist was used for qualitative studies. There was chosen for the JBI checklist because JBI is assessing various aspects such as the risk-of-bias in its design, conduct, and analysis [40].

2.8 Data synthesis

Because of the prevalently qualitative nature of the literature outcomes, a narrative summary was chosen as the synthesis method. With qualitative findings presented in the included studies, a narrative summary provides an appropriate method for capturing and presenting the key themes, patterns, and insights [41]. By using this method, qualitative information is synthesised descriptively and cohesively, making it possible to gain a deeper understanding of the research issue. Study findings and themes were extracted from the identified studies during the synthesis process. Careful analysis of the data revealed similarities, differences, and recurring patterns.

3 Results systematic review

The calculated Cohen's kappa was 0.70, showing that there was substantial to good agreement between the two reviewers in the first stage screening, see appendix C for the calculation.

3.1 Overview of the included studies

Of the 58 potentially relevant articles, 24 were excluded due to the exclusion criteria. Another 2 studies were excluded due to low quality and/or high risk-of-bias. Finally, 32 articles, which originated from 23 different countries, were included in the systematic review. What is noteworthy about the demographic distribution of the included literature is that the studies were conducted mainly in Western Europe and almost no studies were conducted in Eastern Europe, see figure B for the demographic distribution of the frequency that a country is included in the articles used and appendix D for the discontinuous distribution of the frequency that a country is included in the articles used. The study designs that were included were; cross-sectional [42-53], observational [54, 55], qualitative [56-72], and cohort [73] studies. 18 articles were related to primary care [44, 46, 47, 53, 55, 57, 59-63, 65-67, 70-73], four to secondary care [56, 58, 64, 69], one to tertiary care [54], two to primary- and second-line care [49, 50, 68], four to second- and third-line care [43, 45, 51, 52], and two related to all care settings [42, 48]. 21 articles were about AB prescribing in general [42-45, 48, 49, 52, 54, 56-60, 62, 63, 65, 66, 68, 69, 71, 73], six were about AB prescribing by respiratory tract infection (RTI) [46, 50, 53, 67, 70, 72], two were about AB prescribing for upper respiratory tract infections (URTI) [47, 51], one was about AB prescribing for acute respiratory tract infections (ARTIs) [61], one was about AB prescribing for urinary tract infections (UTI) [64], and one was about AB prescribing for acute otitis media (AOM), acute sore throat, rhinosinusitis, and acute cough [55]. See table B for the summary of the characteristics of the included studies and appendix E for the article data.

Figure B
The demographic distribution of the frequency that a country is included in the articles used

*Footnote: *n exceeds total amount of papers, as some were executed in multiple countries.*

Table B

Summary of characteristics of included studies.

Author	Settings	Illness	Physicians	Male/female	Mean age	Mean years of experience	Determinants mentioned
Salm F, et al.	Primary care	General	340	128/212	51.9	16.7	Use of guidelines, perceived patient and/or parental pressure, and time and work pressure
Björkman I, et al.	Primary care	General	20	13/7	N/A	N/A	Perceived patient and/or parental pressure, time and work pressure, and organisational factors
Teixeira Rodrigues A, et al.	Primary care	General	421	207/214	55	N/A	Knowledge, perceived patient and/or parental pressure, and time and work pressure
Poss-Doering R, etl al.	Primary care	General	27	18/9	N/A	26	Work experience, use of guidelines, and uncertainty avoidance
Petursson P, et al.	Primary care	General	16	13/3	N/A	N/A	Work experience, uncertainty avoidance, perceived patient and/or parental pressure, and time and work pressure
Simpson SA, et al.	Primary care	General	40	29/11	N/A	N/A	Knowledge
Brookes-Howell L, et al.	Primary care	General	80	47/33	43	16	Knowledge and time and work pressure
van der Zande MM, et al.	Primary care	General	41	18/23	N/A	N/A	Work experience, uncertainty avoidance, perceived patient and/or parental pressure, and time and work pressure
Vazquez-Lago JM, et al.	Primary care	General	33	19/14	N/A	N/A	Work experience, knowledge, use of guidelines, uncertainty avoidance, and perceived patient and/or parental pressure
Björnsdóttir I, et al.	Primary care	General	10	8/2	48	N/A	Work experience, knowledge, use of guidelines, uncertainty avoidance, perceived patient end/or parental pressure, and time and work pressure

Ryves R, et al.	Primary care	General	32	N/A	N/A	N/A	Work experience, Use of guidelines, uncertainty avoidance, perceived patient and/or parental pressure, and time and work pressure
Strandberg EL, et al.	Primary care	RTI	13	3/10	N/A	N/A	Knowledge and use of guidelines
Ciofi degli Atti ML, et al.	Primary care	RTI	2151	N/A	N/A	N/A	Perceived patient and/or parental pressure
Horwood J, et al.	Primary care	RTI	22	5/17	N/A	N/A	Uncertainty avoidance and time and work pressure
Akkerman AE, et al.	Primary care	RTI	84	57/27	N/A	16	Work experience and Knowledge
Rousounidis A, et al.	Primary care	URTI	33	22/11	N/A	N/A	Knowledge and perceived patient and/or parental pressure
Dekker AR, et al.	Primary care	AOM, acute sore throat, rhinosinusitis, and acute cough	48	N/A	N/A	N/A	Work experience and use of guidelines
Saliba-Gustafsson EA, et al.	Primary care	ARTIs	20	14/6	52	26	Work experience, knowledge, perceived patient and/or parental pressure, and organisational factors
Charani E, et al.	Secondary care	General	10	N/A	N/A	N/A	Work experience and knowledge
De Souza V, et al.	Secondary care	General	22	14/8	N/A	N/A	Work experience, knowledge and use of guidelines
Schouten JA, et al.	Secondary care	General	18	8/10	34.5	N/A	Use of guidelines, uncertainty avoidance, and organisational factors
Eyer MM, et al.	Secondary care	UTI	21	N/A	N/A	N/A	Work experience, uncertainty avoidance, and time and work pressure

Sikkens JJ, et al.	Tertiary care	General	150	N/A	N/A	N/A	Work experience and knowledge
Velasco E, et al.	Primary care and secondary care	General	3,492	2,222/1,200	N/A	N/A	Knowledge and uncertainty avoidance
Thomas H, et al.	Primary care and secondary care	General	21	N/A	N/A	N/A	Use of guidelines, uncertainty avoidance, and time and work pressure
Moro ML, et al.	Primary care and secondary care	RTI	633	244/389	48	17	Uncertainty avoidance and perceived patient and/or parental pressure
Geitona M, et al.	Secondary care and tertiary care	General	275	97/178	37.2	N/A	Uncertainty avoidance and organisational factors
Beović B, et al.	Secondary care and tertiary care	General	2,366	883/1483	N/A	N/A	Work experience and uncertainty avoidance
Simões AS, et al.	Secondary care and tertiary care	General	30	13/17	30	N/A	Work experience, use of guidelines, perceived patient and/or parental pressure, and organisational factors
Grossman Z, et al.	Secondary care and tertiary care	URTI	685	359/326	50.9	N/A	Uncertainty avoidance
Lévin C, et al.	Primary care, secondary care, and tertiary care	General	641	281/360	N/A	N/A	Knowledge, work experience, and use of guidelines
Spernovasilis N, et al.	Primary care, secondary care and tertiary care	General	214	86/128	30.1	4.6	Knowledge and perceived patient and/or parental pressure

Footnote: respiratory tract infection (RTI), upper respiratory tract infection (URTI), acute respiratory tract infections (ARTIs), urinary tract infections (UTI) and acute otitis media (AOM). When information was not reported in the references N/A was noted.

Most studies defined inappropriate prescribing as too many prescriptions or prescribing inconsistent with guidelines, but often no definitional criteria were given [44, 48, 52, 53, 62-65, 68, 70, 71]. Only the studies of Lévin, et al. [42] and Sikkens, et al. [54] has differentiated inappropriate antibiotics in their study using several criteria. The factors found were divided into: 1) personal factors, 2) psychological factors, and 3) organisational factors.

3.2 Personal factors

The personal factors that were found were: 1.1) work experience, 1.2) knowledge, and 1.3) the use of guidelines. Each of these will be elaborated upon below.

3.2.1 Work experience

The amount of work experience was often mentioned as being related to antibiotic prescribing [42, 43, 45, 54, 56-64, 72]. Physicians often use their own experience when deciding whether to prescribe antibiotics or not [42, 43, 56-59]. Beović, et al. [43] and Lévin, et al. [42] conducted a cross-sectional study with 2366 and 612 young physicians, the studies concluded that 42% and 36.1% used their own experience when deciding whether to prescribe antibiotics or not. Physicians with more experience tend to prescribe less antibiotics [45, 54, 60-64]. Although one study of Akkerman, et al. [46] found the opposite, with GPs with more experience, prescribing more antibiotics than GPs with less experience, especially in combination with little knowledge and the feeling of time pressure. Finally, Salm, et al. [44] described that GPs with more than 25 years of work experience assumed less influence on AMR than their colleagues with less than 7 years of experience (95% CI [0.17-0.62], P < 0.001).

3.2.2 Knowledge

Besides work experience, knowledge was also often mentioned as an important determinant that physicians used in deciding to prescribe antibiotics [42, 46, 47, 54, 56-58, 61, 65-67, 73]. Physicians with high levels of education and junior physicians with good perceptions of antibiotic knowledge were more likely to explain appropriate practices related to adverse events by 3.71 times (95% CI [2.09-6.61]) and 1.70 times (95% CI [1.11-2.58]) [42]. So, to prescribe antibiotics correctly, prescribers must be aware of antibiotic prescribing and resistance, but often physicians lack knowledge of this [46, 47, 54, 56, 57, 65]. In the study of Simpson, et al. [65], only a few GPs suggested they need to update their microbiology knowledge and antibiotics prescriptions. Physicians did see antibiotic resistance as a global problem, but several studies had shown that around only 70% (239/340, 162/214, 2444/3492) saw it as a problem in their workplaces [44, 48, 49]. Some studies stated that antibiotic prescribing was influenced by a hierarchical system and that the behaviour and/or knowledge of senior physicians were adopted by junior physicians [56, 58, 59]. In addition to knowledge about correct antibiotic prescribing and resistance, knowledge of existing prescribing guidelines was also important [67].

3.2.3 Use of guidelines

Using guidelines was also mentioned as a determinant that plays a role in the antibiotic prescribing behaviour of physicians [42, 44, 45, 55-57, 62, 67, 68, 72], the use of guidelines can help reduce unnecessary antibiotic prescribing [57, 68]. Most physicians stated that they follow the guidelines [42, 45]. Although guidelines exist, physicians recognized that prescribing antibiotics is often a subjective process [68]. Sometimes physicians made their own ‘guidelines’ instead of using local or national guidelines or they used the guidelines only to decide which antimicrobial to use [59, 68]. A Dutch study showed that physicians did not always agree with the guidelines [69]. Salm, et al. [44] stated that the use of guidelines among GPs under 40 was greater than that of GPs over 60 (OR 3.97, 95% CI 1.32–11.91; P = 0.001). This statement is consistent with the statement of Thomas, et al. [68] that contradicting guidelines were more likely to be mentioned by senior clinicians than by junior clinicians.

3.3 Psychological factors

In addition to physician-focused factors, psychological factors were also identified as determinants of AB prescribing. The definition of psychological factors that has been retained in this study is “Traits and behaviours that are to be derived from people's personality traits”. The most mentioned psychological

determinants were: 2.1) uncertainty avoidance, and 2.2) perceived patient and/or parental pressure. Each of these will be elaborated upon below.

3.3.1 Uncertainty avoidance

Uncertainty avoidance was often mentioned as an important psychological determinant [43, 50, 51, 57, 59, 62, 63, 68, 72]. The articles defined uncertainty avoidance as the fear, anxiety, and overcautiousness about leaving a bacterial infection untreated and/or developing complications [57, 64, 68]. More experience and more/better knowledge provided more confidence in deciding whether antibiotics were appropriate or not, but physicians felt the most confident when their decision was supported by microbiology laboratory results [45, 59, 60, 63, 64, 66, 70]. More confidence can help to reduce diagnostic uncertainty among physicians [66]. Uncertainty can lead to discomfort for physicians [59, 66]. Due to the discomfort and uncertainty avoidance, physicians prescribed antibiotics to be on the safe side or prescribed broad spectrum antibiotics to be sure that the infection of the patient was cured [49, 69]. Another method used by some physicians to deal with uncertainty was delayed prescriptions [57, 61, 62, 70, 72]. In the study of Salm, et al. [44] 44% (151/340) of the GPs stated that when it was just before the weekend and it was uncertain how an infection would progress, an antibiotic was prescribed without a strong indication. However, the study of Geitona, et al. [52] stated that 74% of the physicians never or barely felt uncertainty.

3.3.2 Perceived patient and/or parental pressure

How the physician experiences patient pressure is person-dependent [66]. Many of the included studies found that some physicians experienced conflicts when they don't prescribe antibiotics, which impacts the doctor-patient relationship [44, 47, 53, 59, 60, 63, 64, 66, 68, 70, 72]. While other studies stated that physicians were not influenced by patient pressure and dissatisfaction [53, 61, 73]. To maintain a good doctor-patient relationship, physicians sometimes used delayed prescription [70]. The study of Ciofi, et al.[53] stated that in 77.1% (611/792) cases, paediatricians said they were not influenced by parents' expectations. Despite this statement, the same study found that the relative risk (RR_{adj}) of getting antibiotics, when parents were seen as "somewhat" expecting was 2.2 compared to parents who were seen as not expecting [53]. However, parent demand is not always perceived correctly [50]. Another cross-sectional study that is conducted in Italy with paediatricians found that in 24% of cases, paediatricians thought parents were expecting antibiotics when they were not [50]. Finally, better knowledge among patients/parents may lead to less demand for antibiotics [57, 61]. The disparate results may be explained by the fact that perceived patient and/or parental pressure is often subjective [66, 68].

3.4 Organisational factors

The organisational factors that came out of the literature study were: 3.1) diagnostic tests and results, ease to follow up, ease of referral, and costs [45, 61, 69, 71], and 3.2) time and work pressure.

Sometimes there was no access to diagnostic tests or it takes 3 to 5 days before the test results become available, which could be even longer due to weekends [45, 69]. Björkman, et al. [71] stated that antibiotics were prescribed more often to keep control, as a result of the inability to follow up on patients, what causes the inability wasn't mentioned in the paper. Simões, et al. and Geitona, et al. [45, 52] stated that the cost of antibiotics wasn't taken into account by deciding whether to prescribe antibiotics or not.

3.4.1 Time and work pressure

The most mentioned organisational factor that can play a role in prescribing antibiotics was time and work pressure [44, 59, 60, 63, 64, 66, 68, 70-73]. According to Teixeira, et al. [73] physicians in the emergency room were more likely to prescribe antibiotics incorrectly due to high work pressure (95% CI [0,16 – 0,54] $p < 0,05$), which is consistent with the outcomes of Strandberg, et al. [67]. The results of Teixeira, et al. [73] also show that with a decrease of one patient per day, the probability of being a good prescriber

increased by 3% (OR [95% CI] = 0.97 [0.94-1.00]; p < 0.05). Physicians namely report that prescribing antibiotics was easier and faster than explaining why antibiotics were not given [60, 63, 64, 68, 70]. Because of time pressure and fatigue, some physicians choose the fastest and easiest way for them, which results in prescribing more antibiotics than is medically necessary. Time and work pressure were mentioned as important determinants in not talking to the patient about AMR and educating the patient about it (172/340) [44, 71, 72]. There was also a lack of time for many GPs to discuss problems with their colleagues [59]. In contrast to physicians opinions, the study of Rousounidis, et al. [47] showed that most parents (90%) found that the physician spend enough time explaining their choice of not prescribing and the parents believed that they were well informed about this choice.

The factors found in the literature were divided into: 1) personal factors, 2) psychological factors, and 3) organisational factors. Personal factors were further divided into: 1.1) work experience, 1.2) knowledge, and 1.3) use of guidelines. Psychological factors were further divided into: 2.1) uncertainty avoidance, and 2.2) perceived patient and/or parental pressure. Organisational factors were further divided into: 3.1) diagnostic tests and results, ease to follow up, ease of referral, and costs, and 3.2) time and work pressure. Interviews were used to gain an in-depth understanding of these factors.

4 Interviews method

In this second method section of the mixed-method approach, the method section of the interviews was described.

4.1 Study design

To maintain the natural flow of the conversation and to get an in-depth insight of the found determinants, semi-structured interviews were conducted [74]. The semi-structured individual interviews were conducted with primary, secondary and tertiary care prescribers including physicians and clinical microbiologists working in the Northeaster Netherlands. Clinical microbiologists were included in the study to see if their findings agree with the physicians statements.

4.2 Materials

To capture the key elements of the interview, two interview guides were developed, one interview guide for the clinical microbiologists, see appendix F, and one for the physicians, see appendix G. To understand the factors that influence healthcare practices, the interview guides were loosely based on elements of a similar study, the Theoretical Domains Framework (TDF), and on a study about psychological distance [25, 74, 75]. The TDF was used as a guide for questions about behaviour change [74]. The similar study was used as an example for a semi-structured interview guide on antibiotics and the study on psychological distance was used to help create questions to see if there is psychological distance to the subject of AMR [25, 75]. In addition to assisting in interviewing with little experience, the interview guide ensured that the same topics were covered across all interviewers. The interview guides were pilot tested by the author. A second researcher checked the interview guides to ensure the construct validity and to make sure the interview guides are detailed enough [76]. The interviews were conducted from 11-05-2023 till 16-06-2023. To ensure consistent quality and internal validity, all interviews were one-to-one performed by the same researcher. Interviews with four physicians and two clinical microbiologists were conducted online using Microsoft Teams. The other physician was interviewed face-to-face in his practice. The duration of the interviews was between 20 till 45 minutes. To ensure ecological validity, body language was also considered when interpreting the statements [76]. Participants received no compensation for participating in this study.

4.3 Recruitment of participants

Purposive sampling was used for the requirement of the participants. It was decided to include also physicians from the eastern Netherlands for the study since recruiting physicians was difficult. Two clinical microbiologists and 12 physicians were contacted through email. Both clinical microbiologists agreed and of the 12 physicians, five agreed to participate in the study. Of those who did not respond, three indicated they did not have time to participate, while the others gave no reason. The inclusion criteria for the clinical microbiologists were: 1) working in North-eastern Netherlands, 2) working as a clinical microbiologist, and 3) speaking the Dutch language. The inclusion criteria for the physicians were: 1) being a physician who prescribes antibiotics regularly, 2) working in North-eastern Netherlands, 3) working in general practice or a hospital, and 4) speaking the Dutch language. All participants were informed that participation in the interviews was voluntary and that they were able to withdraw at any moment without explanation.

4.3.2 Ethical approval and informed consent

The study was reviewed and approved by the ethics committee of the Faculty of BMS (domain Humanities & Social Sciences) at the University of Twente (request number: 230712). Identifiable information was removed and all transcripts were anonymised before data analysis. Each participant was referred to by a random number. To demonstrate the source of quotes, participants' numbers were shown alongside quotes. One participant did not permit to use the quotes from the interview. All participants gave written informed consent before the start of the interviews. See appendix H for the informed consent form.

4.4 Analysis

All interviews were audio recorded with the permission of the participants and were imported into Amberscript. Amberscript is a professional transcription service that transcribes recorded audio [77]. To ensure the privacy of the participants, the audio recording was not started until the start of the questions. The author manually checked the transcriptions for accuracy and made adjustments or additions if necessary. After transcribing, ATLAS.ti was used to help with coding the data. Rather than developing concepts and theories, the focus was to gain an in-depth understanding of the physicians' perspective; for this reason, a deductive approach was used. However, because it emerged from the systematic review that not every physician feels the same level of commitment to AMR, deductive questions were also asked to see if physicians felt psychological distance toward AMR. An inductive question was also asked at the end of the interviews, to gain insight into possible other factors that did not emerge from the systematic review. The codes were thus categorized according to the themes that emerged from the systematic review, with the exception of the codes for the psychological distance questions and the final inductive question. Therefore, the author manually coded the data. Thematic analysis with a combination of semantic and latent approach was used for the analysis. By using thematic analysis, a structured framework could be applied to analyse the data and discover similarities and underlying meanings [78]. The added quotes have been translated into English.

5 Results interviews

Five physicians and two clinical microbiologists were recruited. Of these, 5 were male and 3 were female. Three physicians worked as general practitioners in the eastern Netherlands and two physicians, as well as the clinical microbiologists, worked in the UMCG in the northern Netherlands. Two participants had 10-20 years of work experience, four participants 20-30 years, and one participant had more than 30 years of work experience, see table C for the distribution of the participants.

Table C
Distribution of participants

Category	Variables	n
Gender	Female	2
	Male	5
Profession	Clinical microbiologist	2
	General practitioner	3
	Physician in the hospital	2
Location	Urban	7
	Rural	0
Years since qualification	10-20	2
	20-30	4
	>30	1

5.1 Personal factors

The personal factors: 1.1) work experience, 1.2) knowledge and 1.3) use of guidelines that emerged from the systematic review were validated and an in-depth understanding was gained through the interviews. Each of the personal factors will be elaborated upon below.

5.1.1 Work experience

Physicians indicated that work experience contributes to the correct use of antibiotics *"Consensual use of antibiotics is better if you are a bit more experienced*" (physician 2, GP) and "*That the people with more experience, make that decision [wait-and-see policy] easier than the people with less experience"* (physician 5, hospital). Clinical microbiologists agreed that they indicated that they noticed how much experience the physician in question has *"It is true that the more experience a specialist has, the more he or she knows about it and what you notice clearly"* (clinical microbiologist 1) and *"If someone is a beginner, or doesn't get enough supervision or doesn't dare to ask, you see that very clearly"* (clinical microbiologist 2). However, some physicians did indicated that more work experience may also lead to more risk avoidance, having seen cases where withholding antibiotics did not turn out well *"Maybe experience plays a role, if you see things go wrong a few times it can influence your decision"* (physician 2, GP). The physicians indicated that experienced physicians can influence the prescribing behaviour of novice physicians *"Yes, because you are more confidence than when you are just getting started"* (physician 4, GP), but that it also depends on how many years of work experience the novice physician already has. At the same time, novice physicians can influence the prescribing behaviour of experienced physicians by asking critical questions *"People being educated are asking critical questions about my policies, and that includes adjusting my policies, certainly happens from time to time"* (physician 3, GP).

5.1.2 Knowledge

Clinical microbiologists felt that the topic of antibiotic resistance is understudied in physician training *"I think in a general sense you could say that both in the training, in the medical studies, but also in the continued specialization, quite a bit more attention could be paid to microbiology in general and antibiotic resistance and prescribing in particular"* (clinical microbiologist 1) and *"It's not just about resistance and that's even more complex but resistance is one of the parts of it, and that certainly for medical studies is fairly understudied"* (clinical microbiologist 2). Physicians themselves felt that they did know about antibiotics (resistance), but at the same time also indicated that they didn't know everything about it *"In the prescription what, why and how? Maybe so, but what kinds of antibiotics, I think I could have another update on that, of what kinds are out there"* (physician 4, GP) and *"Our knowledge on that [antibiotic (resistance)], it could always be better, because I wouldn't know when I last had any after/refresher training on that*" (physician 3, GP). The physician indicated that patients lack knowledge about antibiotics, but that it is not feasible to teach patients about this and that the focus

would be better on educating physicians, while another physician indicated that more information should be made available to patients on the internet. According to the clinical microbiologists and the physicians, more knowledge by physicians can help reduce perceived pressure from patients and/or parents *"So both general practitioners, paediatricians who do well with infectious diseases and with antibiotics, they won't be so easily persuaded"* (clinical microbiologist 1) and *"So yes, the more knowledge you have, the better you can also explain and justify your policy"* (physician 3, GP). The physicians said they liked getting up-to-date resistance figures and indicated that this can help with the proper use of antibiotics and although GPs already have this information available to them one GP did not use these figures *"But you all think you're doing quite nicely and that you're not prescribing that much, but if I'm prescribing on average twice as much as the rest, it's not because of my patient population, it's because of my prescribing habits. So I would put a lot of value on those numbers actually, but why don't I ask for them [actual numbers]? No, I haven't done that yet"* (physician 3, GP). Another GP indicated that he found up-to-date figures difficult "*Yes, I do that [looking at up-to-date figures] annually. Do I like that, yes, but I also find it difficult, because then I don't really know whether I should compare it positively or negatively"* (physician 4, GP).

5.1.3 Use of guidelines

Clinical microbiologists believed that physicians use the guidelines, but it depends on their knowledge of the guidelines and their workload "*That booklet [i.e. a brief version of antibiotics prescribing guidelines] is consulted a lot for sure, although we also run into the fact that we are therefore called at night by an assistant and sometimes also by a staff member and we notice very clearly in that conversation, that they have not looked in the booklet, but yes sometimes they [physicians] also find it very easy to just collect some information from all sides and not look up a booklet in the computer themselves or that they just have the booklet in the pocket and in the jacket"* (clinical microbiologist 1). It is person dependent on how physicians handle the guidelines. A hospital physician said she didn't deviate from them if used, while the other hospital physician and the GPs said they deviated from them if necessary, provided the deviation could be substantiated. The reason for deviating from the guidelines by GPs is that the guidelines for GPs are different from those of hospital physicians. GPs knew that if they were to refer the patient to the hospital they would be given an antibiotic there according to hospital guidelines *"But sometimes you do have people who can't get through [the guideline], I send them there to an ENT [ear, nose and throat] physician, then they get antibiotics right away. So in some cases you think well, okay I can refer [to the hospital], but I can also first say we're going to try those antibiotics*" (physician 2, GP). Most of the physicians agreed that the guidelines contained accurate information, although one physician did question the scientific basis of the guidelines. The other physician indicated that she does not always agree with the guidelines *"No, I do not always fully support the guidelines. I think those [guidelines] are a bit behind the times often here in the Netherlands"* (physician 4, GP). One clinical microbiologist indicated that novice physicians often do not know about the existence of guidelines, while another clinical microbiologist indicated that novice physicians often use the guidelines. The physicians themselves also indicated that early career physicians make more use of guidelines compared to experienced physicians *"GPs in training, they're trying to get a handle on their work and these guidelines, yeah, that's kind of like a cookbook … so that just tells you"* (physician 2, GP).

5.2 Pyschological factors

The psychological factors: 2.1) uncertainty and 2.2) perceived patient and/or parental pressure, that emerged from the systematic review were validated and an in-depth understanding was obtained through the interviews. The theme 2.3) psychological distance, was further in-depth explored in the interviews. Each of the psychological factors will be elaborated upon below.

5.2.1 Uncertainty avoidance

The clinical microbiologists indicated that there is always uncertainty in medicine and that physicians find it difficult to deal with the uncertainty *"There is always uncertainty and how big it is, that varies with the degree of certainty"* (clinical microbiologist 2) and "*We as humans are not good at dealing with uncertainty and in medicine anyway*" (clinical microbiologist 2). This is in agreement with the statements of the physicians "*So to deal with that uncertainty, that takes years and experience and then you can call yourself confident, but really you're just good at handling an uncertain factor in our profession"* (physician 2, GP) and *"You often tend to give more broad-spectrum antibiotics than are actually needed"* (physician 5, hospital), however, some physicians do indicate that they experience little uncertainty these days *"I'm not so much insecure. It's more that I don't always know exactly, that may be, but then I discuss*" (physician 4, GP). When physicians experience uncertainty of the diagnosis made, both hospitalists and GPs exceptionally use delayed prescription in patients going on vacation for example *"I am also aware of the fact that I am not always sure and I can say today that it is a virus and yet after three days I have to admit that maybe it is a bacterial after all where it is arguable to start taking some*" (physician 2, GP) and *"So on Fridays, when in doubt, you are more likely to prescribe*" (physician 3, GP). GPs indicated using a C-reactive protein (CRP) test when uncertain *"That CRP meter has really been a huge asset. We're really happy with that. It has obviously had a huge impact on our prescribing habits"* (physician 4, GP), while hospital physicians indicated consulting clinical microbiologists in case of uncertainty. Clinical microbiologists also indicated that more experience/knowledge can help reduce uncertainty *"I think those [inexperienced* physician*s] will be a little more uncertain because they haven't built up experience yet"* (clinical microbiologist 1). This is in agreement with that physicians also perceive that novice physicians experience more uncertainty *"I find that* physician*s who are in training to be specialists have a greater need for certainty, demands [diagnostic tests] more than I do, and we once had a program that extracted that [number of demands for diagnostic tests] from our systems and then you could also see very clearly that* physician*s in training to be specialists are often, yes, out of uncertainty or the craving for certainty, often over diagnostic"* (physician 2, GP) and *"Yes, I think ... as a novice GP you are a little more uncertain than in this case you have more than 20 years of work experience*" (physician 3, GP).

5.2.2 Perceived patient and/or parental pressure

The clinical microbiologists indicated that they sometimes felt pressured by physicians and have disagreements with physicians about whether or not to prescribe antibiotics *"We sometimes have spirited discussions about that with surgeons, they are a little quicker to give something [an antibiotic] and we say, well, maybe not yet"* (clinical microbiologist 1) and "*Then the question is: how strong are you, how much experience do you have in this situation and what do you know about this situation?"* (clinical microbiologist 2). The physicians from the hospital indicated that they did not experience patient pressure, although one indicated that they only use delayed prescription when the patient requests it. The GPs indicated that they did barley experience patient pressure at their practice but they did experience pressure at the out-of-hour GP centre. The reason given by the physicians for this is that in their practice, GPs have established a bond of trust with their patients "*Because we've been in practice here for ten years now, at a certain point you also have a relationship of trust with patients, so that was perhaps a bit more difficult in the beginning, because you didn't know them, but now they also know our way of working and if you just substantiate that then it's often not too bad"* (physician 4, GP) and "*People, who have already been to a GP, come into that shift [at the out-of-hour GP centre], don't take it any longer and want something to happen now, so sometimes you think: yes, okay, conflict avoidance let me do it"* (physician 2, GP). When a patient would like an antibiotic, GPs use the CRP meter to justify their choices to patients.

5.2.3 Psychological distance

The physiological distance questions in the interviews showed that some physicians do feel a little geographical, social, and temporal distance about antibiotic resistance, while other physicians don't. Relating to geographic and social distance, one of physicians indicated that developing countries may be affected by antibiotic resistance earlier than the Netherlands, but physicians agreed that the Netherlands is certainly affected as well and that also countries not far from the Netherlands will be affected by antibiotic resistance. Regarding uncertainty, scepticism, and concerns, the physicians indicated that they are not unsure or sceptical about the consequences, although one physician indicated that the seriousness of antibiotics is somewhat exaggerated. The physicians did indicated that they are not worried about the personal consequences of antibiotic resistance, but they are concerned about the patients and society.

5.3 Organisational factors

The organisational factors: 3.1) diagnostic tests and results, ease to follow up, ease to referral, and costs, and 3.2) time and work pressure that emerged from the systematic review were validated and an in-depth understanding was gained through the interviews. Each of the organisational factors is described below.

Physicians indicated that they feel there are sufficient diagnostic tests available and that they have adequate access to them. The GPs stated that they did take into account possible costs when requesting diagnostic tests, while hospital physicians did not; "*That all goes out of the patients' deductible. So yes, if it makes sense, by all means do it. But if you're thinking is this really necessary, we're not going to burden patients with costs"* (physician 3, GP) and *"Well, I don't think so, no [consider costs]. No, nicely not"* (physician 5, hospital). The physicians indicated that they were satisfied with availability of diagnostic tests and the waiting time between requesting the diagnostic test and getting the result *"Yes, I think so, I don't need more diagnostic tests"* (physician 2, GP) and *"I think that's all [test results] fast, so I'm satisfied with that myself"* (physician 3, GP). When physicians cannot reassess a patient themself due to a vacation or the weekend, for example, physicians sometimes use delayed prescriptions *"But if a child does have a fever of, say, 39.5 and I see a clear red eardrum I think, yes, we can wait one, two more days. But yes, then I have to have the child assessed by the GP's office, for example, over the weekend, which you'd rather not do*" (physician 3, GP).

5.3.1 Time and work pressure

The clinical microbiologists indicated that they do not know if time and work pressure affects physician prescribing behaviour, but they do know that perceived time/work pressure affects the questions the clinical microbiologists receive from the physicians "*So yes, I think the stress, the hecticness does affect [physicians' prescribing behaviour]"* (clinical microbiologist 1). While hospital physicians stated experiencing no work and time pressure *"No, that's [time pressure when prescribing antibiotics] not very complicated, no"* (physician 5, hospital). Physicians said they always discuss their choices with the patient and feel little to no work or time pressure in doing so. When GPs indicated that they did sometimes feel time pressure, they indicated that any time pressure does not play a role in prescribing antibiotics *"experienced of course certainly time pressure, but whether that makes my prescribing behaviour different, I don't think so much"* (physician 4, GP). However, one GP indicated that he was sporadically influenced by work pressure in his own practice. *"In general I don't run out of time that much, so I don't feel this time pressure, and by coincidence I recently had the feeling that if you are 20 minutes behind and you still have five people in the waiting room, that sometimes you think I'm taking the easy way out"* (physician 3, GP), while all GPs reported experiencing work pressure while working at the out-of-hour GP centre "*Again, own practice not, also because I find that if I am consistent, then that is also helpful at the next contact. If I do it now, I can't say no next time: but at the out-of-hour GP*

centre, yes then there is a different dynamic. Packed schedule, patients you don't know, and sometimes you never see them again, and yes, then... I sometimes catch myself avoiding conflicts, especially when I have a long shift and still have several hours to go" (physician 2, GP).

5.4 Other factors

Physicians themselves were asked if they had any additional determinants related to their prescribing behaviour. These determinants were placed as 4) other factors, they are explained below.

What was mentioned by the clinical microbiologists is the importance of a good internal relationship between healthcare professionals. "*What I personally find very important is that as a consultant I have a good relationship with that practitioner that they know me"* (clinical microbiologist 1) and *"it [uncertainty] also has to do with trust of course and that you get to know each other and say: okay, I can go to someone if I really can't figure it out"* (clinical microbiologist 2). Good communication between health care providers was also mentioned as a factor by some physicians. What was also mentioned as a possible factor was personal preference of the prescribing physician *"Theoretically, that could be that you think of I like it, let's do it, is not in the guideline, but that's what I personally have a good experience with. I personally don't do that, but it could easily be done, I think"* (physician 5, hospital).

6 Discussion

This study aimed to investigate psycho-socio-cultural factors that are related to antimicrobial prescribing according to physicians. The factors that were found can be divided into: 1) personal factors, 2) psychological factors, 3) organisational factors and 4) other factors. Personal factors were further divided into: 1.1) work experience, 1.2) knowledge, and 1.3) use of guidelines. Psychological factors were further divided into: 2.1) uncertainty avoidance, 2.2) perceived patient and/or parental pressure, and 2.3) psychological distance. Organisational factors were further divided into: 3.1) diagnostic tests and results, ease to follow up, ease to referral, and costs, and 3.2) time and work pressure, see figure C for an overview. This study initially focused on general practices, hospitals, or inpatient settings. However, inpatient settings did not emerge from the literature and were therefore not included in the selection of participants for the interviews.

Physician-related factors of work experience and knowledge go hand in glove. As the physician has more work experience, more patients have been seen with similar symptoms and thus the physician has gained more knowledge of certain symptoms and disease states. This knowledge and experience may lead to better prescribing of antibiotics and more certainty among physicians, which in turn positively contributes to proper antibiotic prescribing. Unlike the other studies, the Dutch study of Akkerman, et al [46] regarding RTIs found that physicians with more experience, prescribe more antibiotics, especially in combination with little knowledge and the feeling of time pressure. This shows again that physicians who are more knowledgeable about antibiotics (resistance) can make better choices regarding antibiotic prescribing. They can also better explain and substantiate these choices to patients [42]. Despite the findings of the clinical microbiologists and multiple studies [46, 47, 54, 56, 57, 65] showing that physicians do not have enough knowledge, the interviewed physicians find they have (enough) knowledge about antibiotics(resistance), but that this knowledge is not all-encompassing and can always be extended. Therefore, improving and broadening knowledge is an important part of reducing PIP. According to the meta-analysis of Zeng, et al. [79], the social norm feedback needs to provide physicians with information about the health consequences of antibiotic use so that physicians become more aware of the influence of their prescribing behaviour and to reduce the psychological distance felt by all small number of interviewed physicians. In addition to knowledge about antibiotics (resistance), knowledge about guidelines is also important [67]. Most of the physicians do deviate from guidelines in a substantiated way. Both the systematic review and the interviews revealed that novice physicians in particular often consult guidelines and protocols [44, 68]. This may be because novice

physicians do not yet have enough work experience to feel confident enough to prescribe antibiotics without the use of guidelines. However, not all cases prescribed outside the guidelines can be classified as 'wrong' prescribing, as guidelines are not laws and physicians may deviate from the guidelines in certain situations [55]. What also plays a role in this is that novice physicians experience a greater degree of uncertainty compared to experienced physicians. Therefore, psychological factors are also related to prescribing antibiotics. These psychological factors are influenced by cultural differences in health systems.

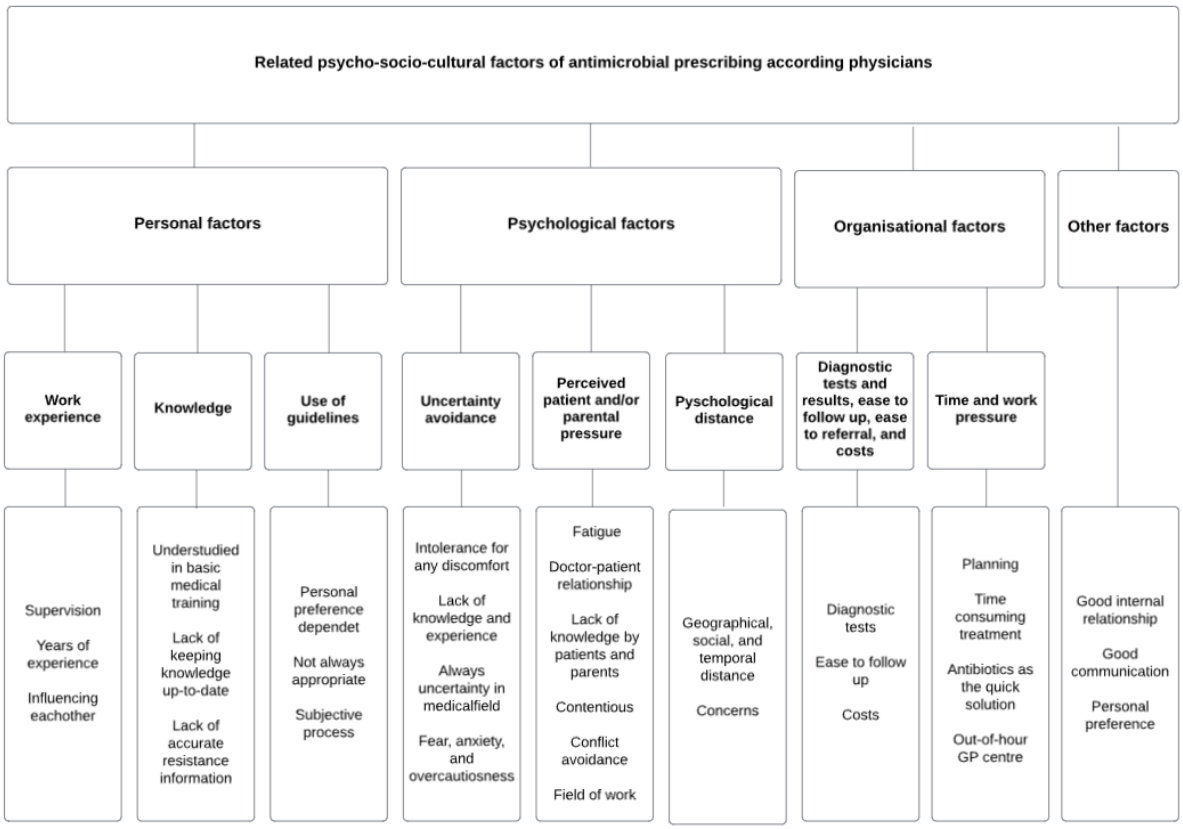
An example in which cultural differences in health care play a role is uncertainty avoidance. In medicine, there is always some level of uncertainty. Uncertainty can lead to anxiety and therefore discomfort among physicians [46, 57, 59]. Therefore, some physicians in countries such as Germany, Spain, Malta, and the United Kingdom (UK) use delayed prescriptions when they are not sure whether the infection is bacterial or viral [57, 61, 62, 70]. Delayed prescription means that prescriptions are written under the condition that the antibiotics will be used only if symptoms do not improve [80]. Little can be found in the literature about delayed prescriptions in the Netherlands, but it emerges from the interviews that the physicians interviewed make use of delayed prescriptions as an exception, mainly when physicians felt insecure and they cannot reassess the patient due to, the weekend or holiday for example [62, 81]. According to the cultural dimensions of Hofstede, the Netherlands scores 53 (out of 100, with 100 being the highest and 0 being the lowest score) on uncertainty avoidance. Having a score of 53 indicates some tolerance for uncertainty and risk, but also some desire for structure and predictability [81]. Compared to countries in northern Europe, this score is relatively high, but compared to countries in southern Europe, this score is relatively low [81]. Physicians feel the least uncertainty when their decision is supported by microbiology laboratory results [45, 59, 60, 63, 64, 66, 70], Dutch GPs mainly use the CRP test. Nevertheless, some microbiology tests can be burdensome for the patient, so this is not always the solution. Noteworthy is that risk aversion, as opposed to uncertainty avoidance, is mentioned only once in the literature found [68], however, the term uncertainty avoidance is also used in the literature to refer to risk aversion. Physicians from the interviews does indicate that risk aversion can play a more important role the more experience a physician has. Thomas, et al. [68] stated that when uncertainty is present, physicians consider it more important that the patient be treated with antibiotics at that time, rather than that physicians consider possible future resistance. This may be due to future discounting. Discounting is “a technique for comparing costs and benefits that occur in different periods. It is independent of inflation and is based on the principle that people prefer to receive goods and services now rather than later” [82]. Thus, relating to antibiotic prescribing, this means that physicians would rather help patients now than consider future resistance.

Cultural differences in health systems not only play a role in uncertainty avoidance but also play a role in perceived patient and/or parental pressure. Unlike other countries, patients in the Netherlands can only obtain antibiotics through a physician. It is the physician's job to make decisions about the duration and choice of antimicrobial therapy [54]. GPs in Italy, get paid per patient and not per consultation. Also, parents are free to change GPs at any time. It may be due to these cultural factors that physicians in Italy overestimate patients' and/or parents' expectations to be prescribed antibiotics and thereby increase their prescribing behaviour, as physicians feel they must acknowledge parents' expectations to maintain a successful physician-parent relationship [50, 53]. In the Netherlands, GPs do receive a small fee per patient, also called a registration fee, but otherwise general practitioners get paid per consultation [83]. The degree to which the physician experiences patient pressure also depends on the physician's field of work. In the found references physicians in primary care more often report experiencing (more) patient pressure than physicians working in secondary or tertiary care [44, 45, 47, 48, 50, 59, 63, 66, 71]. This may be explained by the fact that in primary care, patients play a more active role in treatment, so patient-physician interaction and a trust relationship between physician and patient may be more important [71, 84]. This outcome is partly in agreement with the results of the interviews, wherein patient pressure is primarily experienced during shifts at out-of-hours GP centres, which patients only visit when perceived need for care is high.

But not only cultural differences in health systems may play a role in the psychological factors, also organisational factors may play a role. Organisational factors may also play a role in time limitation and work pressure. According to the literature findings, prescribing antibiotics is easier and faster than explaining why antibiotics are not given and because of the time pressure, physicians don't talk about AMR with their patients [59, 60, 63, 64, 68, 70]. The lack of time is also shown by the statement that physicians do not always have time to consult with colleagues [59]. The literature shows that Dutch hospital physicians experience time and work pressure especially in the mornings [54], the interviews show that GPs experience this pressure mainly during work at the out-of-hours GP centre. This difference may be explained due cultural differences in health systems and organisational factors. When a GP runs a shift at the out-of-hours GP centre, the GP is responsible for many more patients than during the day, resulting in more work and time pressure. Organisational factors and health systems can contribute to this by allowing physicians to see fewer patients, thereby reducing the work and time pressure on physicians. At a withdrawal of one patient per day, the probability of being a good prescriber already increases by 3% [73]. Both the literature and the interviews suggest that any medicine cost to the patient is not a factor in whether or not antibiotics are prescribed. This can be explained because health insurance is mandatory in the Netherlands and the patient is insured for most drug costs. Noteworthy, is that according to the interviews, GPs did take into account possible costs for diagnostics for patients, while hospital physicians did not take this into account. This may be because patients who come to the hospital are less often paying out of pocket than patients who come to the GP. For diagnostic tests, patients must namely first pay their own risk before they are reimbursed from health insurance [85]. All physicians indicated that they have sufficient access to diagnostic tests.

Many interventions can encourage physicians to prescribe antibiotics less frequently; however, different types of support are needed for different types of physicians. For some, it is important to better understand factors related to their own prescribing behaviour and others need training to learn how to deal with uncertainty. However, interventions should focus primarily on physicians' uncertainty. As it turns out, almost all of the factors found are related to uncertainty. This outcome is consistent with the outcome of another systematic review on factors influencing antimicrobial prescribing behaviour [86]. According to the systematic review of Warreman, et al. [86] (lack of) tolerance to uncertainty and fear of adverse outcomes due to untreated infection were prominent determinants of antimicrobial prescribing behaviour. So far, uncertainty has been attempted to be addressed by reducing uncertainty rather than preparing physicians to handle or tolerate uncertainty and the resulting discomfort, and since there is never complete certainty in medicine, it is important to teach physicians how to deal with it [62, 87]. The study of Reis-Dennis, et al. [87] showed that it is important for physicians to become self-reflective about their own response to uncertainty and that there is a need for a culture shift that recognizes and embraces tolerance for uncertainty. The meta-analysis of Zeng, et al. [79] showed that interventions aimed at physicians work better than interventions aimed at institutions. For this reason, it is important to focus interventions on physicians rather than institutions. Nevertheless, health care organisation and planning must recognize that infectious diseases require complex and time-consuming treatment of patients in primary, secondary, and third-line care to improve antibiotic use [62, 71].

Figure C
An overview of the related factors that influence antibiotic prescriptions



6.1 Strengths and limitations

There were several advantages to using a mixed-method approach. For example, a mixed method approach provides deeper insights, increases validity and reliability, and can complement any limitations. The disadvantage of a mixed method approach can be that it is time-consuming [88]. Therefore, AI was used in both the systematic review and the interview processing to save time [89]. Regarding the systematic review, bias may occur because only two databases were used and only English or Dutch articles were included in the systematic review. However, in general, language bias has minimal impact on the conclusions of systematic reviews [90]. These databases were chosen because PubMed contains references to medical scientific articles and Scopus is a more general database, making the two databases together bulky. A possible limitation of ASReview is that ASReview typically finds 95% of the relevant articles, so there is a chance that some relevant articles were missed. However, people often find only 90% of items through the manual way [91]. Systematic reviews are at risk of reporting, detection, and selection bias [92]. The risk of selection bias was minimized by having clearly defined eligibility criteria [92]. To minimalize the impact of other types of bias, risk-of-bias tools were used and only studies with a low to moderate risk-of-bias were included. The risk-of-bias was also minimized by using two independent reviewers in the first stage of screening. Cohen's kappa of 0.70 shows that there was substantial to good agreement between the two reviewers in the first stage screening [93]. Finally, a narrative summary may involve a subjective nature of the interpretations, which could potentially lead to bias [94].

There were also some limitations with regard to the interviews. A major limitation of the interviews was that a small number of physicians and clinical microbiologists were interviewed, which results in a low external validity [45, 76]. However, this study does provide a first in-depth insight into the found determinants. Physicians were interviewed from both the northern and eastern Netherlands, but due to the small number of participants, the interviews need to be repeated on a larger scale in different healthcare settings, such as primary care, secondary care and tertiary care, in different areas of the north-eastern Netherlands to confirm the results found and increase generalizability [58]. Another

limitation can be that the answers were based on physicians' own experiences. Because of this, some of the questions asked may have been prone to social desirability, or physicians themselves may not has realized certain habits [45].

7 Recommendations

The systematic review combined with the interviews revealed several recommendations to reduce potentially inappropriate prescribing (PIP). The recommendations can be divided into two types: recommendations for further scientific research and recommendations to improve antibiotic prescriptions as a result of this study. This study provides related factors that emerge from the literature and interviews as a basis for further scientific research. In the scientific field, it is therefore recommended for ABRZNN to gain more insight into the factors found in North-eastern Netherlands, this can be done by conducting observational research or conducting in-depth interviews on a larger scale, in the different health care settings (general practices, hospitals or inpatient settings) with both novice and experienced physicians from North-eastern Netherlands. To see if the factors found are generalizable to the rest of the Netherlands, a follow-up study could involve other provinces of the Netherlands. Finally, there should be more research on how physicians respond to uncertainty.

As a result of this study, the main recommendation is to develop an effective improvement program to train physicians to gain self-insight on how they respond to uncertainty and to train physicians in learning how to deal with uncertainty so that physicians are less inconvenienced by it. It is also important to reduce uncertainty of physicians. Currently, aside from intervisions and new diagnostic rapid tests, there are no interventions to teach physicians how to manage and reduce uncertainty. Uncertainty can be reduced by paying more attention to antimicrobials during basic medical training, at the same time, it is important to pay more attention during training to physicians self-reflection and learning to accept uncertainty during training. It is also important to continue to educate physicians while working. Because interventions that include multiple determinants seem to be more effective in reducing antibiotic prescribing [95], in addition to increasing general knowledge about antibiotics, it would also be useful to provide all physicians (semi)annually with up-to-date information about their own prescribing behaviour and resistance in their work environment, for example, through a newsletter, so that physicians become more aware of their own prescribing behaviour. Furthermore, at the organisational level, the recommendation is for healthcare facilities to recognize that infectious disease require a complex and time-consuming treatment for patients. Therefore, it is important to give physicians enough time per patient.

8 Conclusion

The study identified several psycho-socio-cultural factors that are related to antimicrobial prescribing. The factors that were found can be divided into: 1) personal factors, 2) psychological factors, 3) organisational factors, and 4) other factors. Personal factors were further divided into: 1.1) work experience, 1.2) knowledge, and 1.3) use of guidelines. Psychological factors were further divided into: 2.1) uncertainty avoidance, 2.2) perceived patient and/or parental pressure, and 2.3) psychological distance. Organisational factors were further divided into: 3.1) diagnostic tests and results, ease to follow up, ease to referral, and costs, and 3.2) time and work pressure. Cultural differences (in health care systems) play a role in these factors. The most important factor of this is uncertainty avoidance. Without support from the practice and the healthcare system, it is difficult for individual physicians to reduce antibiotic prescribing rates. Prescribing physicians feel the least uncertainty when their decision is supported by microbiology laboratory results, but some microbiology tests can be burdensome for the patient, so this is not always the solution. The CRP test, however, provides a good solution. Work experience and knowledge are important factors that helped to reduce uncertainty. Thus, to reduce uncertainty, it is both important to better educate physicians about antimicrobials during their initial

training and to maintain knowledge while working. In addition to reducing uncertainty, it is also important to pay more attention to physicians self-reflection and teach physicians how to manage uncertainty. When physicians experience less uncertainty and cope with it better, physicians will also experience less patient and/or parental pressure, which in turn may contribute to reducing PIP. Lastly, it is important to give physicians enough time per patient to reduce time and work pressure and therefore may reduce PIP.

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Appendix A

Inclusion criterion	Exclusion criterion
The article was written in English or Dutch	Non-English or Dutch articles
The study is a primary data source	The study is a secondary data source
Original articles	Non-original articles
The study was conducted in Europe or the Netherlands	The study was conducted outside of Europe
The study was about psycho-socio-cultural reasons for prescribing antibiotics	The study was only about medical reasons for prescribing antibiotics
The study was about antibiotics prescribed by hospital, inpatient, and general practitioner settings	The study was about antibiotics prescribing by dentists and residential settings
The study was about the physicians' perspective/attitude on antibiotic prescribing	The study was only about the patient's perspective on antibiotic prescribing
The study was about prescription of antibiotics	The study was only about prescription of drugs other than antibiotics
	The study was only about antibiotics by animals or agriculture
	The study was only about veterinarian prescribing antibiotics
	The study was only about telephonic prescriptions for antibiotics
	The study was only about out of office prescriptions of antibiotics
	The study was only about measuring the effect of an intervention
	The study was only about nurse prescribers of antibiotics
	The study is of low quality or high risk-of-bias

Appendix B

General information

Study ID
Title
Abstract
Publishing date
County in which the study is conducted;

- Sweden
- UK
- Netherlands
- Germany
- Spain
- Malta
- Greece
- Belgium
- France
- Italy
- Other

Notes

Methods

Aim of study
Study design;

- Cohort study
- Observational study
- Cross-sectional study
- Qualitative study
- Other

Start date and end date

Participants

The total number of participants invited
The total number of participants who participate
How many participants were excluded and why?
The setting of the study;

- Primary care
- Secondary care
- Tertiary care
- Other

Population description
Inclusion criteria
Exclusion criteria
Method of recruitment of participants;

- Phone
- Mail
- Clinic patients
- Voluntary
- Unknown
- Other

Method to conduct the interview/questionnaire;

- Face-to-face
- Phone
- Mail
- Online call
- Written questionnaires
- Online questionnaires
- Unknown
- Other

Analysis

Which method is used for analysing?

Results

Main outcomes

Which non-medical determinants influence antibiotic prescribing?;

	Determinant	Target population	For which disease	Relating to	Significant effect	Mean	Confidence interval	Percentage
Determinant 1								
Determinant 2								
Determinant 3								
Determinant 4								
Determinant 5								

Discussion outcomes

Other

Study funding sources

Possible conflicts of interest

Ethical approval

Appendix C

Calculation of Cohen's kappa

		Reviewer 2		
		Inclusion	Exclusion	
Reviewer 1	Inclusion	43	17	60
	Exclusion	13	366	379
		56	383	439

43 + 366 = 409

(409 / 439) * 100% = 93.17%

(56 * 60) / 439 = 7.65
(383 * 379) / 439 = 330.65
7.65 + 330.65 = 338.30

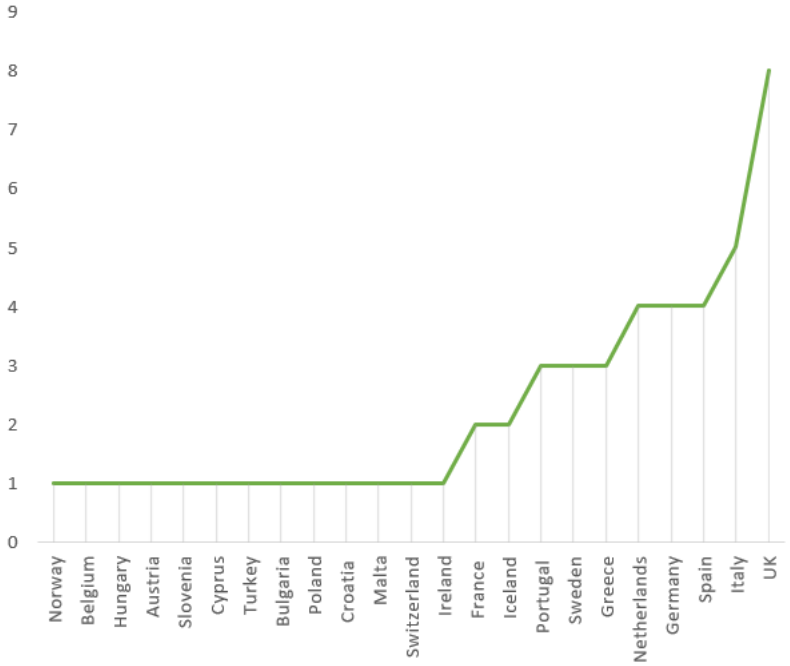
(338.30 / 439) * 100% = 77.06%

93.17 – 77.06 = 16.11%
100 – 77.06 = 22.94%
16.11 / 22.94 = 0.70

Cohen's kappa = 0.70

Appendix D

Discontinuous distribution of the frequency that a country is included in the articles used



Appendix E

Article data of the included studies

Authors	Country conducted	Year of publishing	Study design	Quality	Risk-of-bias	Reference number
Lévin C, et al.	France	2018	Cross-sectional – survey	16/20 high	16/20 low	42
Beović B, et al.	Sweden, United Kingdom (UK), Spain, Greece, France, Italy, Croatia, Portugal, Slovenia, Austria, Bulgaria, and Turkey	2019	Cross-sectional - survey	15/20 moderate	15/20 moderate	43
Salm F, et al.	Germany	2018	Cross-sectional – survey	15/20 moderate	15/20 moderate	44
Simões AS, et al.	Portugal	2018	Cross-sectional – survey	14/20 moderate	14/20 moderate	45
Akkerman AE, et al.	Netherlands	2005	Cross-sectional – survey	16/20 high	16/20 low	46
Rousounidis A, et al.	Cyprus	2011	Cross-sectional – survey	17/20 high	17/20 low	47
Spernovasilis N, et al.	Greece	2019	Cross-sectional – survey	15/20 high	15/20 low	48
Velasco E, et al.	Germany	2011	Cross-sectional – survey	18/20 high	18/20 low	49
Moro ML, et al.	Italy	2009	Cross-sectional – survey	15/20 moderate	15/20 moderate	50

Grossman Z, et al.	Germany, Spain, and Italy	2012	Cross-sectional – survey	16/20 high	16/20 low	51
Geitona M, et al.	Greece	2015	Cross-sectional – survey	16/20 high	16/20 low	52
Ciofi degli Atti ML, et al.	Italy	2006	Cross-sectional – survey	13/20 moderate	13/20 moderate	53
Sikkens JJ, et al.	Netherlands	2018	Observational - surveys	28/34 high	7/9 low	54
Dekker AR, et al.	Netherlands	2015	Observational	22/34 high	8/9 low	55
De Souza V, et al.	Ireland	2006	Qualitative – semi-structured interviews	18/32 moderate	8/10 low	56
Vazquez-Lago JM, et al.	Spain	2011	Qualitative – interviews with focus groups	19/32 moderate	9/10 low	57
Charani E, et al.	UK	2013	Qualitative – semi-structured interviews	24/32 high	9/10 low	58
Björnsdóttir I, et al.	Iceland	2002	Qualitative – interviews and observations	18/32 moderate	7/10 moderate	59
van der Zande MM, et al.	UK	2019	Qualitative – semi-structured interviews	21/32 moderate	10/10 low	60
Saliba-Gustafsson EA, et al.	Malta	2021	Qualitative – semi-structured interviews	17/32 moderate	10/10 low	61
Poss-Doering R, etl al.	Germany	2020	Qualitative – interviews	19/32 moderate	8/10 low	62

Petursson P, et al.	Iceland	2005	Qualitative - interviews	19/32 moderate	7/10 moderate	63
Eyer MM, et al.	Switzerland	2016	Qualitative – semi-structured interviews	24/32 high	9/10 low	64
Simpson SA, et al.	UK	2006	Qualitative – interview	21/32 moderate	10/10 low	65
Brookes-Howell L, et al.	UK, Spain, Hungary, Poland, Norway, Italy, and Belgium	2012	Qualitative – semi-structured interview	24/32 high	9/10 low	66
Strandberg EL, et al.	Sweden	2013	Qualitative – semi-structured interviews with focus groups	15/32 moderate	8/10 moderate	67
Thomas H, et al.	UK	2021	Qualitative – semi-structured interviews	27/32 high	10/10 low	68
Schouten JA, et al.	Netherlands	2006	Qualitative – semi-structured interviews	20/32 moderate	9/10 low	69
Horwood J, et al.	UK	2016	Qualitative – semi-structured interviews	25/32 moderate	9/10 low	70
Björkman I, et al.	Sweden	2011	Qualitative – interviews	22/32 high	8/10 low	71
Ryves R, et al.	UK	2016	Qualitative – semi-structured interviews	19/32 moderate	9/10 Low	72
Teixeira Rodrigues A, et al.	Portugal	2016	Cohort – longitudinal data	28/32 high	8/9 low	73

Appendix F

Interview guide for the clinical microbiologists

Heeft u het gevoel dat het voorschrijf gedrag van artsen is veranderd door de jaren heen op basis van veranderende kennis over antibiotica resistentie?

- Zo ja, waarin of hoe merkt u dit?

Krijgt u wel eens vragen vanuit de voorschrijvende artsen?

- Waar gaan de vragen meestal over?
- Hoe vaak krijgt u vragen vanuit de voorschrijvende artsen? Denkt u dat vaker vragen gesteld zouden moeten worden?
- Zijn er specialismen die u vaker / minder vaak vragen stellen?
- Krijgt u vaker / minder vaak vragen van een bepaalde generatie artsen of is dit ongeveer gelijk verdeeld?
    - Heeft u het gevoel of kennis over antibiotica(resistentie) hierin in een rol speelt?
    - Merkt u verschil in kennis tussen bepaalde generatie artsen? En hoe komt dit volgens u?

Heeft u het gevoel dat artsen voldoende kennis hebben omtrent antibiotica(resistentie)?

- Waardoor heeft u dit gevoel?

Hoe houden artsen momenteel hun kennis over antibiotica(resistentie) up-to-date?

Denkt u dat scholingen aan artsen geven kan bijdragen aan het juist gebruik van antibiotica?

- Zo ja, hoe (en wanneer/ hoe vaak) zou dit volgens u het beste aangepakt kunnen worden?

Heeft u het gevoel dat artsen richtlijnen gebruiken bij hun keuze omtrent antibiotica voorschrijven?

- Waardoor heeft u dit gevoel?
- Zo ja, merkt u verschil in het gebruik van richtlijnen tussen artsen? Ziet u hier een patroon in?

Wat zijn op basis van gesprekken die u met voorschrijvende artsen hebt volgens u niet-medische determinanten die een rol spelen in het voorschrijven van antibiotica bij artsen?

Zijn er bepaalde momenten of tijden (maanden/dagen/uren op de dag) dat u meer vragen krijgt vanuit artsen?

- Zo ja, denkt u dat het weekend hierin een rol speelt?

Heeft u het gevoel dat artsen zich soms onzeker voelen bij de keuze wel of geen antibiotica voorschrijven?

- Zo ja, hoe merkt u deze onzekerheid?
- Zo ja, denkt u dat deze onzekerheid invloed heeft op het onjuist voorschrijven van antibiotica?
- Zo ja, heeft u het gevoel dat u kan bijdragen deze onzekerheid weg te nemen?
- Zo ja, heeft u het gevoel dat artsen met meer ervaring en/of kennis minder onzeker zijn?

Heeft u wel eens het gevoel dat u zich onder druk gezet voelt, doordat de arts graag antibiotica wil voorschrijven?

- Zo ja, waardoor krijgt u dit gevoel?
- Zo ja, merkt u hierin verschil tussen artsen? Is er iets dat die verschillen kan verklaren?

Heeft u het gevoel dat artsen hun keuze laten beïnvloeden door patiënten druk?

- Zo ja, waardoor krijgt u dit gevoel?
- Zo ja, merkt u hierin verschil tussen artsen? Is er iets dat die verschillen kan verklaren?

Heeft u het gevoel dat de patiënten verwachting veranderd is door/na COVID-19?

Heeft u het gevoel dat ervaren artsen het voorschrijf gedrag van jonge artsen beïnvloeden?

- Zo ja, waardoor krijgt u dit gevoel?

Heeft u het gevoel dat artsen hun keuze laten beïnvloeden door tijdsdruk en/of werkdruk?

Heeft u het gevoel dat het ziekenhuis voldoende diagnostische testen beschikbaar heeft?

Krijgt u wel eens vragen / opmerkingen over de wachttijd tussen aanvragen en terugkoppeling van resultaten van diagnostische tests?

Wat vind u van de wachttijd tussen het aanvragen en de van resultaten van diagnostische tests?

Heeft u het gevoel dat artsen rekening houden met kosten voor de patiënt bij de keuze wel of geen diagnostische test te gebruiken?

Merkt u verschil in voorschrijven wanneer artsen de patiënt niet opnieuw kunnen beoordelen?

Zijn er nog aanvullende determinanten die nog niet besproken zijn, die volgens u een rol spelen bij het voorschrijfgedrag van artsen die nog niet benoemd zijn?

- Hoe merkt u deze determinanten terug in de praktijk?

Appendix G

Interview guide for the physicians

Hoeveel jaar werkervaring heeft u als voorschrijvend arts?
Wanneer betrekt u microbiologen bij uw besluitvorming?
Vind u het de taak van de microbiologen om artsen proactief informatie te geven over antibiotica(resistentie)?

- Waarom wel/niet?

Heeft u het gevoel dat uw voorschrijf gedrag veranderd is door de jaren heen?

- Zo ja, schrijft u op dit moment meer of minder antibiotica voor dan eerst?
    - Waarom schrijft u op dit moment meer/minder antibiotica voor dan eerst?
    - Bent u zelfverzekerder geworden door de jaren heen omtrent de keuzes voor het wel of niet voorschrijven van antibiotica?
        - Zo ja, hoe merkt u dit?

Gebruikt u wel eens uw eigen ervaringen buiten de richtlijnen om bij de keuze om wel of geen antibiotica voor te schrijven?
Heeft u het gevoel dat meer ervaring kan bijdragen aan het verminderen van onjuist antibiotica voorschrijven?
Schrijft u wel eens antibiotica voor uit angst voor complicaties bij de patiënt?

- Zo ja, waarin uit deze angst zich?

Schrijft u wel eens geen antibiotica voor omdat u bang bent voor de bijwerkingen bij patiënten?
Ervaart u wel eens angst om niet behandeld te worden bij patiënten?

- Zo ja, beïnvloedt dit uw eigen angsten/onzekerheden?

Heeft u het gevoel dat ervaren artsen het voorschrijf gedrag van jonge artsen beïnvloeden?

- Waarom heeft u dit gevoel?
- Zo ja, wordt u eigen voorschrijfgedrag beïnvloedt door (meer) ervaren artsen?

Speelt het weekend een rol in uw besluitvorming omtrent antibiotica?
Speelt het mee of u iemand kan her beoordelen of niet?
Heeft u het gevoel dat uw collega's gebruik maken van richtlijnen bij het voorschrijven?

- Waardoor heeft u dit gevoel?

Hoeveel vertrouwen heeft u in uw eigen besluitvorming rondom het voorschrijven van antibiotica?
Heeft u het gevoel dat uw zelfvertrouwen groeit naarmate u meer ervaring heeft?
Heeft u het gevoel dat meer kennis uw zelfvertrouwen kan vergroten?
Heeft u het gevoel dat het overleggen met een microbioloog kan helpen om de onzekerheid te verkleinen?
Overlegt u wel eens met uw collega's wanneer u twijfelt of antibiotica de geschikte behandeling is?

- Zo nee, waarom niet?

We weten uit eerdere onderzoeken en uit de praktijk dat het niet altijd haalbaar of wenselijk wordt geacht om diagnostiek aan te vragen voordat antibiotica voorgeschreven wordt. Kunt u vertellen hoe u hier over denkt? Wat zijn situaties om het wel / niet te doen?

- Gebruikt u diagnostische testen voordat u de patiënt antibiotica voorschrijft of ter bevestiging van de keuze die u al gemaakt heeft?

Wat valt volgens u onder onjuist voorschrijven van antibiotica?
Gebruikt u wel eens uitgestelde recepten?

- Zo ja, wanneer en waarom gebruikt u dit?

Heeft u het gevoel dat u voldoende eenvoudig toegang heeft tot richtlijnen en diagnostische testen?
Heeft u het gevoel dat u voldoende gebruiksvriendelijke toegang heeft tot diagnostische testen?
Wat vind u van de wachttijd tussen het aanvragen van een diagnostische test en de resultaten?
Houdt u rekening met eventuele kosten voor de patiënt bij het voorschrijven van antibiotica/ aanvragen van diagnostiek?

- Zo ja, hoe houdt u hier rekening mee?

Bent u op de hoogte van resistentiepatronen binnen uw instelling?

- Waarom ziet u AB resistentie wel/niet als een probleem bij uw eigen werkveld?

Heeft u het gevoel dat u voldoende kennis heeft over antibiotica(resistentie)?

- Waarom heeft u dit gevoel?

Heeft u het gevoel dat patiënten voldoende kennis hebben over antibiotica?
Hoe houdt u momenteel uw kennis over antibiotica(resistentie) up-to-date?
Kunt u de gevolgen omschrijven van het niet juist voorschrijven van antibiotica?

De volgende vragen hebben betrekking op een 5-punts beoordelingsschaal (helemaal niet, een beetje, neutraal, tamelijk vaak, zeer vaak);
In hoeverre schrijft u antibiotica voor als u niet zeker bent van de gestelde diagnose?
In hoeverre ervaart u druk vanuit andere bij de beslissing om wel of niet voor te schrijven?

- Zo ja, door wie/wat ervaart u deze druk?
- Zo ja, hoe beïnvloed deze druk uw voorschrijf gedrag?

In hoeverre ervaart u druk vanuit de patiënt en/of ouder om antibiotica voor te schrijven?

- beïnvloedt dit u bij het maken van een keuze?
- In wat voor frequentie komt deze druk voor?

In hoeverre ervaart u tijdsdruk?

- beïnvloed dit uw voorschrijfgedrag?

In hoeverre bespreekt u met de patiënt waarom u wel of geen antibiotica voorschrijft?

- Waarom wel/niet?
- Heeft u wel eens het gevoel dat u geen tijd heeft om patiënten uitleg te geven?
- Heeft u het gevoel dat patiënten waarde hechten aan de onderbouwing van uw keuze om wel/geen antibiotica voor te schrijven?
    - Waardoor krijgt u dat gevoel?

In hoeverre ervaart u wel eens ontevredenheid bij patiënten wanneer u geen antibiotica voorschrijft?

- Kiest u er wel eens voor om antibiotica voor te schrijven zodat u niet een discussie hoeft aan te gaan?

In hoeverre maakt u gebruik van richtlijnen bij het bepalen om wel of geen antibiotica voor te schrijven?

- Waarom wel/niet?
- Heeft u het gevoel dat uw collega's weten waar ze de richtlijnen kunnen vinden?
- Zo ja, wijkt u wel eens af van de richtlijnen?
    - Zo ja, waardoor komt dit?
- Zo ja, bent u het altijd eens met de richtlijnen?
    - Zo nee, waarom niet?

In hoeverre voelt u zich wel eens onzeker bij het voorschijven van antibiotica?

- In hoeverre ervaart u wel eens ongemak van deze onzekerheid?
    - Kunt u uitleggen waardoor deze onzekerheid/ongemak ontstaat?
- Hoe zou deze onzekerheid verminderd kunnen worden?

In hoeverre heeft u het gevoel dat u door tijdsdruk/werkdruk niet met collega artsen kan overleggen?
Nu volgen er wat stellingen die betrekking hebben op een 5-punts beoordelingsschaal (helemaal niet, een beetje, neutraal, tamelijk vaak, zeer vaak);
Mijn omgeving zal waarschijnlijk worden beïnvloed door antibiotica resistentie
Antibiotica resistentie zal vooral gebieden treffen die ver van hier zijn
Vooral ontwikkelingslanden zullen worden getroffen door antibiotica resistentie
Antibiotica resistentie gaat mij ook persoonlijk treffen
De ernst van antibiotica resistentie wordt overdreven
Het is onzeker wat de gevolgen van antibiotica resistentie zullen zijn
Ik ben er niet zeker van of antibiotica resistentie echt plaatsvindt
Ik ben bereid mijn antibiotica voorschrijvingen sterk te verminderen om antibiotica resistentie te helpen aanpakken
De volgende stelling betreft een schaal van; we voelen nu al de effecten, in de komende 10 jaar, in de komende 25 jaar, in de komende 50 jaar, verder dan 50 jaar, ik denk dat we de effecten nooit gaan merken / geen mening
Wanneer, als dat al het geval is, denkt u dat Nederland de effecten merkt van de antibiotica resistentie?
De volgende stellingen betreffen een schaal van; zeer bezorgd, een beetje bezorgd, neutraal en helemaal niet bezorgd
Hoe bezorgd bent u, als u dat al bent, over antibiotica resistentie?
Gezien de mogelijke gevolgen van antibiotica resistentie die er voor u persoonlijk zouden kunnen zijn, hoe bezorgd bent u, indien überhaupt, over antibiotica resistentie?
Gezien de mogelijke gevolgen van antibiotica resistentie voor de samenleving in het algemeen, hoe bezorgt bent u over antibioticaresistentie?
Zijn er, naast medische gronden, nog andere niet besproken factoren die een rol spelen bij uw overweging om al dan niet antibiotica voor te schrijven?

Appendix H

Informatieblad voor onderzoek 'Antibiotic prescribing'

Doel van het onderzoek
Dit onderzoek wordt geleid door Nienke Beerlage-de Jong, PhD en uitgevoerd door Chiara Lansink. Het doel van dit onderzoek is te onderzoeken welke niet-medische determinanten invloed hebben op het wel of niet voorschrijven van antibiotica bij artsen. De resultaten van dit onderzoek worden anoniem verwerkt in een master thesis voor de Universiteit van Twente en in eventuele daaruit voortvloeiende publicatie en presentaties.

Hoe gaan we te werk?
Voor dit onderzoek willen we u interviewen, waarbij we een audio-opname maken van het interview. Op basis daarvan zal een transcript worden uitgewerkt van het interview. Gegevens die naar u herleidbaar zijn worden uit het transcript verwijderd. Dit transcript wordt vervolgens geanalyseerd voor het onderzoek.

Potentiële risico's en ongemakken
Tijdens uw deelname aan deze studie kunnen u vragen worden gesteld die u als persoonlijk kunt ervaren. Wij stellen deze vragen enkel en alleen in het belang van het onderzoek. U hoeft echter geen vragen te beantwoorden die u niet wilt beantwoorden. Uw deelname is vrijwillig en u kunt uw deelname op elk gewenst moment stoppen, zonder daarvoor een reden te geven.

Vergoeding
U ontvangt voor deelname aan dit onderzoek geen vergoeding.

Vertrouwelijkheid van gegevens
Wij doen er alles aan uw privacy zo goed mogelijk te beschermen. Er wordt op geen enkele wijze vertrouwelijke informatie of persoonsgegevens van of over u naar buiten gebracht, waardoor iemand u zal kunnen herkennen. Voordat onze onderzoeksgegevens naar buiten gebracht worden, worden uw gegevens zoveel mogelijk geanonimiseerd.

In een publicatie zullen anonieme gegevens of pseudoniemen worden gebruikt. De audio-opnamen, formulieren en andere documenten die in het kader van deze studie worden gemaakt of verzameld, worden opgeslagen op een beveiligde locatie bij de Universiteit Twente. De onderzoeksgegevens worden bewaard voor een periode van 10 jaar. Uiterlijk na het verstrijken van deze termijn zullen de gegevens worden verwijderd. De onderzoeksgegevens worden indien nodig (bijvoorbeeld voor een controle op wetenschappelijke integriteit) en alleen in anonieme vorm ter beschikking gesteld aan personen buiten de onderzoeksgroep.

Tot slot is dit onderzoek beoordeeld en goedgekeurd door de ethische commissie van de faculteit BMS (domain Humanities & Social Sciences)

Vrijwilligheid
Deelname aan dit onderzoek is geheel vrijwillig. U kunt als deelnemer uw medewerking aan het onderzoek te allen tijde stoppen, of weigeren dat uw gegevens voor het onderzoek mogen worden gebruikt, zonder opgaaf van redenen. Het stopzetten van deelname heeft geen nadelige gevolgen voor u. Als u tijdens het onderzoek besluit om uw medewerking te staken, zullen de gegevens die u reeds hebt verstrekt tot het moment van intrekking van de toestemming in het onderzoek gebruikt worden. Wilt u stoppen met het onderzoek, of heeft u vragen en/of klachten? Neem dan contact op met de onderzoeker:

Chiara Lansink;

Voor bezwaren met betrekking tot de opzet en of uitvoering van het onderzoek kunt u zich ook wenden tot de Secretaris van de Ethische Commissie / domein Humanities & Social Sciences van de faculteit Behavioural, Management and Social Sciences op de Universiteit Twente via ethicscommittee-hss@utwente.nl. Indien u specifieke vragen hebt over de omgang met persoonsgegevens kun u deze ook richten aan de Functionaris Gegevensbescherming van de UT door een mail te sturen naar dpo@utwente.nl.
Tot slot heeft u het recht een verzoek tot inzage, wijziging, verwijdering of aanpassing van uw gegevens te doen bij de onderzoeker.
Door dit toestemmingsformulier te ondertekenen erken ik het volgende:

1. Ik ben voldoende geïnformeerd over het onderzoek door middel van een separaat informatieblad. Ik heb het informatieblad gelezen en heb daarna de mogelijkheid gehad vragen te kunnen stellen. Deze vragen zijn voldoende beantwoord.
2. Ik neem vrijwillig deel aan dit onderzoek. Er is geen expliciete of impliciete dwang voor mij om aan dit onderzoek deel te nemen. Het is mij duidelijk dat ik deelname aan het onder- zoek op elk moment, zonder opgaaf van reden, kan beëindigen. Ik hoef een vraag niet te beantwoorden als ik dat niet wil.

Naast het bovenstaande is het hieronder mogelijk voor verschillende onderdelen van het onderzoek specifiek toestemming te geven. U kunt er per onderdeel voor kiezen wel of geen toestemming te geven. Indien u voor alles toestemming wil geven, is dat mogelijk via de aanvinkbox onderaan de stellingen.

3. Ik geef toestemming om de gegevens die gedurende het onderzoek bij mij worden verzameld te verwerken zoals is opgenomen in het bijgevoegde informatieblad.	JA □	NEE □
4. Ik geef toestemming om tijdens het interview opnames (geluid) te maken en mijn antwoorden uit te werken in een transcript.	□	□
5. Ik geef toestemming om mijn antwoorden te gebruiken voor quotes in de onderzoekspublicaties.	□	□
6. Ik geef toestemming om de bij mij verzamelde onderzoeksdata te bewaren en te gebruiken voor toekomstig onderzoek en voor onderwijsdoeleinden.	□	□
Ik geef toestemming voor alles dat hierboven beschreven staat.	□	

Naam Deelnemer: Naam Onderzoeker:

Handtekening: Handtekening:

Datum: Datum: