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Rational empiric antibiotic therapy in clinical practice and policy making: uncertainties, probabilities, and ethics

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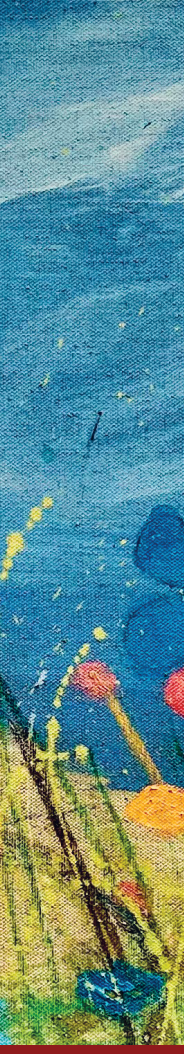
Part II

Decision making in daily clinical practice and antibiotic policymaking



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Determinants of in-hospital antibiotic prescription behaviour: a systematic review and formation of a comprehensive framework

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ABSTRACT

Background: Knowledge of determinants that influence antibiotic prescription behaviour (APB) is essential for the successful implementation of antimicrobial stewardship interventions. The theory of planned behaviour (TPB) is an established model that describes how cognitions drive human behaviour.

Objectives: The objective of this study was to identify the socio-cultural and behavioural determinants that affect APB and construct a TPB-framework of behavioural intent.

Data sources: The following online databases were searched: PubMed, Medline, Embase, Web of Science, Cochrane Library and Central.

Study eligibility criteria: Studies published between July 2010 and July 2017, in European countries, the United States, Canada, New-Zealand or Australia, were included if they identified one or more determinants of physicians' APB.

Methods: A systematic review was conducted according to the PRISMA-statement. Based on the TPB, determinants were categorised in behavioural, normative and control beliefs, thus shaping a conceptual framework of APB.

Results: Nine studies were eligible for inclusion, and identified 16 determinants. Determinants relating to fear of adverse outcome (5/9), tolerance of risk and uncertainty (5/9), hierarchy (6/9) and determinants concerning normative beliefs, particularly social team dynamics (6/9), were most frequently reported. Beliefs about antimicrobial resistance and potential negative consequences of antibiotic use were rarely mentioned.

Conclusions: Behavioural, normative and control beliefs are all relevant in APB. There is a need for quantitative studies assessing the weight of the individual determinants to be able to efficiently design and implement future stewardship interventions. The constructed framework enables a comprehensive approach towards understanding and altering APB.

INTRODUCTION

International guidelines on antimicrobial stewardship (AMS) aim to enhance the rational use of antimicrobial agents and thereby prevent their overuse.[1,2] To successfully implement stewardship strategies, it is essential to understand how physicians make decisions about prescribing antibiotics. Balancing the potential benefits and drawbacks of antibiotic prescription is a substantial challenge in daily clinical practice. Prescribing antimicrobial therapy typically involves decision making under uncertainty.[3,4] Under such uncertainty and in a complex decisional context, behavioural, social and cultural factors gain influence on decisions made with regard to antimicrobial therapy.[5,6] These determinants have been researched in a limited number of prior studies. Insight into their magnitude and relative importance in the process of managing antimicrobial therapy in the hospital setting is lacking. This knowledge is needed to design and successfully implement antimicrobial stewardship interventions that optimize antimicrobial therapy.[4,7,8] There is an urgent need to incorporate insights from behavioural and social sciences in the development of more impactful stewardship programmes.[9] However, very few studies about antimicrobial prescription behaviour (APB) enhancing interventions have focused on applying behaviour change theories.[7]

We considered the theory of planned behaviour (TPB) to be the most suitable model to better understand the cognitive determinants of APB.[10,11] This theory is social-cognitive in nature, positing that the decisions people make on whether or not to perform a certain behaviour are determined and explained by the specific ideas (cognitions) people have about the target behaviour. The theory is explained in Box 1 and visualized in Fig. 1.

Our aim was to develop a framework to explain APB by identifying its cognitive determinants. We conducted a systematic review to map the determinants that potentially affect antimicrobial prescription. The determinants identified by the systematic review were organized according to TPB to display overlap and conceptual differences.

Box 1. The Theory of Planned Behaviour

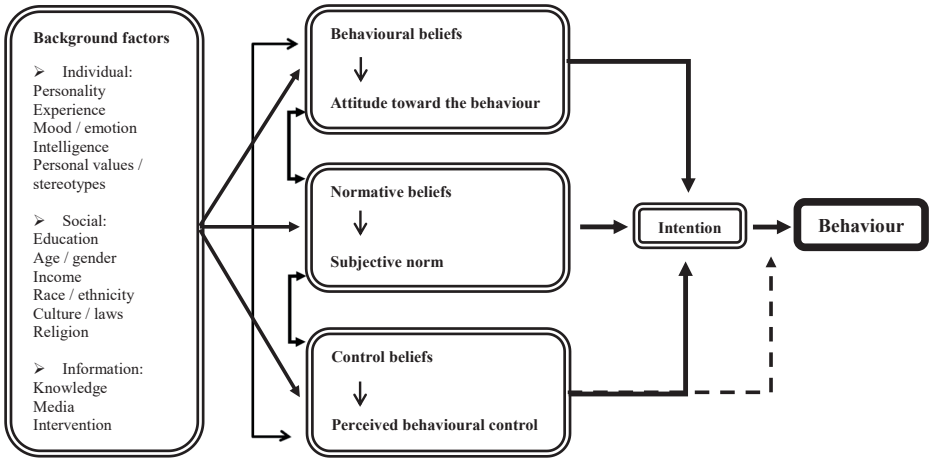
This model postulates that behaviour can be explained by three main concepts: the attitude towards the behaviour, the social norm regarding the behaviour, and the perception of control over execution of the behaviour [10,11]. Each of these concepts is based on a number of specific beliefs. Attitude, social norm and perceived behavioural control determine the intention to perform the behaviour, which is considered the best predictor of actually performing the behaviour.

Behavioural beliefs: Behavioural beliefs are the cognitions about the direct consequences of performing the behaviour - in our case the consequences of APB - for example, the risk of not providing optimal cure, or the long-term consequences for the functionality of antibiotics. A distinction can be made between beliefs pertaining to direct personal outcomes (e.g. the effect of antibiotics on survival in sepsis) and beliefs pertaining to outcomes with a moral bearing (e.g., concerning felt responsibility for the patient's health, irrespective of practical consequences. Because all beliefs constitute expectations that come with a certain degree of uncertainty, each belief is an estimate, qualified by a degree of (un)certainty. Some researchers have proposed to include the moral beliefs as a separate factor, called 'personal norm'. For the current purposes, it makes sense to include this as being part of the set of beliefs that underlie the attitude.

Normative beliefs: Normative beliefs are estimates of how the social environment of the actor will consider his/her behaviour. The relevant social environment for APB will mainly consist of colleagues, superiors, and other persons in the hospital environment. Note that explicit approval or disapproval is not required for a social norm to operate. In their latest description of the TPB Fishbein and Ajzen take also the so called descriptive norm into account: the observation what relevant others do. For APB both kinds of social norms, the explicit and the observation-based social norm, may operate on the behaviour.

Control beliefs: Control beliefs refer to the difficulty or ease of executing the behaviour. For several reasons APB may contain difficulties: for example it may be perceived difficult to get a superiors' permission to withhold antibiotic treatment or it might be difficult to explain to the patient why antibiotics are not prescribed.

Figure 1. The theory of planned behaviour.



Legend. Icek Ajzen's framework of TPB. The striped arrow represents the consideration that perceived behavioural control cannot substitute the actual behavioural control, when the perceived behavioural control is not completely accurate.

METHODS

Literature search strategy

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[12] To include all relevant articles, the following online databases were searched: PubMed, Medline, Embase, Web of Science, Cochrane Library and Central. The search syntaxes were formatted separately for each database. The exact search strategies and dates are listed in Supplementary data. The search output was restricted to articles published in the last 10 years (July 2007 to July 2017). The reason for this time restriction is that medical practice changes rapidly, as does society as a whole; for example, awareness of antimicrobial resistance (AMR) has improved significantly over the past decades[13,14] and antibiotic stewardship has become more prominent in daily clinical practice.[15] The intention was to focus on what currently drives doctors with regard to prescription behaviour. Reference lists of the included articles and relevant reviews were used to screen for missed articles.

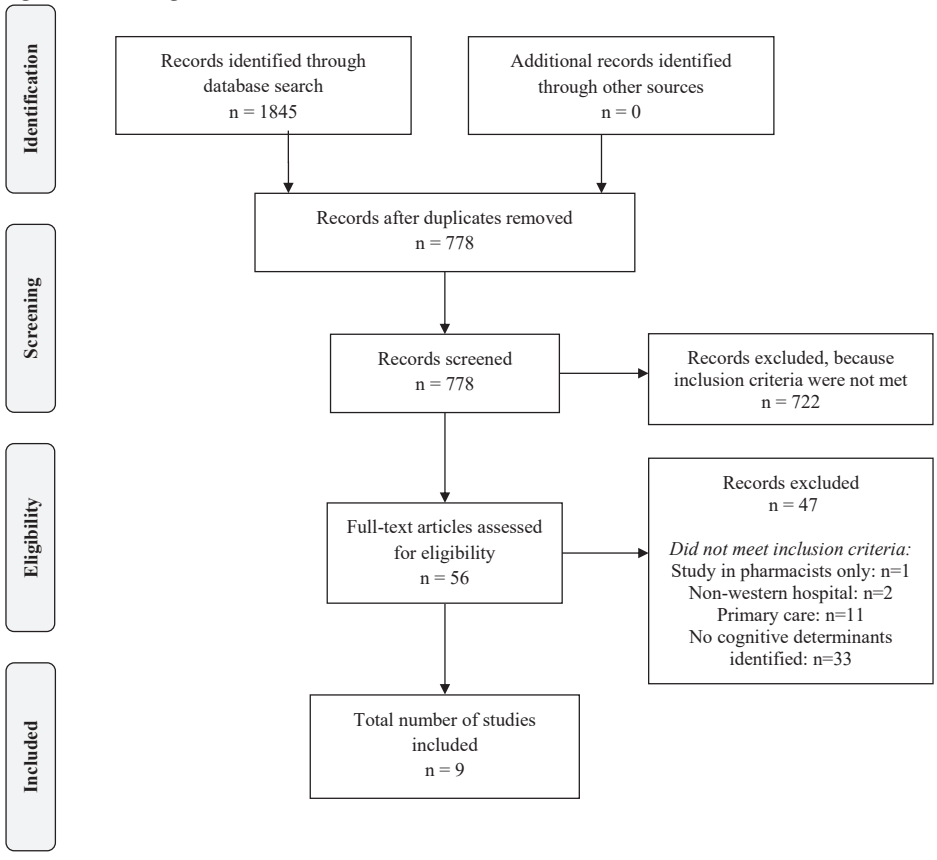
Study selection: inclusion and exclusion criteria

A study was included if it identified one or more self-reported cognitive determinants of any kind (social, personal, logistic, environmental, etc.) of antibiotic prescription behaviour of hospital physicians. Only studies performed in hospitals in European countries, the United States, Canada, New Zealand or Australia were eligible for inclusion. Studies that measured the effect of an antibiotic stewardship intervention and studies that

exclusively focused on the influence of patient-related clinical characteristics (e.g. vital parameters and suspected source of infection) were excluded, because this review is aimed at elucidating behavioural rather than biomedical determinants.

As a first step, all articles were independently screened by two individual investigators (EW and RW) based on title and abstract. Articles that were scored as relevant by at least one of these two investigators were included for the second phase that consisted of a full-text review. Articles judged to be eligible after full-text review were included for quality assessment. If doubt remained in the final phase of inclusion, a third investigator (MB) was consulted to decide on inclusion or exclusion. The result of the screening and inclusion process is displayed in the flow diagram in Figure 2. EndNote software (version X7) was used to remove duplicates and systematically complete the screening process.

Figure 2. Flow diagram (PRISMA) of the article inclusion process.



Data extraction and quality assessment

From each included study, the study design, geographical location of included hospitals, type of hospital, the number of physicians included, and the determinants of APB were extracted (Table 1). The Critical Appraisal Skills Program (CASP) 2017 scoring system for quality assessment of qualitative research was applied (Supplementary data).[16] The quality assessment was performed individually by two researchers (ML and EW) and discrepancies were discussed. If doubt remained, a third investigator (MB) was consulted.

Construction of a conceptual framework according to the theory of planned behaviour

Fishbein and Ajzen state that the TPB is sufficient to understand behaviour, such that all other influences are mediated by the concepts in the model. Personality, values and sociographic characteristics of the population may have an effect, but are extrinsic to the model and are assumed to impact behaviour through their influence on the three sets of beliefs: underlying attitude, social norm, and perceived behavioural control. For the purpose of our analysis, the first column of concept-specific beliefs is most important: the behavioural, normative, and control beliefs (Box 1).

Determinants of APB were identified from the studies and organized according to TPB principles (ML, EW). Classification and allocation of determinants within the framework were discussed within the research group (which consisted of behavioural scientists and infectious diseases specialists). Potential additional determinants that were not identified through the current systematic review, but were identified based on existing TPB literature, theoretical grounds and through discussion, were added to the model (indicated in Fig. 3 in italics)

RESULTS

Systematic review

The database search yielded 761 unique records; 56 articles were included for full-text reading, of which nine articles were selected for analysis after quality assessment.[5,6,8,17-22] The study characteristics of these nine studies are summarized in Table 1. The majority of the studies had a qualitative design, mostly based on semi-structured interviews. Parker *et al*. and Velasco *et al*. performed quantitative studies, and in the study of May *et al*. both quantitative and qualitative methods were used.[8,19,20] In all qualitative studies, between ten and 30 physicians were interviewed, based on the number of interviews needed to reach satisfaction.

Table 1. Study characteristics.

Study	Geographical location	Hospital type	Study design	Number of participants
Broom A et al. 2014 [5]	Queensland, Australia	General metropolitan hospital	Qualitative: semi-structured interview	30
Broom J et al. 2016 [22]	North-East England	1200-bed NHS[a] teaching hospital	Qualitative: semi-structured interview	20
Charani et al. 2013 [21]	West London, United Kingdom	4 hospitals of the ICHNT[b]	Qualitative: semi-structured interview	10
Cortoos et al. 2008 [17]	Belgium	Tertiary care hospital 1900-bed, university hospital	Qualitative: focus group interview	22
Livorsi et al. 2015 [6]	Indianapolis, United States of America	2 hospitals: 316-bed safety-net hospital and 209-bed tertiary-care hospital	Qualitative : semi-structured interview	30
May et al. 2014 [20]	United States of America	8 hospitals: urban tertiary care academic centres, military treatment facilities, county facility, tertiary paediatric centre	Qualitative and quantitative: Questionnaires and semi-structured interviews (non-parametric analysis of important factors and predictors)	150 /21[c]
Parker et al. 2016 [8]	South-West England	3 teaching hospitals including a tertiary referral centre, 1district general hospital	Quantitative: questionnaire (exploratory factor analysis and subsequent pairwise comparisons)	254
Schouten et al. 2007 [18]	South East of the Netherlands	3 secondary care hospitals	Qualitative: semi-structured interview	17
Velasco et al. 2011 [19]	Germany	State medical associations	Quantitative: questionnaire	3492

Legend: a. NHS = National Health Service; b. ICHNT = Imperial College Healthcare National Health Service Trust. c. 150 participants were included in the quantitative study, 21 in the qualitative study.

From the results of the included studies, 16 individual determinants of APB were identified (Table 2). Factors concerning managing risks and tolerating uncertainty were mentioned in five of nine studies. When it comes to fear of adverse outcomes, physicians primarily refer to adverse outcomes by not treating infection (5/9). Adverse effects that may accompany prescribing antibiotics, such as toxicity and *Clostridioides difficile* infection, were identified as a determinant in one study, but the influence of this on antibiotic decisions was assessed to be limited.[6]

One of the identified factors was the perceived tendency of physicians to follow the example of colleagues (3/9). The interviewed physicians referred to the influence of hospital routines and the feeling that mimicking peers is a habit. This influence works in

Table 2. Determinants of antibiotic prescription behaviour (APB) and examples of interventions.

Determinant	Description	Example	Study	Example of potential intervention(s)
The example set by colleagues	The example of others (both peers and senior) physicians in decision making in antimicrobial prescribing	"Whatever attending you are with is the attending you learn from, and if I see them continuously not prescribe antibiotics over and over again, then I feel comfortable not prescribing antibiotics …" [6] "our behaviour is heavily influenced by what we see, and (what) people do around us" [5]	Broom et al. [5] Livorsi et al. [6] Cortoos et al. [17]	Making senior physicians aware of their role model function and training them in explicating their motivation for antibiotic therapy Enhancing young physicians' reflective assessment of their superiors' antibiotic decisions, to discern those aspects that are worth adopting [27]
Social team dynamics	Willingness to intervene in the antimicrobial decisions of peers. Preference of work relationships over questioning treatment decisions of peers	"Out of courtesy to colleagues, no criticism of the chosen antibiotic regime is made at end-of-shift meetings" [18] "The rule of non-interference with the clinical decision of others" [21] "Participants found it inherently difficult to criticize another physician's care. They did not want to 'offend' a colleague or harm a 'good collegial relationship'" [6]	Broom et al. [5] Livorsi et al. [6] Charani et al. [21] Broom et al. [22] Parker et al. [8] Schouten et al. [18]	Training medical students and physicians on giving and receiving feedback Incorporating information on the antibiotic policy (including rationale) at end-of-shift meetings Evaluating antibiotic prescription quality on the department level and acknowledging teams for improvements in quality of prescribing (team effort) [28]
Hierarchic influence	The influence of hierarchy on antimicrobial treatment decisions	"The influence of hierarchies (…..) consultants being 'unquestionable'" [22]	Broom et al. [5] Charani et al. [21] Livorsi et al. [6] Schouten et al.[18] Broom et al. [22] Parker et al. [8]	Training leadership skills (medical students and young professionals) [29] Creating projects aiming at improvement of team performance and a positive work environment
Reputational risk	The risk of being criticised for being too conservative versus for being careless	"I don't want to be criticised for being either a cowboy or too cautious. So I want to do what is recognized as the standard of care" [5]	Broom et al. [5] Livorsi et al. [6]	Promoting a positive error and safety culture [30]

Table 2. Determinants of antibiotic prescription behaviour (APB) and examples of interventions. (*continued*)

Determinant	Description	Example	Study	Example of potential intervention(s)
Logistics	The available time to make a decision (time pressure), available resources, timing of ward rounds, timing of supervision	"Your sole purpose at 3 in the morning is to get them through till 9 in the morning" [22] "Working pressure was mentioned by both resident groups as a cause of not being able to consult guidelines" [17]	Broom et al. [5] Cortoos et al. [17] Broom et al. [22] May et al. [20] Schouten et al. [18]	Improving ward round practice: routine medication review and consideration of antimicrobial de-escalation Improving communication of microbiology results and accessibility of infectious diseases consultation
Antimicrobial resistance (AMR)	Awareness of the need to be careful with antibiotics because of resistance (population level) and ascription of responsibility concerning emerging antimicrobial resistance	"…physicians agreed that their own work has an influence on antimicrobial resistance" [19] "When it comes to individual patients I think sometimes it (resistance) is down the list I guess of considerations" [5]	Broom et al.[a 5] Livorsi et al.[a 6] Parker et al. [8] Velasco et al. [19]	Medical education about 'antibiotic awareness' [31] Facilitating monthly feedback to physicians on their own prescription characteristics (e.g. using ICT programs) Distributing posters/leaflets that enhance 'antibiotic awareness' among healthcare professionals
Benevolence	The desire to do good to patients. The (emotional) interaction between physician and patient	"Your relationship with your patient is much stronger than your relationship with the hospital inpatient population and the microbial ether that we live in …" [5]	Broom et al. [5] Livorsi et al. [6]	Addressing responsibility towards both today's patients and future patients during medical education
Guidelines	Attitude towards (local) practice guidelines/studies and beliefs on applicability of guidelines to the individual patient	"Sometimes it is difficult to use the policy because the policy will be your average sort of thing, it's not looking at someone at the top or the bottom" [21] "I am quite likely to overstep the guidelines if it was left to my devices" [21] "Both surgery groups felt that antibiotic guidelines were not adapted to their practice and that use of antibiotic guidelines in their wards could hamper efficient patient flow" [17]	Charani et al. [21] Cortoos et al. [17] Parker et al. [8] Schouten et al. [18]	Improving applicability of guidelines by adapting them to: - variants of the clinical syndrome - specific patient populations Letting prescribers participate in hospital guideline formation to improve support and adherence [17]

Table 2. Determinants of antibiotic prescription behaviour (APB) and examples of interventions. (*continued*)

Determinant	Description	Example	Study	Example of potential intervention(s)
Professional autonomy	Feeling self-directing and independent in making decisions on antibiotic therapy	"I am a clinician and have some degree of independent practice" [21]	Charani et al. [21] Parker et al. [8]	Training and coaching of young professionals in structured antibiotic decision making [32]
Prior experiences	Prior individual cases influence future treatment decisions. A physician who has lost a patient because of too narrow antimicrobial therapy will be more likely to give broad-spectrum treatment in the future	"My anecdotal experience is that they (immunosuppressed end-stage renal population) get sick very quickly" [21]	Charani et al. [21] Velasco et al. [19]	Facilitating the availability of support groups (peers) to evaluate and discuss adverse outcome in individual cases
Clinical experience and education	Years and type of clinical experience and education	"A junior physician is more likely to prescribe broad-spectrum treatment whereas a senior physician may accept more immediate risk" [5]	Broom et al. [5] Charani et al. [21] Broom et al. [22] May et al. [20] Schouten et al. [18] Velasco et al. [19]	Training on antibiotic therapy and stewardship for medical students and young professionals [31,33]
Tolerance of uncertainty	How much risk a physician is willing to take in case of (potential) infection	"I probably tend to overtreat rather than to undertreat… fear of relapse and uncertainty that they're going to get better" [5] "just in case" [6]	Broom et al. [5] Velasco et al. [19] Livorsi et al. [6] May et al. [20] Schouten et al. [18]	Providing education on dealing with uncertainty in medical practice (in medical school and peer-to-peer groups for young professionals [3,34] Promoting rapid diagnostics to differentiate bacterial versus non-bacterial aetiology [35]
Perceived ability to communicate the decision (not to treat) to the patient	How well the provider feels to be able to communicate about the antibiotic treatment with the patient	"Sometimes the purpose in giving antibiotics sometimes is to keep the family happy" [5]	Broom et al. [5] Broom et al. [22] May et al. [20]	Training communication skills in healthcare professionals (dedicated to antibiotic therapy) [36] Improving the publics' knowledge of antibiotic therapy: antibiotic awareness campaigns [9]

Table 2. Determinants of antibiotic prescription behaviour (APB) and examples of interventions. (*continued*)

Determinant	Description	Example	Study	Example of potential intervention(s)
Complaints/litigation	Fear of complaints or litigation	"I have seen lawsuits for delays in therapy" [6] "More than 75% of those interviewed noted the threat of patient complaints as linked to decisions about antibiotics, indicating that this is an increasingly important pressure" [22]	Livorsi et al. [6] Broom et al. [22]	Training and facilitating shared decision making [37] Executing hospital interventions to improve inpatient understanding of antibiotic therapy [38] Facilitate legal support for medical staff
Adverse outcome (1): Infection	Fear of adverse outcomes by not treating infection	"Oh, fear of relapse and uncertainty that they're going to get better" [5]	Broom et al. [5] Velasco et al. [19] Livorsi et al. [6] Broom et al. [22] Schouten et al. [18]	Providing evidence-based decision support systems for the selection of empirical therapy 39 and for safe de-escalation, e.g. for the intravenous–oral switch [40]
Adverse outcome (2): negative consequences of antibiotic treatment	Fear of adverse outcomes related to the administration of antibiotics (e.g. *Clostridium difficile* infection, renal toxicity)	"…concerns were not expressed about patients' risk for developing *Clostridium difficile* or an infection with an antibiotic resistant microorganism" [6]	Livorsi et al.[a] [6]	Incorporating the topic of side-effects of antibiotics in medical education Enabling electronic registration and review of complications of antibiotic therapy within medical teams

Legend: a: Reports limited influence.

multiple ways, as both positive (role model) behaviour and bad examples were reported to have an influence on APB.

The perceived importance of maintaining a constructive work relationship and the reluctance to intervene in a colleague's antimicrobial prescription decision were mentioned in six studies. The determinant 'hierarchic influences', meaning the extent to which behaviour is affected by advice and instructions from senior physicians, was drawn from six studies.

Awareness of the issue of AMR on the population level was identified as a factor of influence in four out of nine studies. In the study by Livorsi *et al*.[6] this awareness was attributed limited influence on APB, particularly because of low ascription of responsibility. Broom *et al*.[5] described mixed perspectives on the importance of AMR. In general, the issue of AMR on the population level was well recognized by the participants, but it was regarded as a peripheral issue in APB.

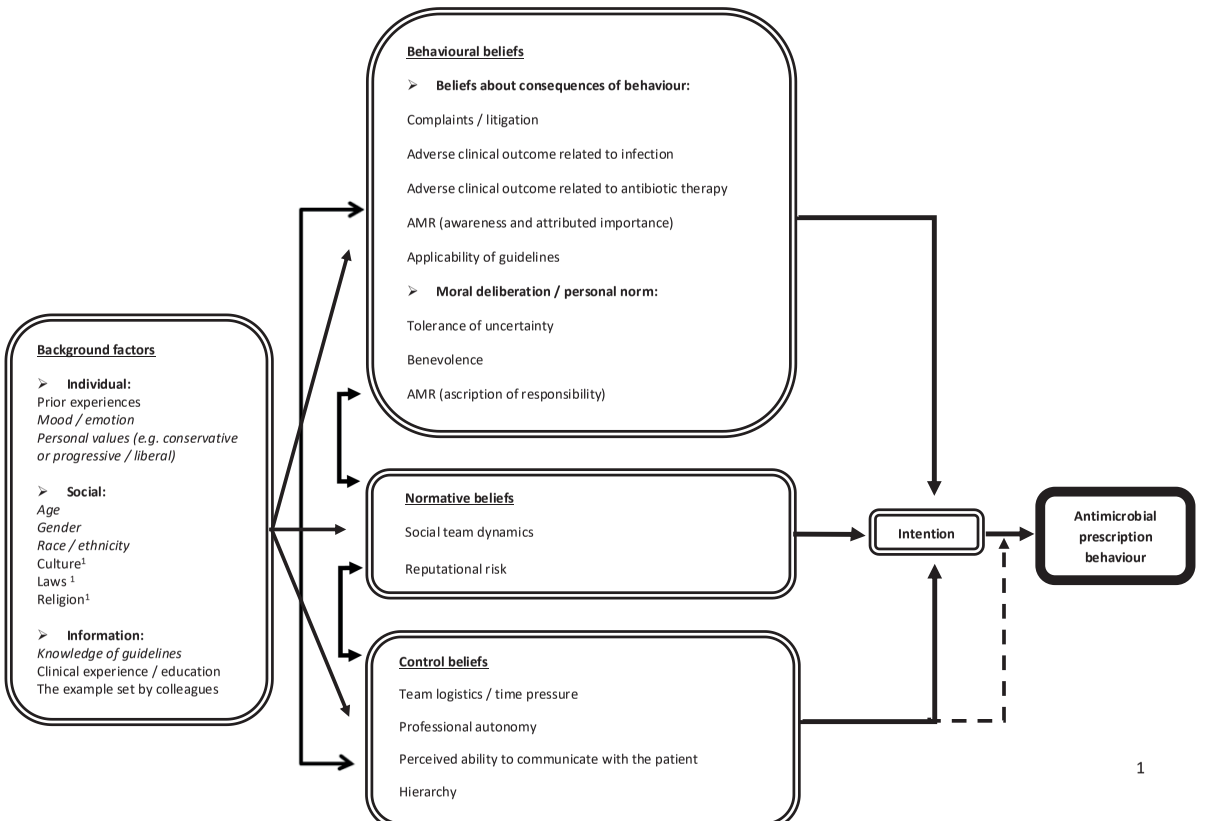
Organisation of the determinants of APB in the framework of TBP

The majority of identified determinants (13/16) were allocated to one of the three major pillars of the model (Fig. 3). The remaining three determinants were identified as background factors.

Three previous reviews focused on the subject of determinants of antibiotic prescription behaviour of physicians in Western hospitals.[4,23,24] Three additional determinants - religion, culture and law -were identified in the review performed by Hulscher *et al*.[24], and were considered relevant as background determinants in our TPB model.[24] Mood, emotion, personal values (e.g. conservative or progressive/liberal), age, gender and race/ethnicity were described as possible (background) determinants based on theoretical grounds and previous studies in fields other than APB.

Attitude towards AMR was separated into: (a) awareness and attributed importance, and (b) ascription of responsibility. For example, a physician may be well aware of the fact that antibiotic consumption drives AMR, but may not feel responsible. The first aspect (awareness) is best allocated to beliefs about the consequences of behaviour, while the second (ascription of responsibility) is best allocated to moral deliberation/personal norm. Determinants concerning the working environment and interaction with colleagues were divided into four aspects. (a) *The example set by colleagues*; the APB of other physicians, both peers and senior physicians, was considered a background factor. (b) *Social team dynamics* were classified as normative beliefs; for example, changing an antibiotic treatment that was initiated by a colleague might harm the working relation-

Figure 3. The theoretical framework of antimicrobial prescription behaviour.



Legend. The results of the systematic review were placed in the theoretical framework of antimicrobial prescription behaviour. The model is based on Icek Ajzen's framework of theory of planned behaviour (TPB). Potential additional determinants that were not identified through the current systematic review, but were identified based on existing TPB literature, theoretical grounds and discussion, were added to the model and indicated in this figure in italic type. The striped arrow represents the consideration that perceived behavioural control cannot substitute the actual behavioural control, when the perceived behavioural control is not completely realistic. AMR = attitude towards antimicrobial resistance. 1. determinant identified from the review by Hulscher ME, Grol RP, van der Meer JW. Antibiotic prescribing in hospitals: a social and behavioural scientific approach. The Lancet Infectious diseases. 2010;10(3):167-75.

ship. (c) *Hierarchy* was separated from *social team dynamics*, as it relates to beliefs on the persistence that is required to execute a desired behaviour; for example, it might be very difficult to persuade a senior physician to agree on discontinuation of antibiotics. (d) *Reputational risk* is closely related to *hierarchy* and *social team dynamics*, but was considered a separate factor as it represents primarily the beliefs on the risk of being criticized for the behaviour.

DISCUSSION

This systematic review shows that fear of an adverse outcome because of untreated infection and (lack of) tolerance of uncertainty are prominent determinants of APB. Moreover, determinants concerning the subjective norm, such as reputation, were frequently identified as being important. It is remarkable that the negative consequences of antibiotic therapy -both at the individual patient level and at the population level - were only scarcely identified by physicians as a determinant of antimicrobial treatment decisions.

One of the strengths of the TPB model is that a plurality of determinants could be summarized in a comprehensive model. It provides insight into the coherence of determinants and forms a base for further understanding of APB. This framework can be of benefit in the design and implementation of stewardship interventions, which serve the ultimate goal of improving antimicrobial prescription by influencing behavioural intent. Using this framework, relevant beliefs regarding a specific antimicrobial prescription issue or antimicrobial stewardship policy can be assessed up front. This allows for modification of stewardship interventions according to the identified determinants, which is likely to contribute to the successful implementation of those interventions.

This study provides 16 determinants that are all potential targets for which interventions can be developed. Examples of potential interventions targeting individual determinants are provided in Table 2. However, not all determinants may be influenced to the same extent. In other words, not all beliefs are equally accessible or pliable. Increasing awareness of AMR, for example, is a more realistic goal than influencing tolerance of uncertainty. To decide how to direct future stewardship interventions, it is essential to assess and consider the relative weight of the individual determinants.[25,26] For example, raising awareness of AMR has frequently been suggested by many contributors as a paramount intervention towards achieving responsible APB.[7,9] Yet the success of raising awareness vis-a-vis other interventional strategies is contingent upon several behavioural assumptions, especially upon the extent to which increased AMR awareness alters

a professional's behavioural intent. Hence, research that elucidates and subsequently validates which behavioural determinants have a substantial impact on APB contributes considerably to designing interventions that are effective, efficient and evidence-based. Empirical research, using a quantitative approach and multiple regression analysis, is mandatory to assess which of the three basic components - attitude, social norm, or perceived behavioural control - and which of the corresponding determinants have a strong influence on behaviour. Interventions could then be directed to target the most influential and thus promising component(s).

Our study has several limitations. In the included studies there were no references to TPB principles or to other established theories within the behavioural sciences. Second, it is possible that researchers' or physicians' unawareness of factors leading to (intended) behaviour may have led to underreporting or omission of relevant determinants. Hence, the content of the provided framework may not be exhaustive. Third, it should be noted that the study was aimed at affluent Western countries. The applicability of the framework to other settings (e.g. different cultural backgrounds, resources and standards with regard to medical practices) may be limited.

In conclusion, our review provides an overview of the cognitive determinants of APB. The theoretical framework of APB classifies the major determinants and provides insight into their interrelationship. This is an important step towards answering the ultimate question: what determinant(s) do we need to target to effectively impact prescription behaviour? To be able to provide answers, quantitative studies based on the TPB and focused on explicit clinical situations are warranted. In the battle against resistance, aimed at preserving adequate antibiotics for the next generation, medical expertise in conjunction with psychological insights may well be one of our most effective weapons.

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SUPPLEMENTARY DATA

Database search syntaxes

Database search was performed on 12 July 2017. In total, 778 references were screened (after duplicates were removed), in the following databases: PubMed (n=598), Medline (n=697), Embase (n=333), Web of Science (n=110), Cochrane Library (n=54), Central: (n=53).

- *Search syntax for PubMed:*

http://www.ncbi.nlm.nih.gov/pubmed?otool=leiden:

((“antimicrobial prescribing”[tw] OR “anti-microbial prescribing”[tw] OR “antimicrobials prescribing”[tw] OR “anti-microbials prescribing”[tw] OR “antibiotic prescribing”[tw] OR “anti-biotic prescribing”[tw] OR “antibiotics prescribing”[tw] OR “anti-biotics prescribing”[tw] OR “antibacterial prescribing”[tw] OR “anti-bacterial prescribing”[tw] OR “antibacterials prescribing”[tw] OR “anti-bacterials prescribing”[tw] OR ((“antibiotic use”[tw] OR “antibiotics use”[tw] OR “antibiotic usage”[tw] OR “antibiotics usage”[tw]) AND prescrib*[tw])) AND (“determinant”[tw] OR “determinants”[tw] OR determinant*[tw] OR factors influenc*[tw] OR influencing factor*[tw] OR factors affect*[tw] OR affecting factor*[tw] OR “Culture”[majr] OR “Attitude of Health Personnel”[majr] OR “Practice Patterns, Physicians’”[majr] OR “Professional Competence”[majr] OR “Guideline Adherence”[majr])) **NOT (“Animals”[mesh] NOT “Humans”[mesh]) AND (“2007/01/01”[PDAT] : “3000/12/31”[PDAT])**

- *Search syntax for MEDLINE:*

http://gateway.ovid.com/ovidweb.cgi?T=JS&MODE=ovid&NEWS=n&PAGE=main&D=prmz:

((“antimicrobial prescribing”.mp OR “anti-microbial prescribing”.mp OR “antimicrobials prescribing”.mp OR “anti-microbials prescribing”.mp OR “antibiotic prescribing”.mp OR “anti-biotic prescribing”.mp OR “antibiotics prescribing”.mp OR “anti-biotics prescribing”.mp OR “antibacterial prescribing”.mp OR “anti-bacterial prescribing”.mp OR “antibacterials prescribing”.mp OR “anti-bacterials prescribing”.mp OR ((“antibiotic use”.mp OR “antibiotics use”.mp OR “antibiotic usage”.mp OR “antibiotics usage”.mp) AND prescrib*.mp)) AND (“determinant”.mp OR “determinants”.mp OR determinant*.mp OR factors influenc*.mp OR influencing factor*.mp OR ((“factor”.mp OR “factors”.mp) ADJ2 (influenc*.mp OR affect*/mp)) OR exp *”Culture”/ OR exp *”Attitude of Health Personnel”/ OR exp *”Practice Patterns, Physicians’”/ OR exp *”Professional Competence”/ OR exp *”Guideline Adherence”/)) **NOT (exp “Animals”/ NOT exp “Humans”/) AND (2007**

OR 2008 OR 2009 OR 2010 OR 2011 OR 2012 OR 2013 OR 2014 OR 2015 OR 2016 OR 2017 OR 2018).yr

- *Search syntax for Embase:*

http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=main&MODE=ovid&D=oemezd:

((“antimicrobial prescribing”.mp OR “anti-microbial prescribing”.mp OR “antimicrobials prescribing”.mp OR “anti-microbials prescribing”.mp OR “antibiotic prescribing”.mp OR “anti-biotic prescribing”.mp OR “antibiotics prescribing”.mp OR “anti-biotics prescribing”.mp OR “antibacterial prescribing”.mp OR “anti-bacterial prescribing”.mp OR “antibacterials prescribing”.mp OR “anti-bacterials prescribing”.mp OR ((“antibiotic use”.mp OR “antibiotics use”.mp OR “antibiotic usage”.mp OR “antibiotics usage”.mp) AND prescrib*.mp)) AND (“determinant”.mp OR “determinants”.mp OR determinant*.mp OR factors influenc*.mp OR influencing factor*.mp OR ((“factor”.mp OR “factors”.mp) ADJ2 (influenc*.mp OR affect*.mp)) OR exp *”Culture”/ OR exp *”Health Personnel Attitude”/ OR *”Clinical Practice”/ OR *”Professional Competence”/ OR *”Clinical Competence”/ OR *”protocol compliance”/)) **AND exp “Humans”/ AND (2007 OR 2008 OR 2009 OR 2010 OR 2011 OR 2012 OR 2013 OR 2014 OR 2015 OR 2016 OR 2017 OR 2018).yr** NOT conference review.pt, NOT (conference review or conference abstract).pt, AND (conference abstract).pt

- *Search syntax for Web of Science:*

http://isiknowledge.com/wos:

((TS=(“antimicrobial prescribing” OR “anti-microbial prescribing” OR “antimicrobials prescribing” OR “anti-microbials prescribing” OR “antibiotic prescribing” OR “anti-biotic prescribing” OR “antibiotics prescribing” OR “anti-biotics prescribing” OR “antibacterial prescribing” OR “anti-bacterial prescribing” OR “antibacterials prescribing” OR “anti-bacterials prescribing” OR ((“antibiotic use” OR “antibiotics use” OR “antibiotic usage” OR “antibiotics usage”) AND prescrib*)) AND TI=(“determinant” OR “determinants” OR determinant* OR “factors influenc*” OR “influencing factor*” OR ((“factor” OR “factors”) NEAR/2 (influenc* OR affect*mp)) OR “Culture” OR “Attitude of Health Personnel” OR “Physicians’ Practice Patterns” OR “Physicians Practice Patterns” OR “Physician Practice Patterns” OR “Physicians’ Practice Pattern” OR “Physicians Practice Pattern” OR “Physician Practice Pattern” OR “Professional Competence” OR “clinical competence” OR “Guideline Adherence”)) **AND py=(2007 OR 2008 OR 2009 OR 2010 OR 2011 OR 2012 OR 2013 OR 2014 OR 2015 OR 2016 OR 2017 OR 2018) NOT ti=(veterinary OR rabbit OR rabbits OR animal OR animals OR mouse OR mice OR rodent OR rodents OR rat OR rats OR pig OR pigs OR porcine OR horse* OR equine OR cow OR cows OR**

bovine OR goat OR goats OR sheep OR ovine OR canine OR dog OR dogs OR feline OR cat OR cats)) OR ((TI=("antimicrobial prescribing" OR "anti-microbial prescribing" OR "antimicrobials prescribing" OR "anti-microbials prescribing" OR "antibiotic prescribing" OR "anti-biotic prescribing" OR "antibiotics prescribing" OR "anti-biotics prescribing" OR "antibacterial prescribing" OR "anti-bacterial prescribing" OR "antibacterials prescribing" OR "anti-bacterials prescribing" OR (("antibiotic use" OR "antibiotics use" OR "antibiotic usage" OR "antibiotics usage") AND prescrib*)) AND TS=("determinant" OR "determinants" OR determinant* OR "factors influenc*" OR "influencing factor*" OR (("factor" OR "factors") NEAR/2 (influenc* OR affect*mp)) OR "Culture" OR "Attitude of Health Personnel" OR "Physicians' Practice Patterns" OR "Physicians Practice Patterns" OR "Physician Practice Patterns" OR "Physicians' Practice Pattern" OR "Physicians Practice Pattern" OR "Physician Practice Pattern" OR "Professional Competence" OR "clinical competence" OR "Guideline Adherence")) **AND py=(2007 OR 2008 OR 2009 OR 2010 OR 2011 OR 2012 OR 2013 OR 2014 OR 2015 OR 2016 OR 2017 OR 2018) NOT ti=(veterinary OR rabbit OR rabbits OR animal OR animals OR mouse OR mice OR rodent OR rodents OR rat OR rats OR pig OR pigs OR porcine OR horse* OR equine OR cow OR cows OR bovine OR goat OR goats OR sheep OR ovine OR canine OR dog OR dogs OR feline OR cat OR cats))**

- *Search syntax for Cochrane Library:*

http://www.cochranelibrary.com/:

ti/ab/kw

(("antimicrobial prescribing" OR "anti-microbial prescribing" OR "antimicrobials prescribing" OR "anti-microbials prescribing" OR "antibiotic prescribing" OR "anti-biotic prescribing" OR "antibiotics prescribing" OR "anti-biotics prescribing" OR "antibacterial prescribing" OR "anti-bacterial prescribing" OR "antibacterials prescribing" OR "anti-bacterials prescribing" OR (("antibiotic use" OR "antibiotics use" OR "antibiotic usage" OR "antibiotics usage") AND prescrib*)) AND ("determinant" OR "determinants" OR determinant* OR "factors influenc*" OR "influencing factor*" OR (("factor" OR "factors") N2 (influenc* OR affect*mp)) OR "Culture" OR "Attitude of Health Personnel" OR "Physicians' Practice Patterns" OR "Physicians Practice Patterns" OR "Physician Practice Patterns" OR "Physicians' Practice Pattern" OR "Physicians Practice Pattern" OR "Physician Practice Pattern" OR "Professional Competence" OR "clinical competence" OR "Guideline Adherence")) **AND py=(2007 OR 2008 OR 2009 OR 2010 OR 2011 OR 2012 OR 2013 OR 2014 OR 2015 OR 2016 OR 2017 OR 2018)**

- ***Search syntax for CENTRAL:***

https://archie.cochrane.org/index.jsp?redirectTo=http://crso.cochrane.org/login.php&key=58c18a4283f80:

All fields

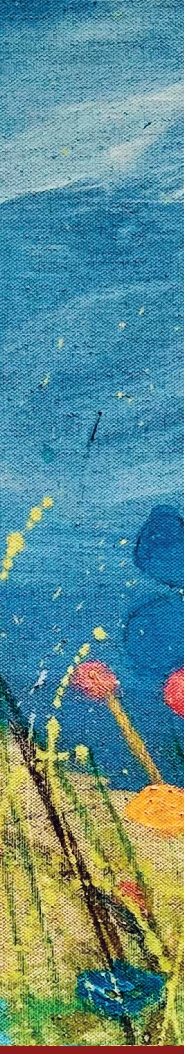
((“antimicrobial prescribing” OR “anti-microbial prescribing” OR “antimicrobials prescribing” OR “anti-microbials prescribing” OR “antibiotic prescribing” OR “anti-biotic prescribing” OR “antibiotics prescribing” OR “anti-biotics prescribing” OR “antibacterial prescribing” OR “anti-bacterial prescribing” OR “antibacterials prescribing” OR “anti-bacterials prescribing” OR ((“antibiotic use” OR “antibiotics use” OR “antibiotic usage” OR “antibiotics usage”) AND prescrib*)) AND (“determinant” OR “determinants” OR determinant* OR “factors influenc*” OR “influencing factor*” OR ((“factor” OR “factors”) AND (influenc* OR affect*mp)) OR “Culture” OR “Attitude of Health Personnel” OR “Physicians’ Practice Patterns” OR “Physicians Practice Patterns” OR “Physician Practice Patterns” OR “Physicians’ Practice Pattern” OR “Physicians Practice Pattern” OR “Physician Practice Pattern” OR “Professional Competence” OR “clinical competence” OR “Guideline Adherence”)) **AND py=(2007 OR 2008 OR 2009 OR 2010 OR 2011 OR 2012 OR 2013 OR 2014 OR 2015 OR 2016 OR 2017 OR 2018)**

Quality assesment

Table S1. Quality assessment.

CASP questions	Clear statement of findings?	Qualitative methodology appropriate?	Research design appropriate?	Recruitment appropriate?	Data collection in a way that addressed the research issue?	Has the relationship between researcher and participants been adequately considered?	Have ethical issues been taken into consideration?	Data analysis sufficiently rigorous?	Clear statement of the aims of the research?
Broom A et al. 2014 [7]	+	+	+	?	+		+	+	+
Broom J et al. 2016 [20]	+	+	+	?	+	+	+	+	+
Charani et al. 2013 [19]	+	+	+	+	+	?	+	+	+
Curtoos et al. 2008 [15]	+	+	+	?	+	?	+	+	+
Livorsi et al. 2015 [8]	+	+	+	+	+	+	+	+	+
May et al. 2014 [18]	+	+	+	+	+	?	+	+	+
Parker et al. 2016 [9]	+	n.a.[1]	+	+	+	?	+	+	+
Schouten et al. 2007 [16]	+	+	+	+	+	+	+	+	+
Velasco et al. 2011 [17]	+	n.a.[1]	+	+	+	?	+	+	+

Legend. The Critical Appraisal Skills Programme (2017) scoring system for quality assessment of qualitative research was applied. 1 = This was a quantitative study, the question is not applicable. + = The study meets the requirements for this aspect of the quality assessment. - = The study does not meet the requirements for this aspect of the quality assessment. ? = Insufficient information is provided in the article to judge this criterion.



Cognitive biases in the decision-making process of antibiotic prescribing

Letter

In response to our study described in the first part of this chapter, a letter was published by Peiffer-Smadja *et al*. In their letter the authors address the importance of cognitive biases in antibiotic decision making. They argue that the theory of planned behaviour (TPB) may not be the most suitable framework to consider the common cognitive biases in antibiotic decision making. As a reply, this second part of Chapter 7 discusses how biased or inaccurate beliefs are still relevant determinants of prescription behaviour and how they fit into the TPB.

Merel M.C. Lambregts, Leo G. Visser, Mark G.J. de Boer, Henk Staats, Eric Van Dijk

Clin Microbiol Infect. 2019; 638-639

We highly appreciate the response of Peiffer-Smadja and colleagues to our article, confirming the importance of using social sciences to understand antibiotic prescription behaviour (APB).[1,2] In their Letter, Peiffer-Smadja *et al*. advocate to supplement the proposed conceptual framework with insights from cognitive science, most notably on cognitive biases.[2]

We agree on the importance of addressing decision makers' cognitive limitations and biases, which already constitute an integral part of the theories and research in the social sciences. In our previous work we published on several of the listed cognitive limitations and biases, e.g. on the sunk cost effect, loss aversion, and omission/commission biases.[3-5]

It is important, however, to acknowledge our main study aim, to use the Theory of Planned Behaviour (TPB) as a conceptual framework to identify the beliefs and attitudes that drive APB. Notably, a biased or inaccurate belief, may still drive APB. Therefore, the biases listed by Peiffer-Smadja all fit with (and in) the framework of the TPB. The model makes no assumptions about rationality, but primarily focuses on internal consistency (e.g., does attitude follow from belief). Discussing the nature of TPB, Azjen stated: *"Whether true or false, biased or unbiased, beliefs represent the subjectively held information on which attitudes are based. Social psychology stipulated from the outset that people may hold beliefs about many objects and issues that are derived not from a logical process of reasoning but instead are biased*." [6]

Just as the authors of the TPB model embraced these insights, we underscore the importance of including and addressing people's cognitive limitations. Not as an element that should be seen as separate from the TPB framework; but as an element that may find its place in the framework. From an antibiotic stewardship perspective, all beliefs a doctor holds on antibiotics prescriptions are relevant, biased or not, as long as they influence the prescriptions they make. Again, we would like to quote Ajzen "*Although subjective and not necessarily accurate, these beliefs guide the decisions people make, and it is by examining the beliefs people hold that we can gain an understanding of decision-making in real-life situations* "[6]

Therefore, the first step is to identify the main determinants, e.g., by identifying what beliefs – valid or erroneous - doctors base their attitudes on, and by determining their relative importance. Eventually, this may provide the building blocks to subsequently base our stewardship interventions on. Nevertheless, we fully agree with Peiffer-Smadja *et al*. that in the future course of action, insights on decision heuristics and on cognitive or motivational biases are relevant and we concur with others on the call to study biases

in medical settings.[7] These insights from cognitive limitations and biases may have explanatory power as to the origin of people's beliefs and may therefore be relevant when designing specific interventions. For example, doctors may overestimate the medical risk of withholding antimicrobial therapy. In that case, correcting the misperceptions, and providing factual information may be a successful stewardship intervention.

Peiffer-Smadja *et al*. listed 17 cognitive limitations and biases; a list that we envisage could easily be enlarged to include other biases and effects as a well. Consider, for example, the disjunction effect illustrating that decision-makers often insufficiently engage in consequential reasoning when facing uncertainty.[8] Or the fact that people may display a self-serving bias in their attributions, denying responsibility for negative outcomes.[9]

However, generating a long(er) list of cognitive or motivational biases, may not be the most promising path towards a better understanding of APB. We run the risk of ending up with (again) a long list of effects and biases that lacks structure. But an organizing framework of relevant biases that provides structure might be helpful. It could be useful to distinguish between motivational and cognitive biases; or between biases affecting subjective probabilities and biases affecting the perceived severity of consequences; or between biases affecting social/normative factors and those impacting on one's perception of control over behaviour. Combined with the conceptual framework provided by the TPB this may enable us to further improve our understanding of APB and target antimicrobial stewardship interventions.

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