# Improving antibiotic use through educational interventions

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The growing rates of antimicrobial resistances demand the improvement of antibiotic use worldwide. The antibiotic misprescription by physicians, the antibiotic dispense without prescription by pharmacists, and the misuse by patients, are some of the most important factors underlying the increasing rates of antimicrobial resistances. Accordingly, it is of major importance to develop educational interventions targeting the different actors in the chain of antibiotic resistance, aiming to increase knowledge, understand attitudes and improve antibiotic use. In this chapter, readers can find a proposed design model which aims to improve the effectiveness of the educational interventions, presenting and developing each step that should be considered when implementing an educational intervention.

**Keywords** antibiotic resistance; educational intervention; pharmacists; physicians; patients

## 1. The scope

The discovery of antibiotics for clinical use in the 1930s transformed the treatment of infectious diseases worldwide and had an essential role on the development of modern medicine [1]. However, infectious diseases are still one of the most important leading causes of death in the world [2], demanding prompt counter measures to combat them.

Growing rates of antimicrobial resistance published worldwide [3, 4] made this a global concern. Antimicrobial resistance is defined by the ability of a microorganism to survive to clinical effective exposures of an antibiotic to which it was previously sensitive [5]. In a worldwide perspective, antimicrobial resistance has several clinical, economic and social consequences: (i) antimicrobial resistance is the cause of death of at least 150.000 persons a year [6]; (ii) antimicrobial resistance increase the difficulty to control infectious diseases, prolonging the illness period and increasing the probability of death [7]; (iii) antimicrobial resistance increase the costs of infections treatment [7, 8]; and (iv) antimicrobial resistance threatens several achievements in medicine and the return to a pre-antibiotic era [6].

Underlying the development of antimicrobial resistance is the use of antibiotics [9], without an evident benefit to public health [10]. In fact, the selective pressure that antibiotic use cause leads to mounting rates of resistant organisms, demanding a global action to improve antibiotic use by health professionals and patients: "Combat drug resistance: no action today, no cure tomorrow"[6]. European Surveillance of Antimicrobial Consumption (ESAC) reports reveal unexplained differences in antimicrobial consumption between European countries that show that actions must be taken to combat antibiotic misuse [11].

Antibiotic access is, in many countries, limited by medical prescription, revealing the central role that physicians have is this field. However, the antibiotics dispense without prescription and counselling by pharmacists [12] or the misuse of antibiotics by patients make them also important players in this global problem. Accordingly, it is of major importance to develop educational interventions directed to different actors in the chain of antibiotic resistance, aiming to increase knowledge, understand and change attitudes, improve antibiotic use and diminish resistances. About health professionals, and considering that physicians and pharmacists have a direct role on patient antibiotic use, improve their education and clinical performance seems to be essential to improve patient antibiotic use.

An educational intervention, to be effective as a strategy to improve antibiotic use, must be designed to be multifaceted (educational programs must comprise different types of interventions), to take into account the characteristics and barriers presented in the specific setting, to be feasible to implement, and to target more than one group of health professionals, patients and general public [13]. Cochrane review (2005) described several types of interventions [13]: (i) distribution of educational materials; (ii) educational meetings; (iii) local consensus process; (iv) educational outreach visits; (v) local opinion leaders; (vi) patient-mediated interventions; (vii) audit and feedback; (viii) reminders; (ix) marketing; (x) mass media; and (xi) financial interventions. The selection of the most effective type of intervention is specific for each setting, target population and target behaviour, and must be carefully analysed to improve the effectiveness of the main intervention.

Several educational interventions have been developed and published targeting to improve antibiotic prescribing, dispense and use [14-16] . Those interventions are considerably different in terms of study design, setting, target

population, target behaviours, intervention effectiveness, acceptability by the target population and follow-up analysis. Considering that the impact/effectiveness of an educational intervention in the clinical practice is directly affected by the design, development and implementation process, Figure 1 present a proposed model to develop educational interventions.
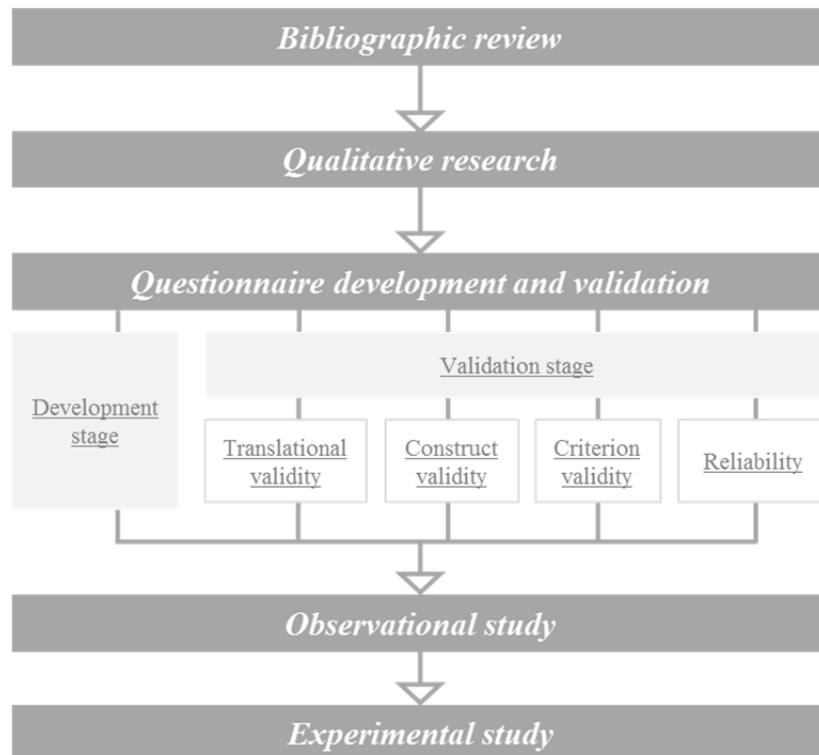


**Fig. 1** Educational intervention design model.

Accordingly to Figure 1, the model purposed present 5 different steps: (i) Bibliographic review; (ii) Qualitative research; (iii) Questionnaire development and validation; (iv) Observational study: Relating health professional attitudes and antibiotic use; (v) Experimental study: a cluster-randomized controlled trial.

## 2. Bibliographic review

The world is living in the information era and it is important for health professionals, researchers and general public to have access to tools that allow them to search and choose the most appropriate source of information in the less consuming frame time. That's where reviews have their part of importance in the information path, once they summarize amounts of information into easy and fast consuming tools.

A review is used to compress, analyse and communicate an amount of information compiled with the goal of comparing the different results obtained by several research teams over the years throughout the world [17, 18]. A review can be defined as a compilation of the results and conclusions of publications of certain subject, while an overview or a systematic literature review comprehends a broad search and identification of all publications of the selected subject. A meta-analysis is the use of statistical methods to compile and summarize the results (odds ratio, medians, …) into comparable values [17]. There are many advantages of a systematic review: they allow investigators and curious to have at their disposal a study of the scientific findings, and have them classified accordingly to their consistency of results, and permit to generalize results across populations and settings [18].

Accordingly to the Cochrane Collaboration in the Cochrane Handbook for Systematic Reviews of Interventions (2011) [19], there are several steps that must be taken to conduct an effective review: (i) define the question to be answered by the systematic review; (ii) literature search, in different electronic databases; (iii) define inclusion and exclusion criteria; (iv) evaluate the quality of the selected studies; (v) merge the results and, if possible, perform a meta-analysis, in order to obtain comparable data to discuss and take conclusions; and (vi) put the results into perspective and have the conclusions of the review.

A review must have a defined protocol that registers the method how studies were identified, selected and the process of information collection [20]. The protocol will be the document where authors address the method followed to answer the research question [20]. To assist the authors to report systematic reviews and meta-analysis, several tools were

created aiming different topics. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was designed to assist researchers when conducting a review, helping them to develop systematic review and meta-analyses that are full and transparent. PRISMA Statement is composed by a checklist (27-items) and a flow diagram (4 phases), and was designed to be a document that evolves during the development of the review [21]. The checklist was developed to evaluate both benefits and problems derived from interventions directed to healthcare professionals, included in the review. It also has support tools that allow authors to collect information and to access the importance of the selected paper. The flow diagram presents information running through the review: Identification, Screening, Eligibility and Included [22]. This flow is very useful to assess the number or articles included and/or excluded in each phase of the review.

The results and conclusions of a systematic literature review are directly influenced by the inclusion and exclusion criteria selected. There are some steps that are taken, accepted, and followed by several published studies of systematic analysis and meta-analysis. They are important to avoid bias of selection, and are the selection of the time frame of the review, the primary selection of articles that must be conducted by two investigators screening for studies independently and having discrepancies solved by consensus and with the opinion of a third investigator [19, 23, 24]. Following the suggested steps, researchers will be able to have a systematic review reliable, with transparent methods of research, limiting the bias of the investigation.

## 3. Qualitative research

Data collection in epidemiologic studies seems to be one of the most important steps to the methodological value of the study. Factors as the target population, the associated costs or the target behaviour are on the basis of the data collection method chosen, qualitative and/or quantitative.

Qualitative research is a methodology used in scientific research and, in general consists in producing finds to answers a question and is very useful to discuss opinions [25].

There are 3 most common methods of qualitative research and the choice of each one depends on the aim of designed study [25]: (i) participant observation is appropriate for collecting data on naturally contexts; (ii) in-depth interviews are important to analyse personal stories and experiences and (iii) focus groups are very useful for exploring different overviews of specific issues.

Considering that the subject of antibiotic prescribing and dispensing without medical prescription are sensitive topics, we defend that focus group is a useful methodology to initiate a research about attitudes, knowledge, perceptions, beliefs, behaviours or actions regarding antibiotic use of physicians and pharmacists.

Focus group methodology is a qualitative methodology used to collect data and consists in the engagement of a small number of persons in an informal group discussion, focused around a particular topic or set of issues [26]. It is a form of group interview that enables researchers to collect qualitative data [26, 27]. This informal discussion around a particular topic is conducted by a moderator, and the purpose is to have people sharing similar characteristics or common interests following an agenda. The predetermined programme is composed by a series of questions, in order to facilitate and help the flowing of the discussion, enabling all group members to participate, and discouraging that one participant pass over another [26-28]. The successful of research and the high quality of data obtained depends on the moderator which must be effective and of well-prepared sessions. This method is useful to explore people´s knowledge and experiences and is an important methodology to identify "what people think, how they think and why they think that way" [27].

Group discussion could actively facilitate the discussion because the more uninhibited members of the group break the ice for shyer participants [27], promoting reflexion of each participant and discussion between all intervenients. During focus group sessions with pharmacists [29] or with physicians [30] it is possible to create information on participants´ attitudes and knowledge and identify suggestions to improve antibiotics misuse.

These qualitative methodologies have as main advantages the interaction between participants, which could allow reach several aims [26, 27]: (i) highlight attitudes and priorities of participants; (ii) encourage all participants to analyse their own experiences; (iii) encourage open conversation about embarrassing topics and (iv) facilitate the emergence of ideas and experiences that would hardly arise with other methodology.

As a qualitative study, it does not usually have predetermined sample sizes [31]. Sampling stops when information is saturated, the phenomenon is well understood and there is no more new information being added by new sessions. It can involve few or many groups, with single or repeated sessions. The number of participants for each group is flexible and can involve as few as two, or as many as twelve, being the norm between four and eight [26]. Selection of professionals to involve in each focus group, could occurred naturally, being recruitment helped by key informants or be drawn by researcher in the beginning of the study [27].

When inviting health professionals to participate in the sessions, just a brief presentation of the topic should be given because the aim is that participants do not prepare themselves to the session. Participants should be informed that sessions will be audio-recorded to facilitate interpretation of data, and it is important to reinforce information about confidentiality of all content will be respected and that data will be treated without identification of any participant [27]. Data protection authorities and ethics committees must approve studies, and all participants must sign an informed consent, before taking part in the focus groups [29, 30].

Sessions must be conducted by a moderator, a member of the research group, following an agenda constructed in basis of bibliographic review [26]. The presence of an observer to take notes during the sessions could be relevant to obtain complete information. Discussion must be maintained until no new ideas are added by the participants [27].

To avoid any possible interpretation biases, transcriptions of audio-taped obtained data must be made by a different researcher. Information collected must be compared with notes taken by observer present in the meetings (if it is the case). To maintain confidentiality is important coding focus group data, coding each group discussion, each participant mentions and gives a code to all mentions, across groups or participants [32]. During analysis it is important to distinguish between individual opinions expressed in spite of the group from the actual group consensus [26].

As mentioned above, focus group methodology allows to explore health professionals' characteristics, such as attitudes, knowledge, perceptions, behaviours or opinions, of pharmacists [29] and physicians [30], and the identification of these factors is an important methodology to construct a questionnaire to apply a in the study population.

## 4. Questionnaire development and validation

In the field of antibiotic use, psycho-social approaches have been developed and implemented to assess health professionals and patients characteristics, aiming to improve antibiotic use worldwide. Questionnaires are well-established data collection tools and the publication of health sciences related questionnaires has increased over the past years, targeting health professionals' [33] or patient/parent [34] populations. However, there's a lack of fully validated tools published in the literature to assess factors underlying antibiotic overuse [35], which is an essential step to design and implement interventions to tackle this global concern.

Questionnaire development and validation is an integrated process which starts with the bibliographic review and includes several stages to establish full validity and reliability of the questionnaire. Accordingly, Figure 1 presents a purposed flow diagram about all stages of questionnaire development and validation.

### 4.1. Development stage

The development of a questionnaire to assess health professionals (physicians and pharmacists) characteristics should be based on an extended, systematic and transversal bibliographic review [36, 37], which precedes the qualitative research [29, 30], as presented in Figure 1. Considering the problem of antibiotic misuse and the specific aim of each study, the development of the items to include in the first version of the questionnaire should assess (purposed domains of construction): (i) Health professional attitudes, knowledge, perceptions, beliefs, behaviours or actions regarding antibiotic use; (ii) Determinants in antibiotic prescribing/ dispensing; (iii) Health professional sociodemographic characteristics.

### 4.2. Validation stage

There are several models published about the concepts of validity that should be assessed to full validate a questionnaire. We present the definition of the main concepts that cannot be forgotten when assessing health professional characteristics regarding antibiotic use.

#### 4.2.1. Translational validity: face validity and content validity

*Face validity:* Defined as a subjective assessment of validity [38], face validity is the weakest form of validity [39] and means that the face of the questionnaire allows assessing the construction base concepts. The face validity evaluation is usually made by a panel of experts which review the grammar, syntax, organization, appropriateness and logic sequence of the items in the questionnaire [38].

*Content validity:* Described as the extent to which the concepts of interest are comprehensively represented by the items in the questionnaire, content validation demands a clear description of the measurement aim, the target population, the concepts that intent to measure, the item selection/reduction and the items interpretability [40].

Content validity evaluation could be established in two different steps [41]: (i) the development step, which is essential to assess if the items development was based on an adequate bibliographic review and on qualitative research methods (as presented above) [38]; and (ii) the judgment step, which include the professional subjective judgment of the health professionals regarding each item of the questionnaire, and it could be evaluated using qualitative methods (construction of expert panels and analysis of the results using the Delphi technique [35]) or by quantitative methods (Content Validity Ratio –CVR [42] or Content Validity Index –CVI [43]).

### 4.2.2. Construct validity

Construct validity, a term now seen as encompassing all forms of validity, is defined as the estimation of the degree to which variance in the measures reflect variance in the underlying construct concepts [44]. Accordingly, it allows evaluating if the items developed assess the concepts that we intent to include in the questionnaire, like if we can assess some subjective attitudes or perceptions related with antibiotic prescribing, which usually are difficult to assess.

Several methods have been published to evaluate construct validity of an instrument [38]: (i) Contrasted groups approach: this method aims to evaluate the statistical difference between two different samples that are the opposites in the concept that is being measured; (ii) hypothesis analysis: this method indicates the expected direction of the responses obtained accordingly to a theoretical framework developed before; (iii) factor analysis is a statistical method that allows analysing relationships between items in an instrument [38]; and (iv) Multitrait-Multimethod (MT-MM) approach, developed by *Campbell and Fiske* (1959) [45], is a method that allows assessing convergent validity and the discriminant validity: an instrument must be convergent and discriminate validated to be construct valid.

### 4.2.3. Criterion validity

Criterion validity is the degree to which the attributes in a measurement are associated with relevant variables (gold standard) that are considered direct measures of the characteristic (attitude, knowledge or perception, for example) being examined [35, 38, 40]. Criterion validity could be assessed at the same time (concurrent validity), in the future (predictive validity) or in the past (postdictive validity) [44].

### 4.2.4. Reliability

Reliability refers to the ability of an instrument to consistently measure an attribute/ factor [38], namely, a specific attitude or perception of a health professional regarding antibiotic use. There are several ways to assess the reliability of a questionnaire [38], and we will analyse the methods most published in the literature: (i) Reproducibility assessment: refers to the stability in time of the answers from the same person. Usually reproducibility is evaluated using the test-retest method, which consist  in the administration of the same instrument to the same group in two different times and calculate the correlation between both scores (intraclasse correlation coefficient) [46]; and (ii) Internal consistency assessment: refers to the extent to which items in a questionnaire measure the same concept/ construct factor [47]. Internal consistency is usually assessed using Cronbach's alpha, which must be calculated for each concept that is being assessed in the questionnaire (for each attitude or perception, for example) and it must vary between 0.70 and 0.950.

Questionnaire development and evaluation ends with the construction of an instrument to collect data, fully validated, that allows to assess the specific characteristics of the setting that we are studying (hospital care or primary care), of the target population (physicians or pharmacists) and of the target behaviours (attitudes, knowledge, perceptions or actions regarding antibiotic use), which is fundamental to design, develop and implement educational interventions and to improve antibiotic use.

## 5. Observational study: relating health professional attitudes and antibiotic use

Observational study, also known as nonexperimental studies, aims to assess the influence of health professionals' characteristics (attitudes, knowledge, perceptions, behaviours or actions) in antibiotic prescribing/ dispensing.

Observational studies are the choice to reach quantitative conclusions about the association between health professionals' characteristics, such as attitudes, knowledge or perceptions, and the number and quality of the physicians' prescriptions of a particular health area, region or country. Cohort studies are from an epidemiological standpoint, the "gold standard" of the observational epidemiology [48]. In this case, since the attitudes and knowledge are quite stable over time, we may choose other observational studies: as case-control or cross-sectional.

Conducting a cohort study will allow us: (i) analyse the prescription of antibiotics by physicians with prescription quality indicators and with prescription quantity indicators and (ii) see the association between antibiotic prescribing (dependent variable) and the independent variables: the knowledge and attitudes of physicians evaluated with the questionnaire.

The quality of antibiotic prescriptions can be evaluated in various ways. To analyse dependent variable: antibiotic prescriptions, the best option is use prescriptions quality indicators as homogeneous as possible to facilitate comparability with similar studies. At European level, we have available quality indicators developed by the ESAC (European Surveillance of Antimicrobial Consumption) [49]. Table 1 present the ESAC drug-specific quality indicators for outpatient antibiotic use [50].

**Table 1** ESAC drug-specific quality indicators for outpatient antibiotic use.

| Label | Description |
|---|---|
| J01_DID | consumption of antibacterials for systemic use (J01) expressed in DID |
| J01C_DID | consumption of penicillins (J01C) expressed in DID |
| J01D_DID | consumption of cephalosporins (J01D) expressed in DID |
| J01F_DID | consumption of macrolides, lincosamides and streptogramins (J01F) expressed in DID |
| J01M_DID | consumption of quinolones (J01M) expressed in DID |
| J01CE_% | consumption of b-lactamase-sensitive penicillins (J01CE) expressed as a percentage [a] |
| J01CR_% | consumption of combinations of penicillins, including b-lactamase inhibitors (J01CR) expressed as a percentage [a] |
| J01DD+DE_% | consumption of third- and fourth-generation cephalosporins [J01(DD+DE)] expressed as a percentage [a] |
| J01MA_% | consumption of fluoroquinolones (J01MA) expressed as percentage [a] |
| J01_B/N | ratio of the consumption of broad- {J01[CR+DC+DD+(F-FA01)]} to the consumption of narrow spectrum penicillins, cephaloporins and macrolides [J01(CE+DB+FA01)] |
| J01_SV | seasonal variation of total antibiotic consumption (J01) [b] |
| J01M_SV | seasonal variation of quinolone consumption (J01M) [b] |

[a] Percentage of total consumption of antibacterials for systemic use (J01) in DID.
[b] Overuse in the winter quarters (October–December and January–March) compared with the summer quarters (July–September and April–June) of a 1 year period starting in July and ending the next calendar year in June, expressed as a percentage: [DDD (winter quarters)/DDD (summer quarters)21]×100.

After developing cohort study: (i) we have a quantitative and qualitative data of the antibiotic prescriptions, which is the basis for comparing the control group and the intervention group after the experimental study; and (ii) we can establish an association between the dependent variable (antibiotic prescribing) and independent variables (knowledge and attitudes).

If we have individual data by indication, antibiotics that each physician has prescribed and to the pathology that have been prescribed, we can use the disease-specific quality indicators developed by the ESAC at 2010 [51].

To analyse antibiotic dispensing by pharmacists, the best option is to design a cross-sectional study. This means that we would disregard the timing from the viewpoint of data collection. We collect at the same time data of antibiotic dispensing and data of the attitudes/knowledge of pharmacists. The dependent variable should be individualized dispensing data by pharmacy, in order to assess if the antibiotics were dispensed under medical prescription. It could be also obtained by simulated client [12] or by a questionnaire assessing the dispense without medical prescription. Another approach at the case of pharmacists would be to analyse the ratio between sales data and prescription data (prescriptions by physicians) [52]. This study arises from an ecological point of view, because we do not get individualized findings by pharmacy.

## 6. Experimental study: a cluster-randomized controlled trial

Once the gaps and barriers associated with worse prescription, have been identified by observational studies, intervention is designed to modify it. Before implementing the intervention in the target population, the ideal is (i) to test materials to see the: readability, usability, understanding of messages, and (ii) to make a pilot in a different population to the population study [53].

Experimental studies, because of the random allocation of subjects to study groups are the only ones that allow adequate control of potential confounding variables: known and unknown. The best design to test the effectiveness of an intervention is randomized controlled experimental studies.

However, when interventions are educational, there is the possibility of cross contamination between the intervention group and the control group. The control group subjects could receive the intervention through the intervention group subjects. To decrease the possibility of cross-contamination, the design choice is to assign intervention by clusters rather than by individuals.

The characteristics and barriers of each professional community are very important factors that can determine the difference in efficacy between the same interventions at two different professional groups [13].

Many studies have established that, in terms of improving professional practice (antibiotic use), multiple are more effective than single interventions [54].

There are several studies showing that interventions such as the dissemination of educational materials or clinical guidelines do not influence "alone" the use habits of health professionals. Likewise, the "audit" and "feedbacks" poorly designed, with too much information, and no clinically relevant posts, have not proved "by themselves" effective to improve or promote changes in clinical practice. The different forms of payment, namely incentives or penalties, seem to influence the prescribing habits of physicians, with incentives being more effective than penalties. This leads to the conclusion that passive dissemination of information "alone" is ineffective [55].

The relevance of educational interventions to improve antibiotic prescription has been demonstrated [56]. Multifaceted interventions, where there are educational interventions at different levels have proved to be the most effective. There are many reasons to explain medical malpractice when an antibiotic is prescribed; so it is important to individualize interventions to overcome specific barriers of each setting [52]. There is evidence demonstrating the increase effectiveness of small group discussions or clinical case reviews versus traditional continuing medical education in large groups [57].

Published studies about educational interventions on pharmacists are fewer than those on physicians. However, some studies [14, 58] demonstrate reduction on total of antibiotics dispensed and improvement of quality of pharmacists' practices on dispensing antibiotics. These interventions included group sessions, outreach visits and enforcement of regulation.

The educational intervention must be carried out by a professional in the field for two reasons: (i) convey confidence to the professionals involved and (ii) ensure a more fluid to discuss questions and problems generated during the intervention. If the intervention is performed by the same professionals, we can ensure a better reproducibility, and therefore more internal/external validity of the same.

The intervention must be designed in a systematic way, emphasizing wrong attitudes and knowledge about antibiotics discovered in the previous phases.

In the last years there has been much emphasis on the use of clinical decision support systems to improve drug prescribing. Clinical decision support system grouped a number of tools to aid physician decision making. The most popular systems are computer-based decision support, because they are more effective than manual processes for decision support [59]. There is evidence of the effectiveness of the clinical decision support systems together with other interventions to improve the prescription of antibiotics [60] .

In addition, to health professionals, patients are a vital point for the effectiveness of interventions. It has been described in the literature the importance of implementing multiple interventions aimed at professionals and patients, to reduce antibiotic prescribing [61].

We can conclude that with the knowledge that exists in our days, the improvement in the prescription and the use of antibiotics is based on multiple interventions designed with a base in an educational intervention. Educational interventions should be directed to small groups and be specific depending on the population of professionals to whom they are addressed, with emphasis on attitudes / knowledge that has been seen that they are wrong and are associated with poorer prescribing antibiotics in the case of physicians, or associated with inappropriate practices of antibiotic dispensing in the case of pharmacists. The use of clinical decision support systems is important for the design of these interventions to improve antibiotic prescribing in terms of both quality and quantity. Development guidelines to pharmacists' management patients with infections symptoms could be useful tool to improve practices quality in pharmacies.

Interventions should be multifocal and targeted to various professionals and patients, aiming to improve health professionals' clinical practice. Thus, when the ultimate goal is to improve antibiotic use through educational interventions, it is essential to follow a stepwise model. The development of each step should be considered when designing these types of studies, with the purpose to increase its effectiveness.

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