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PARS, a system combining semantic technologies with multiple criteria decision aiding for supporting antibiotic prescriptions

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ABSTRACT

Objective: Motivated by the well documented worldwide spread of adverse drug events, as well as the increased danger of antibiotic resistance (caused mainly by inappropriate prescribing and overuse), we propose a novel recommendation system for antibiotic prescription (PARS).

Method: Our approach is based on the combination of semantic technologies with MCDA (Multiple Criteria Decision Aiding) that allowed us to build a two level decision support model. Given a specific domain, the approach assesses the adequacy of an alternative/action (prescription of antibiotic) for a specific subject (patient) with an issue (bacterial infection) in a given context (medical). The goal of the first level of the decision support model is to select the set of alternatives which have the potential to be suitable. Then the second level sorts the alternatives into categories according to their adequacy using an MCDA sorting method (MR–Sort with Veto) and a structured set of description logic queries.

Results: We applied this approach in the domain of antibiotic prescriptions, working closely with the EpiCura Hospital Center (BE). Its performance was compared to the EpiCura recommendation guidelines which are currently in use. The results showed that the proposed system is more consistent in its recommendations when compared with the static EpiCura guidelines. Moreover, with PARS the antibiotic prescribing workflow becomes more flexible. PARS allows the user (physician) to update incrementally and dynamically a patient's profile with more information, or to input knowledge modifications that accommodate the decision context (like the introduction of new side effects and antibiotics, the development of germs that are resistant, etc). At the end of our evaluation, we detail a number of limitations of the current version of PARS and discuss future perspectives.

1. Introduction

The risk of antibiotics misuse has been documented as early as 1945 by Alexander Fleming himself. Today we are facing a global threat to public health due to antimicrobial resistance that causes 25000 deaths per year in Europe alone, as reported by the European Center for Disease Prevention and Control (ECDC)[1]. This antimicrobial resistance is mainly caused by inappropriate antibiotic prescription and overuse. Fearing an imminent post-antibiotic era, researchers and experts in related fields are striving to find a solution [25].

As part of this larger effort and in collaboration with the EpiCura hospital center, we are working to establish a decision support system to recommend prescriptions for antibiotics that we call PARS (P.atient A.ntibiotic R.ecommendation S.ystem).

There are several stakes for dealing with antibiotic recommendation systems. First of all, there is the critical context of the medical decision. The impact of a mistake is high and has harmful consequences to human health. Then, there is the required criteria explaining a decision, since the decision maker (DM) strongly needs such criteria in order to understand and approve recommendations. Moreover, we are facing the problem of knowledge fragmentation, with dispersed and heterogeneous sources (Patient knowledge, Antimicrobial knowledge, etc). These sources are created separately, in different contexts and by different experts. Finally in the presence of frequent change of medical procedures, maintainability of the recommendation system becomes a significant issue.

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[1] http://ecdc.europa.eu/.

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In order to overcome the challenges described above, we propose in this paper an approach that combines semantic technologies with MCDA (Multiple Criteria Decision Aiding) for a DSS (Decision Support System) that is knowledge-driven. Such a knowledge-based DSS can support domain-specific problems in need of expertise, by using stored rules, procedures, facts or equivalent abstractions [88]. In our context the specialized problem can be translated as follows:

> *Which prescription for antibiotic (alternative) is adequate for a patient (subject) suffering from a bacterial infection (issue), if we take into consideration the clinical characteristics of the patient, like allergies, cardiac problems, etc (specificities of the subject).*

We applied our approach on a Clinical Decision Support System (CDSS), called PARS, that combines different prescription knowledge sources for recommendation. According to Gupta and Sharda [52], while there are many CDSS for administrative decision making and clinical task management, those that "improve the efficiency of specific clinical functionalities such as drug management …are lacking". The combination of MCDA with ontologies can facilitate the work of physicians by providing a list (sorted) of antibiotics, that have been evaluated based on their suitability for a given patient and disease. Antibiotic pharmacology characteristics, that are structured into an ontology are used by PARS, together with an ontology describing knowledge of the local hospital center in terms of infection names and germ sensitivity/resistance. PARS is based on a two level decision model. The first level aims to assess and to select the alternatives (antibiotics) by their effectiveness on the issue (disease). While in the second level PARS uses a variation of the ELECTRE TRI model [94], the model of Majority Rule Sorting (MR–Sort) with Veto [67], to link knowledge structures through a set of structured rules and to sort the alternatives into ordered categories. This process can provide physicians with antibiotic prescription recommendations that are accompanied by explanation. The recommendations are categorized by their effectiveness and their risk of harmful impact on the patient. PARS applies general parametric rules (with a small, limited number of parameters) to ensure the maintainability (discussed in detail in Section 5.4) and and generality of the solution.

The central contributions of our work are:

- The proposal and analysis of a generalized architecture for assessing the adequacy of alternative-subject-issue triplets in a particular context;
- A detailed, extended model for Clinical Decision Support Systems using MCDA with Ontologies;
- A tested implementation of our variation of the ELECTRE TRI method for recommending prescriptions;
- An extensive set of validation experiments for our proposal, concerning the categorization and selection of antibiotics via disease interaction and toxicity of side-effects;
- A sensitivity and robustness analysis for PARS.

The paper is structured as follows: Section 2 presents our problem statement, while Section 3 the related work, briefly covering additional domain-specific information. Section 4 gives an architectural overview of PARS, while Section 5 details the knowledge structures that PARS uses. Section 6 presents the internal functionality of our system, during the production of recommendations. Section 7 covers our validation of PARS through an extensive analysis of our case studies. Finally Section 8, concludes the paper and presents future perspectives.

2. Problem statement

Our problem statement is twofold. We first consider the theoretical problems of critical decision contexts, in general. These are contexts (like the medical domain) where bad decisions have very harmful consequences. Then we discuss the specific challenges of medical applications in particular, that deal with the problems of antibiotic prescriptions.

2.1. Methodological challenges

The first issue we are trying to address is related to theoretical and methodological aspects of critical DSS (Decision Support Systems). We are targeting a model of Knowledge based DSS that assesses the suitability of triplets *(alternative, subject, issue)* of separated knowledge structures (such as ontologies) in a particular *context*. These separated structures need to be linked in a way that fulfills the recommendation requirements. This composition of diverse sources can be highly problematic due to representational inconsistencies. Using machine learning in such cases can cause additional problems. On the one hand, having "good" (i.e. large and well structured) training sets is improbable for most actors with critical decision needs (which is the case with our partners as well). On the other hand, for such decision systems, where lives are at risk and mistakes can be extremely costly, we need a solution that can provide explanations for its recommendations. This last requirement is a major concern (both socially and scientifically) that cannot be currently addressed by deep learning or other machine learning approaches.

2.2. Applicative issues

From the point of view of concrete applications for antibiotic prescriptions, both the drug events that are adverse and the danger of the increasing antibiotic resistance are a cause of major concern, specifically:

- After analgesics and sedatives, the second (most common) cause of adverse effects related to drugs is antibiotics [41,53,40]. This is on top of being one of the most common class of drugs, related to claims of medical malpractice [91]. If the seriousness of the adverse event attributed to drugs is considered, then these events are the most important mortality causes in healthcare. Causing between 700 K and 1.5 million deaths in the U.S alone [62].
- The danger of the resistance is often caused by inappropriate antimicrobial prescribing (antibiotic prescription) [46]. This danger is an increasing problem worldwide. According to World Health Organization, antibiotic resistance is a major threat to public health and has the potential to affect anyone, of any age, in any country [79]. Several physicians assert that intensive and inappropriate use of antibiotics, have led us into an impasse. Today antibiotic resistance bacteria is a global public health problem. In Europe, the antibiotic resistant bacteria cause 25,000 deaths per year [78]. Moreover antibiotic-resistant infections will cause the death of 10 million people per year worldwide by 2050 (that is more casualties than cancer today) and end up costing 100 trillion dollars (in total lost global production) [78]. Unless the many stakeholders do not act in a coordinated manner urgently, the world is moving towards a post-antibiotic era, where current and minor injury infections who were treated for decades could kill again [79].

On the upside, implementing antibiotic decision support systems has been shown to be a promising direction for reducing inappropriate antibiotic prescription and decreasing local resistance to antibiotics [38,107,82].

3. Related work

We now discuss five main categories of work relating to our problem statement, namely: *Medical Guidelines, Rule-based systems, Semantic Technologies, Machine Learning and MCDA*.

3.1. Guidelines

Guidelines are a coherent recorded form of expert knowledge, expressed in generally used, standard terminologies. They are developed based on the Evidence-Based Medicine (EBM) paradigm. Given a specific disease, guidelines will try to summarize the existing body of knowledge, in the form of a recommendation narrative. In general, these recommendations are formulated on the basis of available evidence resulting from clinical trials and observations [105]. Nevertheless, there are different degrees of recommendations depending on the confidence level and scientific consensus around a given subject. In the case where no direct studies on an issue are available, recommendations can be purely based on expert opinions. In the case of the EpiCura guidelines for example, recommendations depend both on clinical observations and local expert opinion, when no direct data is available.

The EpiCura hospital center [87], has been using a hundred-page guideline since 2011. Unfortunately as internal evaluations show, nothing has really changed in terms of sub-optimal prescription practices.

Moreover, these guidelines consider diseases only in general terms and group patients into categories (defined by overall indicators such as allergies to chemical components). This leads to suggestions of single solutions for entire groups of patients, without being able to provide targeted recommendations to specific individuals. In summary, the main disadvantages of guidelines from the perspective of our work are: a) Maintainability. The guidelines are static. They contain very explicit rules. As an example, when a germ becomes resistant to an antibiotic (meaning that the antibiotic is not effective anymore on that infection) a big part of the guidelines needs to be rewritten. b) Straightforwardness. In complex cases, the physician has to reason about, cross-check and manually combine several different sections of the textual guidelines. c) Specificity. The guidelines give recommendations for a group of patients considering as similar, many different patient criteria. But in order to be effective, physicians need recommendations that consider the patient's specificity, taking into account additional clinical characteristics.

3.2. Rule-based systems

There are several rule based systems developed to deal with the issue of antibiotics prescription. One of the first decision support systems for antibiotic therapy is the information system HELP "Health Evaluation through Logical Processing" [116,90,89]. With several later works providing additional functionality [37,36]. The HELP environment includes partial support for antibiotics, aiming to improve the treatment of bacterial infections [85] and to enhance the empirical antibiotic therapy [35]. Another DSS, named Q-ID [117] uses diverse infectious disease data and a set of if-then rules, to calculate (based on probabilities) possible antibiotic treatments. At first glance rule-based and probabilistic inferences may seem at odds with each other. But in the context of Q-ID, rules can be thought of as deterministic automata (i.e. as transitions between states given a certain input) that are augmented by weights (i.e. probabilities of a certain transition taking place), similarly to a PA (Probabilistic Automaton) [84]. Similarly, Terap-IA [5,4] uses a rule based system for the recommendation of antibiotics for pneumonia, as does the semi-automatic monitoring program for antimicrobial therapy of the Del Mar hospital in Barcelona, Spain [47,45].

ProForma ([104]) is a language/formalism for representing medical knowledge (rather than a medical decision system itself, as the one we propose). ProForma is specific to the authoring applications (for medical guidelines) build by the project, that conform to the ProForma specification. As such ProForma is a non-standarized alternative to the Semantic and Ontological languages that we advocate (OWL, RDF, SWRL, XML) which are world-wide accepted standards. The trade-off here is between domain-specificity and standardization. On the one hand, ProForma has indeed a helpful domain-specific vocabulary, but is not inter-operable with other data-sources or solutions (unless it becomes a global standard). On the other hand semantic and ontological languages are general purpose languages that are standardized, and as such are easily inter-operable with other data-sources and solutions (even with knowledge bases that are not specific to medicine). Finally, the ASTI system [12] is a rule-based support system for drug prescription based on guidelines.

The common methodological aspect of all aforementioned work is the explicit knowledge representation of "if–then" rules that is hard-coded directly into these systems. This approach results in systems that are static and hard to maintain, given the large number of explicit rules involved. Moreover, in order to add new knowledge (such as a new antibiotics or new patient constraints) we must re-encode impacted rules and modify them. In large hard-coded rule bases, these operations are complex, and they can become even more cumbersome if the consistency of the rule base needs to be re-validated after each change.

3.3. Semantic technologies

Gruber defines ontologies as "an explicit specification of a conceptualization" [48,49]. Since their definition, ontologies have been used in different domains and applications, including e-commerce [42], transportation [24] and education [1]. On the medical domain recent research using ontologies has been based on Semantic Web technologies [8], treating issues such as differential diagnosis of both general and particular diseases. Ontology-based approaches have been used to support clinical task management, for instance, by providing flexible clinical workflows for patient care [119]. An important reason to focus on technologies related to the Semantic Web is the need to share and reuse domain knowledge. Furthermore, the general medical knowledge and information related to patients is expressed with a medical terminology, which can be ambiguous and may contain many implicit assumptions [105]. In this area funding for medical procedures making use of semantic technologies (see PSIP [9] and REMINE projects [20]), try to reduce the adverse effects of drugs, by employing data mining techniques.

From the antibiotics point of view, the study by Bright et al. [17,18], described the empirical guidelines of NYP (New-York Presbyterian Hospital) through an ontology, using Protégé [44]. The main drawback of this approach though, is that even the simplest of relationships between basic data, needs to be explicitly expressed (ı.e. no generalization for new data-sources), rendering the maintainability of this system extremely difficult. More recently, [19] proposed an alert system for detection of patients at risk of antimicrobial therapy failure, focusing on the issue of antimicrobial resistance. Their method combined ontologies with expert rules.

Another model developed as part of the European project DebugIT[2] uses semantic web tools to implement fuzzy cognitive maps [80] for tracking antibiotic resistance. The knowledge base in this work was built from clinical guidelines using fuzzy rules, but does not consider prescription scenarios. The bacterial clinical infectious diseases ontology (BCIDO) [46], was developed to assist clinical infectious disease treatment and decisions. It is based on a semi-automated method to generate new infectious disease knowledge using the Infectious Disease Ontology IDO[3] [23] as an upper ontology. While BCIDO can integrate available knowledge from known international repositories, it does not adapt to the local specificities of hospital centers.

Despite all aforementioned projects, no standardized or widely accepted framework currently exists that can help doctors with their everyday prescription needs. Research in this domain [30,31] does aim on

[2] http://www.debugit.eu/.

[3] http://infectiousdiseaseontology.org/.

drug-disease and drug-drug interactions, but without coverage of specific patient characteristics regarding drug side effects.

3.4. MCDA

Multiple Criteria Decision Aiding (MCDA[4] for short) encompasses several methods and algorithms that are designed to provide useful recommendations in a diversity of domains [16]. It requires both the integration of quantitative data and qualitative considerations [81]. MCDA methods have been applied in many areas including Transportation [13], Tourism [73,69,11], Civil Engineering [66,86] or other appropriate domains [for e.g., [10]], in order to solve: *a)* Choice problems, such as the identification of the best alternative, *b* Ranking problems, such as the identification of the rank ordering of alternatives from best to worst and *c* Sorting problems, such as the assignment of alternatives to pre-defined ordered categories [16,27].

In healthcare, however, their application has been limited [106]. The first study regarding the evaluation of healthcare interventions was published in 1990 [63]. Since then MCDA has been applied in related areas such as investment (coverage and reimbursement), authorization [115], prescription [33,21,70], resource allocation [50] and research funding decisions. Types of interventions that were assessed by these projects include: pharmaceuticals, public health interventions [26,118], screening [71,112,120] as well as surgical interventions [76].

More closely to our problem statement, MCDA has been recently applied to identify the most common and important cardiovascular diseases [22] and to make preanesthetics [102]. In the case of antibiotic treatment, a study published by Erjaee et al. [33] uses AHP[5] [95] to choose antibiotherapies, but only for the Helicobacter pylori Infection in children. Finally, regarding CDSS for antibiotic prescription, the work of [72] proposed a method to extract indicator metrics from cumulative antibiograms, such as: cumulated efficacy (ANNF[6]) and weighted accumulated efficacy (WANNF[7]) to evaluate antibiotics in terms of antimicrobial resistance.

3.5. Machine learning

A growing body of research for antibiotic and drug prescriptions has used machine learning and statistical methods [98,96,97,64,83,60,111,110,108,109,65]. Unfortunately, despite some exceptions of mid-to-large sized clinical trials [83,60,65] and the fact that antibiotic prescriptions are very common, most hospitals lack the expertise to appropriately gather and anonymize the training data needed to apply this kind of approach. In the case of the EpiCura hospital center for example (our own case study), it's currently impossible to train such a complete system as a standard platform, taking into account all crucial requirements and limitations of machine learning methods [3,29]. Moreover, despite recent advances of AI in medicine [113,114], deep learning methods are still very closely bound to their training set, which presents complications when adapting to new contexts. These include both quantitative adaptations (problems with over–fitting) or qualitative variations to the system they are modeling [29]. Moreover machine learning lacks the naturalness and modularity of symbolic rules and is currently unable to provide recommendations with complete explanations [51]. However as we saw earlier, explanations are crucial in several domains [54], including medicine, with which we are concerned in this work.

[4] MCDA and MCDM may be used reciprocally with identical meaning.
[5] Analytic Hierarchy Process.
[6] Accumulated Number Needed to Fail.
[7] Weighted Accumulated Number Needed to Fail.

Table 1
Comparison of different approaches for prescription recommendation.

Evaluation criteria	Knowledge base methods		Learning methods	MCDA	ST&MCDA
	Rule based methods	Semantic technology (ST)			
Requirements					
Maintainability			✓	✓	✓
Reusability		✓			✓
No training-set required	✓	✓		✓	✓
Explanation	✓	✓		✓	✓
Specificity	✓	✓		✓	✓
Generalization	✓	✓	✓	✓	✓
Desired Characteristics					
Knowledge standard representation		✓			✓
Synthetic rules			✓	✓	✓
Inference	✓	✓			✓

3.6. Requirements

Given our analysis of state–of–the–art approaches, we present the requirements for a desirable solution in Table 1. These requirements cover the following themes that were discussed in this section: *Maintainability, Reusability, Availability of Training Sets, Explanation, Specificity, Validation, Generalization, Knowledge Representation, Synthetic Rules and Inference*.

As we can see from Table 1, the only way to satisfy all discussed requirements, is by combining MCDA techniques (covering our need for decision explanations and structured synthetic rules without relying on huge training sets) with semantic technologies (as a reusable standard knowledge representation supporting inference). This combination has shown promise in contexts other than antibiotic prescription, such as dental restoration [81] and selection of diabetes treatments [21].

4. Proposed model: Overview

In the most general case, the type of problem we want to solve can be thought of as categorizing depending on the adequacy of several alternatives (such as drugs, trips, construction locations etc) by taking into account the specificity of the issue (e.g. infection, recreation, construction) and the characteristics of the subject (for e.g. patient, client, city). This is exactly the goal of recommendation systems, the difference being that for our purposes, there is no way to learn the subject "preferences" from examples that are categorized. In our case, an explicit preference (or adequacy) model needs to be build that assesses in the one hand, the matching quality between the properties of each alternative with the issue. While in the other hand linking the alternatives with the related subject properties.

Our model performs this assessment through assignment of each triplet (alternative, subject, issue) to a selected category, part of a predetermined ordered set. This is accomplished by using a two level decision model. In the first decision phase we consider the selection of potential alternatives according to the issue (fulfilling the subject's needs). In the second phase we assign the potential alternatives to ordered categories by suitability to the subject. This is accomplished by further assessing the remainder of the characteristics of a subject.

Our approach aims at achieving the three main goals for prescribing antibiotics (described in Ankomah and Levin [2]), namely: (a) Maximization of cure rate and likelihood (b) Minimization of deleterious or toxic side effects and (c) Risk reduction for antibiotic resistant bacteria. We believe that our particular approach is potentially transferable to

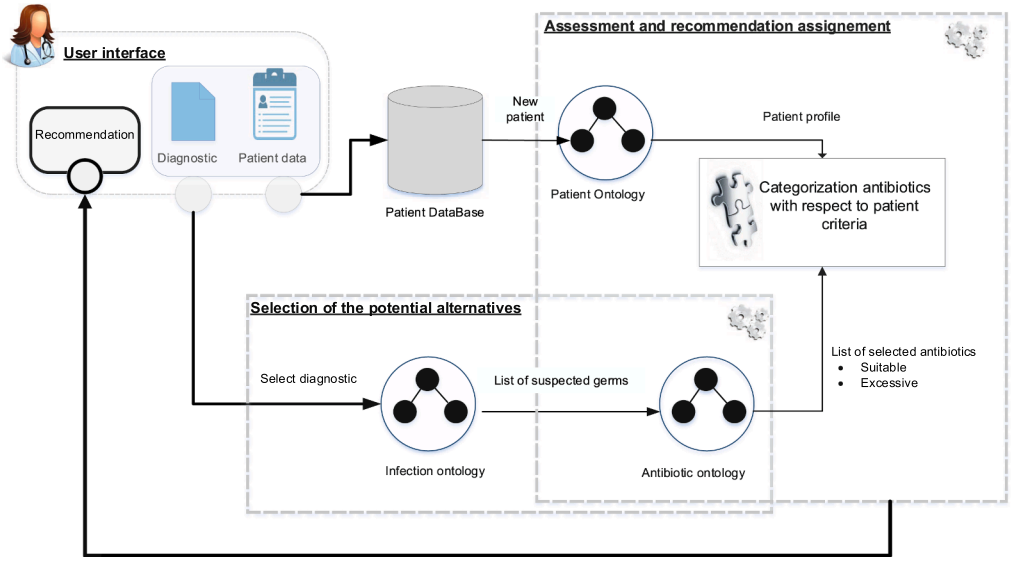

Fig. 1. PARS Architecture.

domains beyond antibiotic prescription, such as for e.g. the touristic [73] and similar sectors.

4.1. PARS: Decision components

In the antibiotics prescription domain, our goal is to express the infectiologist's (our domain expert) strategy, as a synergetic model combining MCDA with ontologies. In order to achieve this we proposed the PARS architecture depicted in Fig. 1, consisting of the following high-level components:

- **The UI[8] Component**: which serves as the primary interaction layer between our users and PARS. Its accompanying input–output interfaces and program logic include facilities to: a) introduce data into the system such as new patients, infections etc and b) summarize the various system responses, including: i) the list of all pathogens suspected of causing the infection, ii) the set of potential antibiotics categorized according with their coverage and spectrum and iii) the potential antibiotics sorted according with their adequacy to the patient (recommendation). Our experiments used both bulk authoring (through proxy) and individual editing of patient records (through the UI) to facilitate the validation process.
- **The Patient Database**: which contains individual patient information. This includes data that institutions such as hospitals routinely keep for their patients and with which our system needs to interact with.
- **The Patient Ontology**: which contains all relevant patient criteria, extracted from the patient database in a logically consistent form. These criteria allow the construction of the *patient profile vector*, which is then used by our algorithms to evaluate the adequacy of alternatives (antibiotics) to this specific patient.
- **The Infection Ontology**: which describes the knowledge of an institution (such as a hospital) concerning local infections. It presents the names of these infections, the infected organs as well as the list of pathogens for each infection. The pathogenic bacteria for each infection are deduced by the experts of the hospital, according to the sensibilities and the local resistances.
- **The Antibiotic Ontology**: which in turn contains all the antibiotics used in the country (or wider area) of the hospital. It describes the effectiveness of antibiotics against the pathogenic organisms, their susceptibility and their resistance to antibiotics. For each antibiotic, it also lists its side effects and their severity.
- **Our First Reasoning Engine**: which through reasoning and ontological matching of the infection and antibiotic ontologies, selects potential alternatives (potential antibiotics) according to a presented issue (infection).
- **Our Second Reasoning Engine**: which in turns matches and reasons upon the antibiotic and patient ontologies, to assess the adequacy of potential alternatives (potential antibiotics) to the characteristics of the subject (patient).

4.2. PARS: Decision processes

Given the above components, our recommendation flow for *bacterial infection prescriptions* using our system, is shown in Fig. 1. It consists of the following series of steps:

Step 1: *PARS accesses the patient database and structures the new patient data (from the user interface) within the patient ontology.*
Step 2: *The User (physician prescriber in our case) indicates the diagnosis.*
Step 3: *PARS sends queries to the hospital's local ontology and it gives the set of germs suspected of causing the infection revealed by the diagnosis. This is achieved using the two relations (detailed below in Section 5) that bind the Infectious_Disease and Antimicrobial_Spectrum concepts, given an infection name.*
Step 4: *Then PARS takes the set of germs produced in Step 3 and prepares a set of queries for the antibiotic ontology. As an answer for this step, it yields different sets of antibiotics according to their germ coverage.*
Step 5: *Subsequently, PARS classifies the patient ontology, and through SWRL[9] infers the critical clinical criteria of the new patient.*
Step 6: *Using an adequate MCDA sorting method, PARS produces an assessment of the antibiotics (from step 4) according to their toxicity for the patient. This is done by taking into account the critical clinical criteria of the new patient (produced in step 5).*
Step 7: *Finally, PARS assists the physician prescriber by providing him/her with a list of antibiotics sorted in ordered categories of adequacy for the patient. An explanation for the assignment is also produced.*

[8] **User Interface.**

[9] Semantic Web Rules Language: https://www.w3.org/Submission/SWRL/.

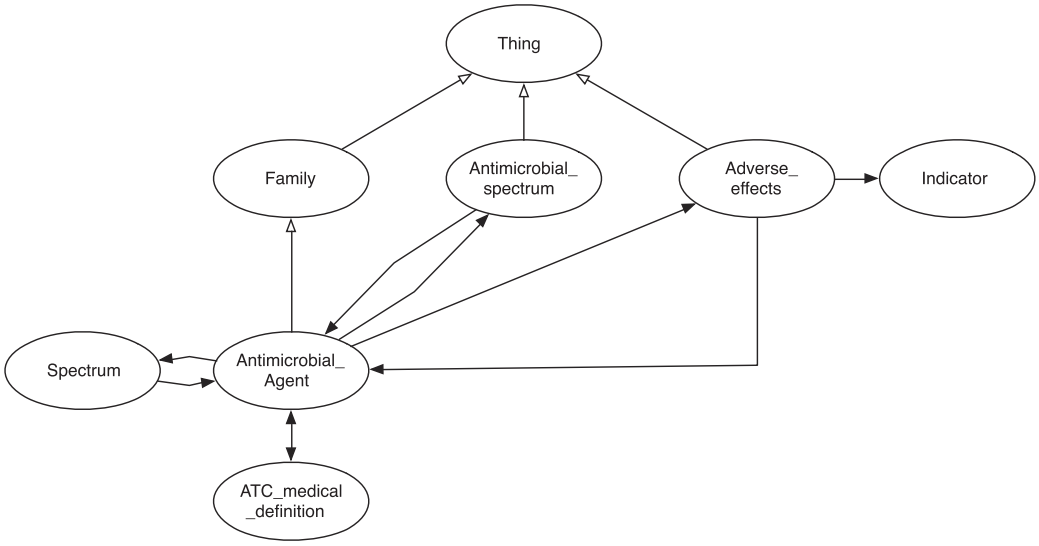

Fig. 2. Antibiotic ontology.

Among the different MCDA methods that we considered, we chose to base our solution on an adaptation of the *MR–Sort with Veto* model. MR–Sort with Veto [67,14,15,103,102] is an ELECTRE TRI simplification [121,94,74,39], which in turn is part of the ELECTRE family of models [39,92,6]. The ELECTRE family itself, is part of the larger set described as the Outranking methods [94,92]. The goal of MR–Sort and ELECTRE TRI [74] is to access the performance of alternatives (under several criteria), so as to sort them in ordered categories. The main motivations behind our choice are:

1. MR–Sort with Veto is a NCS ("non-compensatory sorting") method. This means that good assessments do not compensate for bad evaluations, which fits our domain better than the alternative.
2. The Notion of Veto. Certain criteria performances are explicit eliminators in the prescription domain. Veto can correctly model the assignment of an alternative (antibiotic) in a worst category for such cases.
3. The method operates under simple and synthetic rules with small set of parameters which facilitates maintenance and evolution.

While all the variants of ELECTRE TRI methods [74,39] provide the first two advantages from the list above, it is only MR–Sort that supports the simplicity and maintainability of synthetic rules with a small set of tuning parameters (third requirement in our list above). We thus chose to adapt the MR–Sort with Veto model for the needs of the prescription domain. The next sections will explain in more details this adaptation as well as the rest of the components and processes we have just introduced.

5. Knowledge containers

While re-using existing knowledge structures (as proposed in Noy et al. [77]), is generally preferable, for our specific domain of antibiotics prescription, there was no pre-existing work satisfying our objectives (see also Sir et al. [100]).

Thus, for our knowledge containers module, we have modeled from the beginning three seperate ontologies: the antibiotic, the patient and the infection ontologies. Moreover, in order to facilitate model interoperation and forward compatibility, we have strived to use widely accepted standard notations throughout our designing process.

Our three ontologies are mutually linked, can interact and exchange queries between each other. To allow for such inter-operation we made use of *ontology matching* methods [34], as the primary solution to the heterogeneity of data in ontology-based applications. Matching ontologies essentially involves finding correspondences between the entities and concepts (classes, properties or instances) of the domains under consideration.

Table 2
Object type properties of antibiotic ontology.

Name	Domain	Range
Is_Effective_against	Antimicrobial_Agent	Antimicrobial_spectrum
Is_Affected_by	Antimicrobial_spectrum	Antimicrobial_Agent
Is_spectrum_of	Spectrum	Antimicrobial_Agent
Has_spectrum	Antimicrobial_Agent_Effect	Spectrum
Hasadverse_Effect	Antimicrobial_Agent	Adverse_effects
IsAdverse_Effect_of	Adverse_effects	Antimicrobial_Agent
With_indicator	Hasadverse_Effect	Severity

5.1. Antibiotic ontology

Our ontological model for antibiotics is detailed in Fig. 2. Each antibiotic belongs to a particular family which groups similar chemical molecules together and thus gathers comparable characteristics. The data model of an antibiotic provides us with the entire spectrum of pathogens that it can reach, as well as the set of all germs the antibiotic is effective against. Given the fact that bacterial resistance to certain antibiotics can vary depending on the region or country [43], we developed a dedicated knowledge structure describing this specificity. Moreover the usage policy of specific antibiotic molecules can also change from country to country, which we also described. Finally, the model includes all possible side effects and their grades for each antibiotic of the knowledge base. For drug classification we use the standard ATC (Anatomical Therapeutic Chemical classification) annotation (for e.g. J01AA02 for Doxycyclin, J01D F01 for aztreonam etc).

In Table 2 we present the relations used by our ontology. These were modelled using data from: (a) the Belgian Center for Pharmacotherapeutic Information CBIP[10] (b) the EpiCura guidelines [87] and (c) the feedback of different experts from EpiCura. The effectiveness of an antibiotic (Antimicrobial_Agent) against a germ (Antimicrobial_spectrum) is modeled through the relation Is_Effective_against (seen on Table 2 above). Similarly, the sensitivity of a germ to an

[10] http://www.cbip.be.

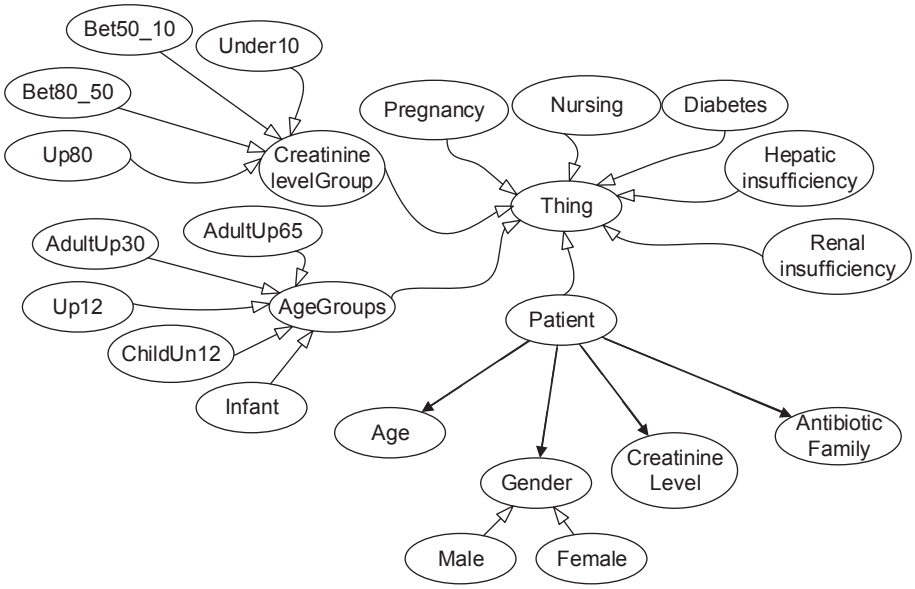

Fig. 3. Patient ontology.

Name	Rule
R1	Patient(?p) ^ Hasage(?p, ?a) ^ swrlb:lessThanOrEqual(?a, 1) -> Infant(?p)
R2	Patient(?p) ^ Hasage(?p, ?a) ^ swrlb:lessThanOrEqual(?a, 12) ^ swrlb:greaterThan(?a, 1) -> ChildUn12(?p)
R3	Patient(?p) ^ Hasage(?p, ?a) ^ swrlb:lessThanOrEqual(?a, 30) ^ swrlb:greaterThan(?a, 12) -> Up12(?p)
R4	Patient(?p) ^ Hasage(?p, ?a) ^ swrlb:lessThanOrEqual(?a, 65) ^ swrlb:greaterThan(?a, 30) -> AdultUp30(?p)
R5	Patient(?p) ^ Hasage(?p, ?a) ^ swrlb:greaterThan(?a, 65) -> AdultUp65(?p)

Fig. 4. Patient SWRL rules example.

antibiotic is described by the relation Is_Affected_by (with domain Antimicrobial_spectrum, and range Antimicrobial_Agent).

5.2. Patient ontology

Our patient ontology is seen in Fig. 3. Each patient is identified by a unique identifier, last name, first name, and age (with additional descriptive criteria such as *size, weight* and *gender*). When querying the system for recommendations, a patient instance is created with the introduced patient data from our user interface and the extracted data from the patient database. This instance is then loaded in the patient ontology and linked with the appropriate concepts for each case, through properties such as HasGender, HasAge, HasCreatinine, HasAllergyTo (other information such as *size and weight* are *"Data Property"* identifiers while *Gender* is a class). Subsequently the reasoner, using RDFS inference and SWRL rules (such as the ones presented below), infers all implicit data needed for the patient's criteria.

A sample of these SWRL rules used by the patient ontology can be seen in Fig. 4. For example rule *R4:*

$$Patient(?p) \wedge Hasage(?p,?a) \wedge swrlb{:}lessThanOrEqual(?a, \text{“65”} \wedge\wedge xsd{:}int) \wedge swrlb{:}greaterThan(?a, \text{“30”} \wedge\wedge xsd{:}int) \rightarrow AdultUp30(?p)$$

classifies the patient *?P* to the class *"AdultUp30"* which is a subclass of *"AgeGroups"*, when the age of the patient is between 30 and 65 years old.

All "disjointed" concepts were explicitely modeled in our system. For instance, since a pregnant patient cannot also be an infant, the *"Pregnancy" and "Infant" concepts are disjointed*. Similarly, since a breastfeeding patient cannot be male, *"Nursing"* and *"Male"* concepts are also disjointed.

These formal aspects make it possible to verify the logical features of the patient's criteria. Since it is indeed possible that the user enters inconsistent data, the ontology can safeguard the knowledge base by checking whether the information entered is logically consistent or not.

5.3. Infection ontology

Germ resistance and sensitivities change from hospital to hospital even when they are located in the same region or country. Since there is a significant local specificity for germs [43], we have designed a dedicated Infection ontology. This ontology (presented in Fig. 5) structures this knowledge of local infectious diseases and local resistances and sensitivities.

Fig. 5 presents the 3 main classes of this ontology. Class *Infectious_Disease* which is associated with the class *Target_Organ* through the relation *Touch*. *Touch* is an *ObjectProperty* that has *Infectious_Disease* as its *"Domain"* and *Target_Organ* as its *"Range"*.

The two relations (of type *ObjectProperty*) that bind the *Infectious_Disease* and *Antimicrobial_Spectrum* concepts are: *Is_caused_by* and *Cause* (which are the inverse of each other). The object property *Is_caused_by* connects the infection (whose domain is *Infectious_Disease*) to the germs that caused it (whose range is *Antimicrobial_Spectrum*).

5.4. Knowledge-base & maintainability

Although, our proposed solution does not solve the problem of knowledge-base maintenance in general. It does significantly facilitate maintainability, taking into account the following:

- *Standardization of knowledge bases.* Such as the use of Semantic Web and Ontological Technologies, for storage and inference, that we advocate facilitates maintainability. There is a wealth of tools, algorithms and methodologies for data-migration, synchronization and reasoning. More than one thousand tools exist[11], the majority of which are open-source and battle-tested in a series of other domains

[11] As listed in https://www.w3.org/2001/sw/wiki/Tools and http://www.mkbergman.com/sweet-tools/.

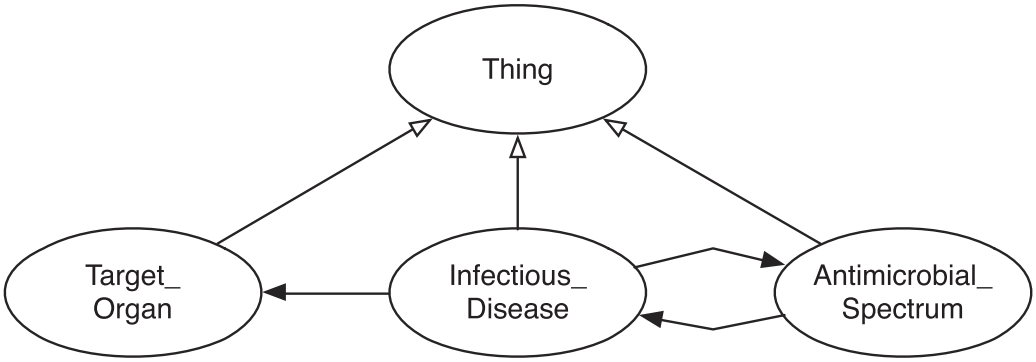

Fig. 5. Infection ontology.

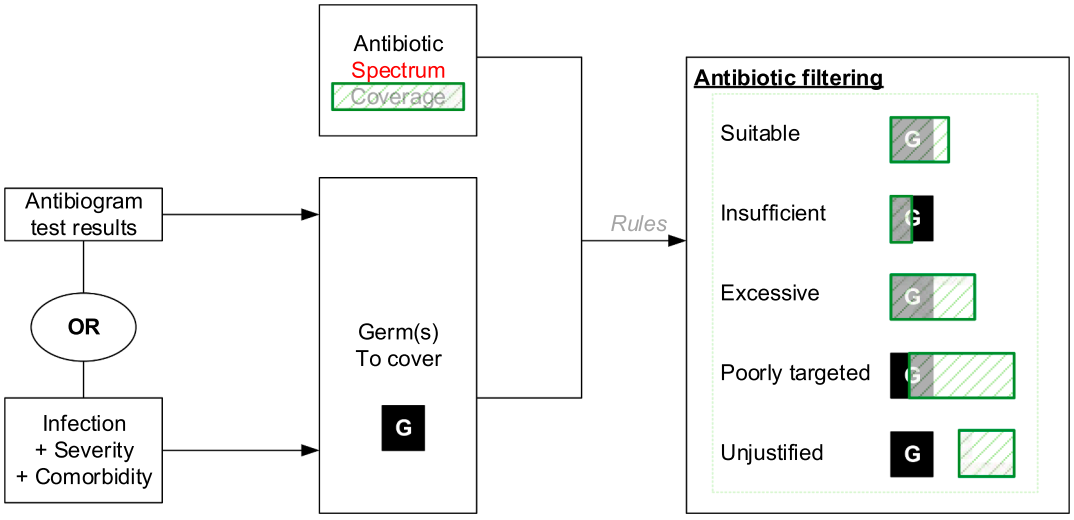

Fig. 6. Ontology request process.

(even beyond bio-informatics and medicine). These tools can (and in our case are) put to good use for maintaining knowledge bases for antibiotic prescription. These tools minimize authoring and migration costs, compared to non standardized protocols. Taking the introduction of new antibiotics as an example, although the updating process is not fully automated, it is supported by a wealth of readily available tools (such as Protégé[12]) for authoring and updating ontological data. When a new molecule is introduced in the market, it is only two relations in the antibiotic ontology that need to be added, namely the antibiotic's relation to germs (Is_Effective_against, Is_Affected_by) and its relation to Adverse_effects (Hasadverse_Effect, Is_Adverse_Effect_of). No other kind of action is needed for PARS, to immediately start considering the new entry as an alternative.

- *Extensive use of meta-data.* Maintaining costs are also minimized through the use of meta-data. That is the ability to incorporate (and edit, evolve) in the same knowledge base both base-level facts but also the schema (meta-level) that describes the "kinds" (classes) of facts and their relations. It is through the use of meta-data that systems built using semantic technologies (including PARS) are able to **(a)** reason over diverse ontologies of facts that can be created, edited and evolved independently of the system that uses them and **(b)** allow for distributed authoring by different organizations (for different purposes), yet result in a single federated model. This has been proven to work extremely well by platforms such as *DBpedia* (the ontological version of Wikipedia) with its English version describing consistently an astounding number of facts (4.58 million facts/things including diseases[13]), that have been contributed and edited in a federated fashion by the wikipedia community and volunteers. It is precisely our reliance on semantic-web and ontological technologies that allows us to model our system with more precise local ontological models, while retaining compatibility (through common nomenclature and meta-data) with more general medical ontologies. Using SPARQL[14] or other standard tools, our ontologies can easily be linked to all other related knowledge bases, that share the same drug classification standards and annotations, such as ATC (Anatomical Therapeutic Chemical classification).
- *Inference over direct facts.* Finally, and in relation with the points made above: Direct facts, are easier to maintain than expert rules. For example in order to add a new antibiotic for our system for e.g., we only need to provide its relations with germs (Is_Effective_against, Is_Affected_by) and Adverse_effects (Hasadverse_Effect, Is_Adverse_Effect_of). These facts are normally detailed in pharmacotherapeutic repositories like CBIP, that we used. When compared with hard-coded expert (if/then rules) about specific prescribing situations (regarding the patient and their history), these direct facts prove to be *more robust* (i.e. are the result of more stable scientific consensus) and *less complex*, in the sense that do not require to be further validated by prescribing physicians. They are thus more maintainable.

[12] https://protege.stanford.edu/.

[13] https://wiki.dbpedia.org/about/facts-figures.

[14] https://www.w3.org/TR/rdf-sparql-query/.

6. Reasoning

In this section we describe our reasoning process which is comprised of two reasoning phases, each own with its own dedicated reasoning engine. The first such phase, focuses on assessment and selection. It consists of the selection process for the sets of alternatives (antibiotics) that overcome the issue (infection). These alternatives have the potential to be among the desired solutions (recommendations). The second phase aims to assess and sort these alternatives in ordered categories, according to their adequacy to the specific subject (patient).

6.1. Selecting the potential alternatives

At this stage we aim to select the potential antibiotics. Potential antibiotics are the antibiotics that are effective against the suspected germs. We also consider the number of germs that are additionally covered by the antibiotic, as well as the antibiotic's spectrum. The rules we apply to distinguish the different classes of potential antibiotics, follow:

- If the antibiotic only covers the set of suspected germs and it is not designated as *"very broad spectrum"*, then this antibiotic is considered to be in the *"Suitable"* class.
- If the antibiotic covers more than the set of suspected germs (with the upper limit defined as the sum of suspected germs, plus the parameter α, with α defaulting to four) and it is not designated as *"very narrow spectrum"*, then this antibiotic is considered to be in the class *"Excessive"*.
- If the antibiotic is *"very narrow spectrum"* and covers all the suspected germs, then this antibiotic is considered to be in the *"Suitable"* class.
- If the antibiotic is *"very broad spectrum"* and covers all the suspected germs, then this antibiotic is considered to be in the *"Excessive"* class.
- If the antibiotic covers a part of the suspected germs and is not *"very broad spectrum"*, then this antibiotic is considered to be in the class *"Insufficient"*.
- If the antibiotic covers a part of the suspected germs as well as a large number of other germs and it is not *"very narrow spectrum"*, then this antibiotic is considered to be in the *"Poorly targeted"* class.
- If the antibiotic is *"very narrow spectrum"* and it covers a part of the suspected germs, then this antibiotic is considered to be in the class *"Insufficient"*.
- If the antibiotic is *"very broad spectrum"* and it covers a part of the set of suspected germs, then this antibiotic is considered to be in the *"Poorly targeted"* class.

More formally, we are considering here a) the suspected germs coverage (full, partial or no coverage) b) the spectrum attribute associated with antibiotics (*VN*: Very Narrow, *N*: Narrow, *MB*: Moderately Broad, *B*: Broad, *VB*: Very Broad) and finally c) the number of additional germs (designated below by the greek letter α). A formal description of the steps taken so far by our algorithm is presented in B (*"Formal Selection Model for Potential Antibiotics"*).

The best class for selecting potential antibiotics (among the selected set) are the ones found in the *"Suitable"* class. This class contains those antibiotics that have at the same time: full coverage of the suspected germs, good spectrum and an accepted amount of additional germs. From the remaining antibiotics, the *"Excessive"* class contains only those that have full coverage. Finally, the *"Insufficient"* and the *"Poorly Targeted"* classes contain antibiotics with partial coverage, that require the combination of more than one antibiotic to be effective against the set of the suspected germs.

6.2. Assessment and sorting recommendation

6.2.1. MR-Sort with Veto Adaptation

At this point, we adapt the ELECTRE TRI MR–Sort with Veto to assess the potential alternatives and to sort them into ordered categories according to their suitability (see also Section 4 and Souissi et al. [7]). The basic goal of ELECTRE TRI and Sorting models in general is to assign each alternative to an ordered category based on its performance regarding the required criteria. Since the categories are ordered, alternatives assigned to an upper category are better than the ones assigned to lower ones.

With ELECTRE TRI, the categories are defined through profiles. The lower profile $t^{-}(C_h)$ of category C_h, where $h = 1, \ldots, p$, is also the upper profile $t^{+}(C_{h-1})$ of C_{h-1}. The profile $t^{-}(C_h)$ is a vector of levels for each

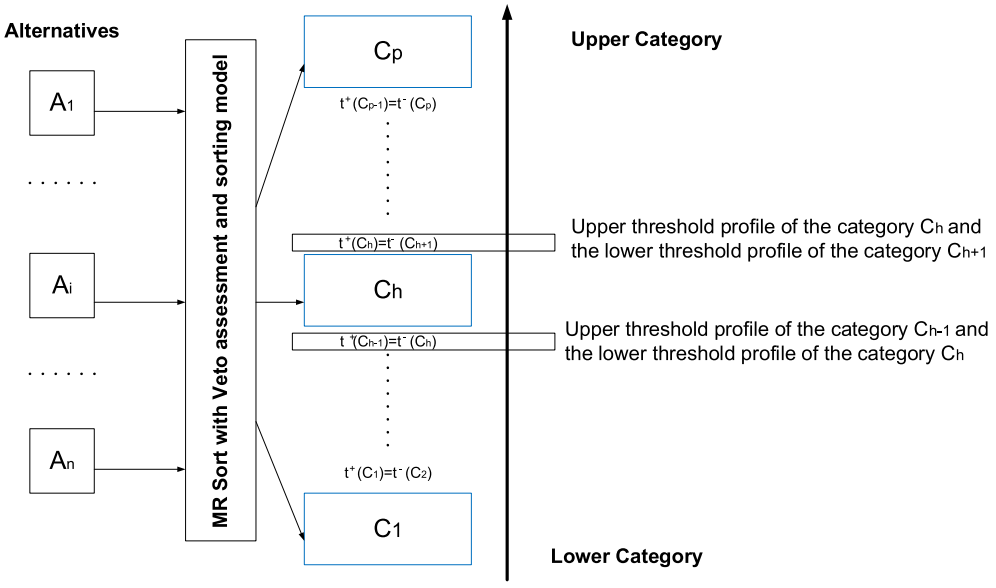

Fig. 7. Categories and their Separating profiles.

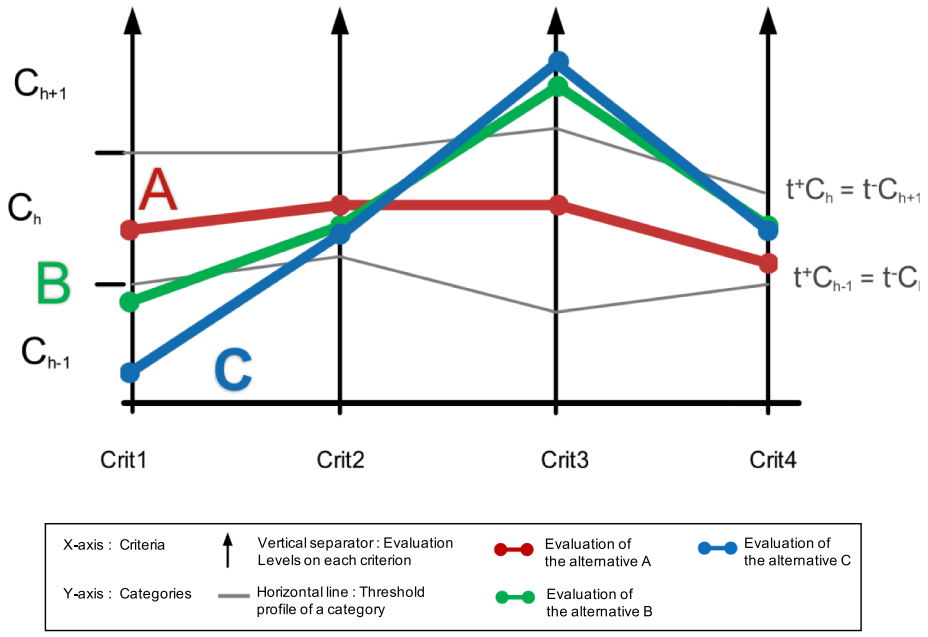

Fig. 8. Examples of Assignment rule applications.

required criterion. Every alternative should compete with those vectors, in order to be assigned to a category C_h or better (i.e. C_{h+1} up to C_p). The assigned alternatives should be at minimum as good as the lower profile $t^-(C_h)$ of the corresponding category on most (i.e. majority) of the criteria. Fig. 7 shows the schema of the different profiles and the ordered categories.

The MR–Sort with Veto variant, has additional rules. We describe these rules through Fig. 8. The figure represents the evaluations of three alternatives (A, B and C) on four criteria. Our goal is to assign these alternatives to their appropriate category (C_{h+1}, C_h or C_{h-1}). It is obvious that alternative A will be assigned to the category C_h since its performances w.r.t. *all* criteria (*Crit*1, *Crit*2, *Crit*3 and *Crit*4) are better than $t^-(C_h) = t^+(C_{h-1})$, the lower profile of C_h. Moreover its performances are worst than $t^-(C_{h+1}) = t^+(C_h)$ the upper profile of C_h and lower profile of C_{h+1}. The alternative B has different performances. We can see that, on criterion *Crit*1, where the performance of B is slightly worse than $t^-(C_h)$ but the rest of the performances are better than the lower profile of C_h. The alternative B will be assigned to the category C_h because its performances on *a majority* of criteria are better than the lower profile $t^-(C_h)$ while these performances are not unacceptably bad (even the one associated with *Crit*1). The alternative C has performances similar to alternative B with the exception of its performance on *Crit*1, which is unacceptably bad. *Veto thresholds* determine unacceptably bad performances for every criterion. In this case, even though the alternative C is as good as the lower profile of C_h on *a majority* of criteria, its performance on *Crit*1 triggers a veto that prevents it from being assigned to category C_h. It will thus be assigned to a lower category (in our case C_{h-1}).

Taking this analysis into account, we use MR–Sort with Veto for assessing and modeling the matching quality between a subject (patient) and an alternative (antibiotic). The classic way to use and apply MR–Sort with Veto is by evaluating alternatives and valorizing how good they are as solutions, in order to assign them to better categories. However in our work, in order to better reflect the needs of the medical domain, we use MR–Sort with Veto by downgrading alternatives, considering instead how bad they are as solutions. This way alternatives are assigned to worst categories, by judging them according to the impact of their disadvantages on the subject.

6.2.2. Application to antibiotics prescription

The second Reasoning Engine of PARS, sorts the potential antibiotics[15] in three categories ($p = 3$) : R (for "Recommended"), P (for "Possible") and TBA (for "To Be Avoided"). The application of our adaptation of the MR-Sort MCDA model evaluates antibiotics by the impact of their toxicities on the patient. For this evaluation the ontologies O_p (patient ontology) and O_A (antibiotics) are linked, by matching patient clinical criteria to antibiotics, using side effects (see Fig. 9).

In Section 5.2, we presented the O_P ontology describing both the clinical aspects of the domain as well as the patient characteristics. O_P references all pertinent patient information with the goal of assessing the risk-efficiency of antibiotics. It is at this stage that we calculate the sensitivity level of a patient, corresponding to each side effect. In turn, the O_A ontology provides all side effects of every antibiotic A_i, while representing the severity level of each side-effect – antibiotic combination. The term $DAS_{ij} \leftarrow \{0, 1, 2, 3\}$ links the O_p and O_A ontologies while assessing the severity of every side effect and antibiotic for the specific patient.

By using the MR–Sort with Veto rules engine (Algorithm 1 and Table 3), PARS computes how many side effects the patient has a sensitivity on (i.e., for which $DAS_{ij} \geqslant 1$), by evaluating each antibiotic. Two thresholds (λ_R and λ_P) and two vetoes (*VetoRecommended* and *VetoPossible*) are implemented in the model.

The vetoes are triggered according to how harmful the impact of a side effect of the antibiotic is to the patient. *VetoRecommended* forbids the antibiotic to be assigned to category R (Recommended) and *VetoPossible* forbids the antibiotic to be assigned to the P (Possible) category.

For every antibiotic, the total number of its side effects that can evoke a reaction on the patient, is compared with the first threshold (λ_R). If it is inferior to λ_R and no *VetoRecommended* was triggered for the antibiotic, it will be assigned to the R (Recommended) category. If alternatively it is superior to λ_R but inferior to λ_P (second threshold), while there is no *VetoPossible*, then it will be assigned to the P category (Possible). Finally, if none of the above conditions are met, the anti-

[15] The list of potentials antibiotics is the output of the first Reasoning Engine (as we show in Section 6.1).

biotic will be assigned to the TBA category (see Algorithm 1 and Table 3).

For more details regarding the specific variations of our implementation of MR–Sort with Veto, the reader can consult our previous work on the subject, Ben Souissi et al. [7].

Algorithm 1. Sorting by toxicity

```
1: procedure SECOND_CLASSIFICATION
2:   for all A_i ∈ 𝒜 do
3:     VetoRecommended ← False
4:     VetoPossible ← False
5:     for all S_j ∈ 𝒮 do
6:       If DAS_ij = 2 then
7:         VetoRecommended ← True
8:       else If DAS_ij = 3 then
9:         VetoPossible ← True
10:    DAS_i ← ∑_j DAS_ij
11:    If (DAS_i < λ_R) and ( ¬ VetoRecommended) then
12:      A_i ∈ Recommended
13:    else if (DAS_i < λ_P) and ( ¬ VetoPossible) then
14:      A_i ∈ Possible
15:    else
16:      A_i ∈ ToBeAvoided
```

7. Implementation and validation

In this section we will first present the implementation details of PARS and subsequently evaluate our proposal as a recommendation system. We will do so through logical, but also operational methods that assess the theoretical and experimental behavior of our system. Finally, we will investigate the system's response in terms of sensitivity analysis and robustness.

7.1. Implementation

We implemented PARS for the EpiCura Hospital center[16] in Belgium, using the Java and NetBeans platforms [17] (version 7.3.1) for the algorithmic and UI components of our solution. For our semantic components we utilized the OWL API library [101,56] [18] to manage our ontologies, which were modeled in Protégé [75].

Our modeling of the infection ontology covers the local-specific knowledge of our hospital center including: infectious disease names, corresponding set of local germs causing the infections, infected organs etc. Our antibiotic ontology is based on knowledge from the wider area of Belgium describing, among other things, the available antibiotics and their effectiveness against pathogens. Finally, our modeling of the patient ontology includes data for patient identification alongside all required clinical criteria.

PARS is able to produce detailed logs of its reasoning process, covering the effects of: *vetoes, toxic scores and side effects impacting a specific patient, for each antibiotic*. The system shows through the UI, an overview of the antibiotics that may be prescribed. Giving the classification of Suitable, Insufficient, Excessive and Poorly targeted (i.e. the result of the first reasoning engine) to potential antibiotics according to their effectiveness against the targeted germs. Moreover, it provides the practitioner with three categories of antibiotic adequacy to the patient for the Suitable and the Excessive groups. This allows the prescriber to understand which antibiotic to give (Recommended or Possible[19]), which to avoid (in the "To be avoided category") and why.

[16] http://www.epicura.be.
[17] https://netbeans.org.
[18] http://owlapi.sourceforge.net/.
[19] For which it is best to first consult an infectiologist.

For dealing with alignment issues between our ontologies, the *EditDistNameAlignment* method (implemented as part of the OWL alignment API[20]), based on the Levenshtein measure [68], proved most appropriate for our domain. For reasoning, we used the HermiT OWL reasoner [99], which provides good support for rule languages such as SWRL [57]. Finally, the OWL DL (description logic) sub-language [59] was used for all our semantic queries. PARS was implemented and tested on a Dell Latitude E5530, using an Intel Core i7 3540 M with 3.00 GHz base frequency and 16 GB of primary (RAM) storage.

7.2. Validation by cases

In order to validate our proposal, we constructed a variety of scenarios by closely cooperating with practitioners (infectiologist and microbiologist) of the EpiCura hospital center [87]. All case-studies presented were prepared so as to emulate real-world cases, as closely as possible. Fine-tuning of our parameters (sensitivities and thresholds), was finally achieved after several sessions, with the parameter α of the first assessment, λ_P and λ_R being set respectively to 4, 15 and 5. The cases that follow, illustrate this work:

> ***First Case:*** *Molly is a 34 years old woman, she is pregnant, she is in very good shape with clean medical history. After making the needed laboratory tests, they reveal her level of creatinine clearance to be 88 ml/min (at the normal pregnancy interval) with no allergies. Molly has CAP1*[21] *of Pneumonia.*

The guidelines (Fig. A.11) give us further details regarding the cause of the infection, and more specifically about the relevant pathogens. For our case, this is *streptococcus pneumoniae* (Fig. A.11, line 2). Three cases are distinguished by the guidelines for penicillin, in order to prescribe an antibiotic that is appropriate: (a) no allergy for penicillin, (b) only minor allergic reaction, (c) major allergic reaction. Two distinct antibiotics are suggested, for cases (b) and (c).

As a result of our first reasoning phase (discussed in Section 6.1), the effective antibiotics that cover or are effective against the infection germs of *Molly*, are:

Suitable:	**Excessive:**
Penicillin_G (Penicillins)	*Amoxicillin_clavulanic (Penicillins)*
Ampicillin (Penicillins)	*Cefuroxim_axetil (Cephalosporins)*
Amoxicillin (Penicillins)	*Vancomycin*
Clindamycin	*Moxifloxacin (Quinolones)*
	Piperacillin_Tazoboctam (Penicillins)

Our second reasoning engine, will then attempt to offer an ordered recommendation list to the doctor, by receiving the results of the first phase and augmenting it with the profile of the patient. For this case, the resulting output is then sorted by adequacy to *Molly*:

R: *Penicillin_G (Penicillins)*
R: *Ampicillin (Penicillins)*
R: *Amoxicillin (Penicillins)*
R: *Cefuroxim_axetil (Cephalosporins)*
R: *Amoxicillin clavulanic*
R: *Cefuroxim axetil (Cephalosporins)*
R: *Piperacillin_Tazoboctam*
P: *Vancomycin*
TBA: *Moxifloxacin (Quinolones)*

The assignment of *Vancomycin* to class P is a result of the "pregnancy" criterion raising a VetoRecommended (where $SP_j = 2$, $SA_{ij} = 1$). *Moxifloxacin* is categorized in the TBA class, since antibiotics of the *Quinolones* family are contraindicated for pregnant patients ($SA_{ij} = 2$) and therefore a VetoPossible is raised. We can validate this result by referring to the guidelines [87], which include a coarse-grained pregnancy categorization (Table A.8). We subsequently validated more

[20] http://alignapi.gforge.inria.fr.
[21] *Community-Acquired Pneumonia.*

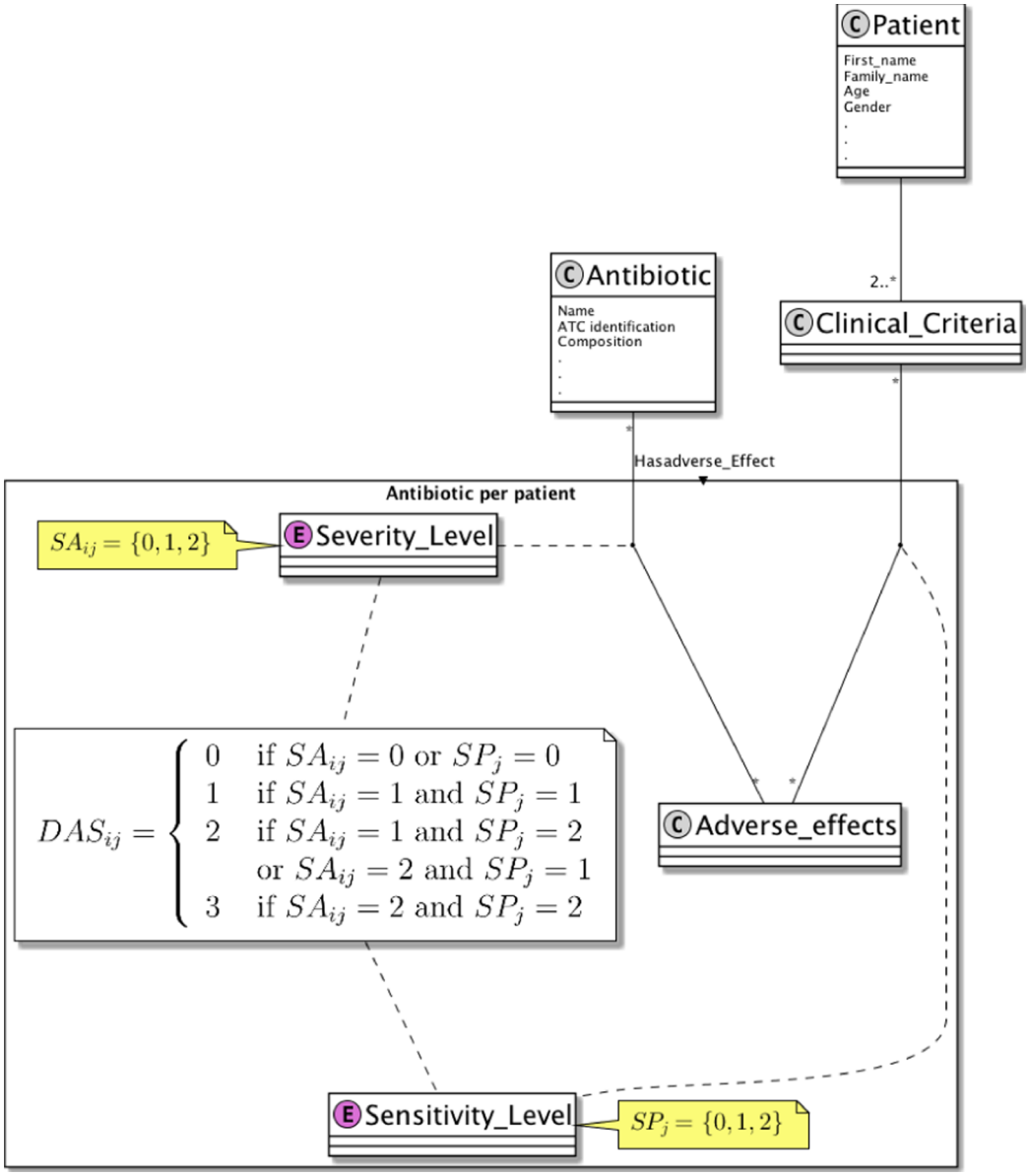

Fig. 9. The matching between the alternatives (antibiotics) and the subject (patient).

Table 3
The membership conditions

	$<\lambda_R$	$\lambda_R < <\lambda_P$	$\lambda_P <$
¬*VetoRecommended*	*Recommended*	*Possible*	*ToBeAvoided*
¬*VetoPossible*, *VetoRecommended*	*Possible*	*Possible*	*ToBeAvoided*
VetoPossible	*ToBeAvoided*	*ToBeAvoided*	*ToBeAvoided*

complicated cases, by analyzing scenarios involving more than 60 antibiotics. PARS succeeded in producing the correct classifications, given the equivalences that follow: R ("recommended") ≈ Probably safe, P ("possible") ≈ Only indications that are compelling and TBA ("to be avoided") ≈ Contraindicated.

We note here that, given current practices, if the physician wants to get similar results (without the help of our system), he has to combine and check manually a lot of different guidelines sections, in order to successfully reason about his recommendation and adapt it to the exact criteria of every patient.

As a second variation, let us consider that *Molly has a major penicillin allergy*. Then $SP_j = 2$, for j corresponding to the "allergy to penicillin" side effect. The PARS output for this case would be:

R: *Clindamycin* $SA_{ij} = 0$, $DAS_{ij} = 0$, $DAS_i = 2$

P: *Cefuroxim_axetil (Cephalosporins)* SA_{ij}=1, $DAS_{ij} = 2$, $DAS_i = 2$

P: *Vancomycin* $SA_{ij} = 0$, $DAS_{ij} = 0$, $DAS_i = 2$

TBA: *Penicillin_G (Penicillins)* $SA_{ij} = 2$, $DAS_{ij} = 3$, $DAS_i = 6$

TBA: *Ampicillin (Penicillins)* $SA_{ij} = 2$, $DAS_{ij} = 3$, $DAS_i = 6$

TBA: *Amoxicillin (Penicillins)* $SA_{ij} = 2$, $DAS_{ij} = 3$, $DAS_i = 6$

TBA: *Amoxicillin_clavulanic* $SA_{ij} = 2$, $DAS_{ij} = 3$, $DAS_i = 6$

TBA: *Piperacillin_Tazoboctam* $SA_{ij} = 2$, $DAS_{ij} = 3$, $DAS_i = 6$

TBA: *Moxifloxacin (Quinolones)* $SA_{ij} = 0$, $DAS_{ij} = 0$, $DAS_i = 2$

Concretely, when we have a major Penicillin ($SP_j = 2$) allergy, then both Vetoes (VetoRecommended and VetoPossible) are activated (since $SA_{ij} = 2$ for the Penicillin family). These antibiotics are TBA classified. Furthermore, Cefuroxim_axetil will activate a VetoRecommending, having $DAS_{ij} = 2$. The result will be Cefuroxim_axetil being classified in the Possible category. For the family of quinolones (having $DAS_{ij} = 0$), the side effect S_j major allergy, will not raise a veto. Nevertheless, with *Molly* being a pregnant woman, Moxifloxacin will be TBA classified. This brings the total number of recommended or possible antibiotics down to 3 (from 8 initially), which is a substantial help for a physician striving to makes his/her decision.

Second Case: *Aksil is a 27 years old male patient, he has no negative incidents in his medical history and in overall good health. The lab tests measured his creatinine clearance levels at 82 ml/min (inside the normal range) and reported no allergies. His diagnostic reveals that he is suffering from Exacerbation of Chronic Bronchitis, with dyspnoea and increased viscosity, as well as increased volume of purulence sputum.*

The textual guideline document (Fig. A.12) informs us about the pathogens which cause the infection. These are *moraxella, streptococcus pneumoniae, haemophilus influenza* (Fig. A.12, line 2). In order to prescribe a matching antibiotic, as in the previous case, the guidelines describe three eventualities (minor, major and no allergy) regarding penicillin.

The output (as produced by our first reasoning engine) follows, giving us the effective or covering antibiotics against *Aksil's* infection germs:

Suitable: *Amoxicillin_clavulanic*
Suitable: *Cefuroxim*
Excessive: *Moxifloxacin*
Excessive: *Piperacillin_Tazoboctam*
Excessive: *Ceftriaxon*

Our second reasoning phase sorts this list by adequacy to *Aksil*. The output of our system for this case is the following:

R: *Amoxicillin_clavulanic*
R: *Cefuroxim*
R: *Piperacillin_Tazoboctam*
R: *Ceftriaxon*
R: *Moxifloxacin (Quinolones)*

Let us now analyze the case where *Aksil has a minor penicillin allergy*. Then $SP_j = 1$. Giving us the following output:

R: *Cefuroxim* $SA_{ij} = 1$, $DAS_{ij} = 1$, $DAS_i = 2$

R: *Moxifloxacin (Quinolones)* $SA_{ij} = 0$, $DAS_{ij} = 0$, $DAS_i = 2$

R: *Ceftriaxon* $SA_{ij} = 1$, $DAS_{ij} = 1$, $DAS_i = 2$

P: *Amoxicillin_clavulanic* $SA_{ij} = 2$, $DAS_{ij} = 2$, $DAS_i = 4$

P: *Piperacillin_Tazoboctam* $SA_{ij} = 2$, $DAS_{ij} = 2$, $DAS_i = 4$

This profile update reduces the recommended antibiotics from 5 to 3. The remaining two are marked only as possible, which will provide additional help to the doctor reasoning about his/her decision.

As the above cases show us, PARS is a more dynamic and flexible decision making tool than the static guidelines used today. We use the terms "static" and "dynamic" here to describe how configurable each tool is (text guidelines or PARS) at the time of decision making. In both cases the decision process is ultimately driven by the physician. In the case of the textual guidelines, which are static (i.e. cannot be parameterised at decision time) general advice and patient cases are given, that do not fully describe each and every decision context. Several different prescription cases covered in the text, have to be manually consulted and combined, in order to approximate an actual case. With

Table 4
Patients data.

	Patient						
Criteria	Pat1	Pat2	Pat3	Pat4	Pat 5	Pat 6	Pat7
First name	Lin	Joe	Marie	Nermine	Ali	Susie	Aline
Family name	Valle	Lee	Wang	Dubois	Gaste	Apllimed	Nema
Age	25	30	35	75	80	70	10
Gender	Male	Male	Female	Female	Male	Female	Female
Critical state	∅	Hepatic insufficiency	Pregnancy	Renal insufficiency Diabetes	Hepatic insufficiency Diabetes	Diabetes	∅
Allergy to penicillin	∅	Minor allergy	Minor allergy	∅	Minor allergy	Major allergy	Minor allergy
Creatinine clearance level	85 ml/min	88 ml/min	90 ml/min	20 ml/min	82 ml/min	81 ml/min	75 ml/min

PARS on the other hand, the specific context of each prescription case is configured dynamically, at decision time and a tailor-made recommendation is given to the physician, with possible alternatives.

With static texts the doctor needs to manually reason about, cross-check and combine a lot of different sections of coarse-grained guidelines. Moreover, the guidelines have no way (or guarantees) of directly fitting suggested prescriptions, for all different types of patients. Neither provide a way to update context information incrementally (which is a real need when resistant germs appear, or new antibiotics/side effects need to be taken into account). With PARS on the other hand, there is a direct decision process, that can be dynamically updated with new properties that are added incrementally to the patient's profile (consider for e.g. the allergy to penicillin, discussed previously). These dynamic additions can help the physicians even further by reducing the set of matching antibiotics for each case.

7.3. Extensive analysis

7.3.1. Experiments description

We now extend our analysis with a structured validation comprising a total of a 57 scenarios presented in Table 5. These scenarios consider all possible combinations of the patients in Table 4 (seven different patients with critical criteria such as Age, Allergy etc), when combined with ten possible (for each patient) infection cases extracted from the guidelines [87], presented in Table A.9.

The information for these cases was extracted by cross-checking a lot of different guideline sections, and are detailed here in a concise way to facilitate our validation process. For every diagnostic name of the infection, the set of the germs suspected for causing the infection is included as well as the recommendation for the cases where the patient has (minor, major or not at all) allergy to penicillin.

Table 5
Soundness, toxic score and timing results.

Case	Patient	Soundness	Toxic score	Time	Case	Patient	Soundness	Toxic score	Time
Case1	Pat1	✓4/4	0 − 2 (VetoR)	5178 ms	Case1	Pat2	✓4/4	1 − 1	4819 ms
Case1	Pat3	✓4/4	1 − 1	3980 ms	Case1	Pat4	✓4/4	1 − 2 (VetoR)	6616 ms
Case1	Pat5	✓4/4	1 − 1	6096 ms	Case1	Pat6	✓4/4	2 − x	6290 ms
Case 1	Pat7	✓4/4	1 − 1	5056 ms	Case2	Pat1	✓9/9	0 − 2	1827 ms
Case2	Pat3	✓9/9	1 − 1	2340 ms	Case2	Pat7	✓9/9	1 − 1	4104 ms
Case3	Pat2	✓4/4	1 − 1	3548 ms	Case3	Pat4	✓4/4	1 − 1	5829 ms
Case3	Pat5	✓4/4	1 − 1	5898 ms	Case3	Pat6	✓4/4	2 − x	6057 ms
Case4	Pat2	✓4/4	1 − 1	4265 ms	Case4	Pat4	✓4/4	1 − 1	6691 ms
Case4	Pat5	✓4/4	1 − 1	7739 ms	Case4	Pat6	✓4/4	2 − x	7051 ms
Case 5	Pat2	✓1/1	P(2)(VetoR)− x	3880 ms	Case5	Pat4	✓1/1	P(4)(VetoR)− x	6351 ms
Case5	Pat5	✓1/1	P(6)− x	7159 ms	Case5	Pat6	✓1/1	–	6412 ms
Case6	Pat1	✓4/4	0 − 2 (VetoR)	3193 ms	Case6	Pat2	✓4/4	1 − 1	4132 ms
Case6	Pat3	✓4/4	1 − 1	3889 ms	Case6	Pat4	✓4/4	1 − 2 (VetoR)	6140 ms
Case6	Pat5	✓4/4	1 − 1	5956 ms	Case6	Pat6	✓4/4	2 − x	6275 ms
Case6	Pat7	✓4/4	1 − 1	4967 ms	Case7	Pat1	✓10/10	0 − 2	1887 ms
Case7	Pat2	✓10/10	1 − x	2596 ms	Case7	Pat3	✓10/10	1 − x	2691 ms
Case7	Pat4	✓10/10	1 − x	4882 ms	Case7	Pat5	✓10/10	1 − x	5423 ms
Case7	Pat6	✓10/10	2 − x	5357 ms	Case7	Pat7	✓10/10	1 − x	4772 ms
Case8	Pat1	✓10/10	0 − 2	2082 ms	Case8	Pat2	✓10/10	1 − x	2923 ms
Case8	Pat3	✓10/10	1 − x	3315 ms	Case8	Pat4	✓10/10	1 − x	5726 ms
Case8	Pat5	✓10/10	1 − x	5405 ms	Case8	Pat6	✓10/10	2 − x	4920 ms
Case8	Pat7	✓10/10	1 − x	4217 ms	Case9	Pat1	✓4/4	0 − 0	3603 ms
Case9	Pat2	✓4/4	1 − 1	5563 ms	Case9	Pat3	✓4/4	1 − 1	4569 ms
Case9	Pat4	✓4/4	1 − 1	6815 ms	Case9	Pat5	✓4/4	1 − 1	6945 ms
Case9	Pat6	✓4/4	2 − x	6893 ms	Case9	Pat7	✓4/4	1 − 1	5390 ms
Case10	Pat1	✓2/2	0 − x	3464 ms	Case10	Pat2	✓2/2	2 − x	3933 ms
Case10	Pat3	✓2/2	–	4486 ms	Case 10	Pat4	✓2/2	2 − x	6325 ms
Case10	Pat5	✓2/2	P(6)− x	6319 ms	Case10	Pat6	✓2/2	–	6549 ms
Case10	Pat7	✓2/2	2 − x	5191 ms					
Average	57 scenarios	100%	− 0.3	5508 ms					

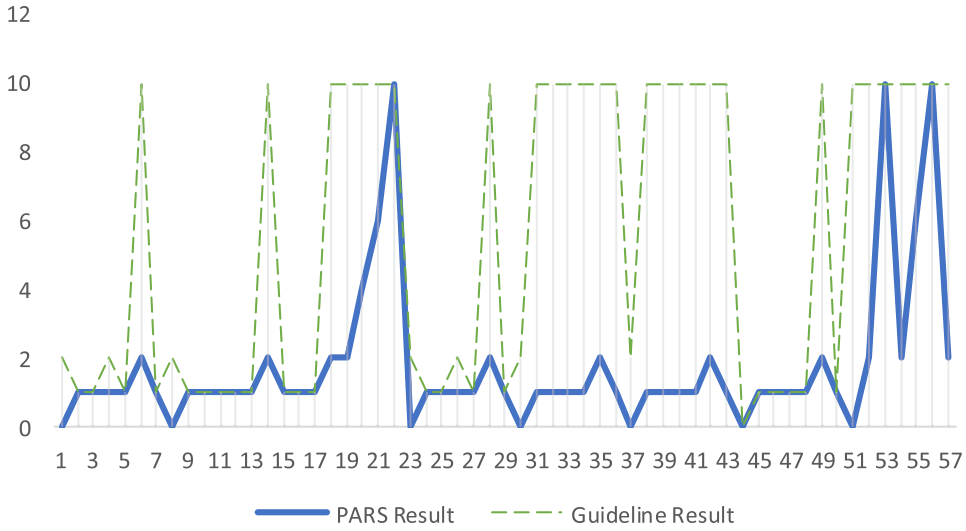

Fig. 10. The toxicity level of the recommeded antibiotic for 57 scenarios (smaller toxicity is better).

Table 6
To Be Avoided coverage comparison.

Patient criteria	TBA Guidelines Covered	TBA Guidelines Total	TBA PARS Covered	Intersection (Covered)
Pregnancy	0	6	1	0
Penicillin allergy	4	4	4	4
Diabetes	1	1	2	1
Renal insufficiency	0	1	1	0
Hepatic insufficiency	0	1	0	0
Age <12	2	3	2	2
Total	7	16	10	7

The goal here concerns the validation of:

1. The recommendation soundness when compared to the guidelines.
2. The response time of the system for the cases considered.
3. The behavior of PARS when examining the system's sensitivity.

7.3.2. Comparative analysis

Description. For our operational validation [16, p. 43], the *soundness* indicator, represents the consistency of our assessment regarding the alternatives. We use the term *soundness* as in [28] to describe the logical consistency checks for our model (see also consistency checks in [58]), which ensure that an MCDA solution does not contradict expert knowledge. We further quantify the metric as a ratio representing the number of correctly categorized alternatives by PARS over the total number of alternatives yielded by the system. We thus, consider having an "unacceptable" result, if we categorized an alternative belonging to TBA into either the R or P categories. As well as a "negative" result if an alternative normally belonging to R or P is categorized in TBA.

The *toxic score* for each scenario S represents the difference between the toxicity level DAS_i of the best solution of PARS and the toxicity level DAS_k of the solution given by the guidelines [87]. Antibiotic i is the best recommendation given by PARS and k is the recommendation given in the guidelines [87]. In Table 5 we calculate the toxic score as $\Delta_s = DAS_i - DAS_k$ (where s is the number of the scenario). For example, $\Delta_1 = 0 - 2$, with $DAS_i = 0$ and $DAS_k = 2$ (for Case1, Pat1).

The designation x represents an unknown DAS_k because either there is no recommendation in the guidelines or the recommendation of the guidelines is not among the recommendations of PARS. Moreover, in specific cases, with P(DAS_i) we highlight the fact that the best solution of PARS came from the P and not the R category. Finally, in order to ensure that our system responded with efficiency, inside an acceptable timeframe, we measured the time in *ms* that PARS needed to answer every scenario.

Results and discussion. As we can see from Table 5 the *soundness* score for PARS is indeed 100%, which shows us that out of these 57 scenarios: *a)* there was no case where PARS recommended an antibiotic that should have been categorized in TBA and *b)* there was no case where PARS categorized in TBA a *Possible* antibiotic.

Furthermore, in Table 5 we can also see our comparison of the toxicity levels (using the *toxic score* metric) between PARS and the guidelines. The average toxic score over 57 cases is $\Delta_{\mathscr{S}} = -0.3$, meaning that on average PARS gives slightly better recommendations regarding toxicity. This advantage is even more pronounced in certain cases as we can see in Fig. 10. For the scenarios without recommendation (in either system), we consider the toxicity level equal to 10.

From this comparison we also deduced that PARS can provide results for complicated scenarios that the guidelines either cannot handle directly (unless using cross-checking) or cannot handle at all. 33 out of 57 scenarios were complicated cases that had to be cross-checked. While for 24 scenarios the guidelines could not give recommendations at all.

In terms of coverage, our validation process managed to cover a large part of the guidelines. Table 6 presents the antibiotic families that have *To Be Avoided* according to the patient criteria present in our scenarios (such as pregnancy, age etc). These criteria were chosen because they are the only specific patient criteria that are structured inside the guidelines [87]. By comparing TBA families, we found that the 57 scenarios we considered are a very representative sample (as seen in Table 6) that covered 10 antibiotic families (with a total of 16 antibiotic families present in the guidelines). PARS manages to cover 3 antibiotic families more than the corresponding part of the guidelines (which only covers 7) for a total number of 10 antibiotic families covered. This is because PARS can treat additional cases or additional sensitivity patterns using a more detailed knowledge base.

7.3.3. Consistency analysis

Description. We now turn our focus on *sensitivity analysis* and *robustness*. Our goal here is to evaluate the stability of our assessment and assignment of alternatives. This analysis tackles the issue of *parameter change* for our model, essentially answering the following question: *"How will the suggested solution vary when the parameters of the model are perturbed?"* [16]. To achieve this we need to measure the dependency of our solution to the technical parameters of the system, taking into

Table 7
Threshold sensitivity.

scenario		($\lambda_1 = 5$) ($\lambda_2 = 15$)		($\lambda_1 = 1$) ($\lambda_2 = 6$)		($\lambda_1 = 7$) ($\lambda_2 = 10$)		($\lambda_1 = 3$) ($\lambda_2 = 13$)	
Case	Patient	Soundness	Toxicity score	Soundness	Toxicity score	Soundness	Toxicity score	Soundness	Toxicity score
Case1	Pat1	4/4	0 − 2 VR	4/4	0 − 2	4/4	0 − 2	4/4	0 − 2
Case1	Pat2	4/4	1 − 1	2/4	1 − 1	4/4	1 − 1	4/4	1 − 1
Case1	Pat3	4/4	1 − 1	4/4	1 − 1	4/4	1 − 1	4/4	1 − 1
Case1	Pat4	4/4	1 − 2 VR	4/4	1 − 2	4/4	1 − 2	4/4	1 − 2
Case1	Pat5	4/4	1 − 1	1/4	1 − 1	4/4	1 − 1	4/4	1 − 1
Case1	Pat6	4/4	2 − x	4/4	2 − x	4/4	2 − x	4/4	2 − x
Case1	Pat7	4/4	1 − 1	1/4	1 − 1	4/4	1 − 1	4/4	1 − 1
Case2	Pat1	9/9	0 − 2 VR	9/9	0 − 2	9/9	0 − 2	9/9	0 − 2
Case2	Pat3	9/9	1 − 1	9/9	1 − 1	9/9	1 − 1	9/9	1 − 1
Case2	Pat7	9/9	1 − 1	4/9	1 − 1	9/9	1 − 1	9/9	1 − 1
Case7	Pat1	10/10	0 − 2 VR	10/10	0 − 2	10/10	0 − 2	10/10	0 − 2
Case7	Pat2	10/10	1 − x	5/10	1 − x	10/10	1 − x	10/10	1 − x
Case7	Pat3	10/10	1 − x	10/10	1 − x	10/10	1 − x	10/10	1 − x
Case7	Pat4	10/10	1 − x	10/10	1 − x	10/10	1 − x	10/10	1 − x
Case7	Pat5	10/10	1 − x	5/10	1 − x	10/10	1 − x	10/10	1 − x
Case7	Pat6	10/10	2 − x	10/10	2 − x	10/10	2 − x	10/10	2 − x
Case7	Pat7	10/10	1 − x	5/10	1 − x	10/10	1 − x	10/10	1 − x
Average		100%		77.6%		100%		100%	

account that assignment in PARS is determined by "veto thresholds".

We do so through *robustness*[22] which is a metric focusing on cases where some of the model parameters are imprecise or uncertain [93]. Robustness can be defined in terms of "true" conclusions or "optimal solutions" [93]. For PARS, the definition of a "true" conclusion, or an "optimal solution" for an assignment problem can be determined through our model's thresholds, for cases where there is no assignment of TBA antibiotics to R or P categories, and conversely, no assignment of R or P antibiotic to TBA. As we saw, this is expressed by our *soundness* metric in Tables 5 and 7, only this time we need to consider the system's response for alternative thresholds.

We thus performed our sensitivity and robustness analysis by varying thresholds λ_R and λ_P. Table 7 presents part of this soundness variation for PARS when the thresholds change. When $\lambda_R = 1$ and $\lambda_P = 6$, the average soundness is reduced to 77.6%. For the other tuples, the system remains stable, with soundness at 100%. The exact interval of stability is when:

$\lambda_R <= 7$ *and* $\lambda_P >= 8$, *for all* $\lambda_R > 0$ *and* $\lambda_R < \lambda_P$.

PARS will thus remain stable (given our soundness metric) when: $\lambda_R \in [1\ 7]$ *and* $\lambda_P \in [8\ \ \infty\ ]$.

We note here that in all experiments, the alternatives assigned to TBA category according to VetoP, stay in TBA. Also, for those alternatives with no side effects, we observe that they also remained in their initial category, which is normally R. We thus conclude that within the intervals shown above, PARS is robust under λ_R and λ_P variation.

7.4. Discussion

To recap our results from this Section, our validation process showed us that PARS is a more flexible and dynamic decision making tool, when compared with the static guidelines that Epicura currently uses. The doctor has to manually combine, cross-check and reason about a lot of different parts of the guidelines, when static text is used. On the other hand, with PARS the decision workflow is more direct, while allowing for dynamic updates of new data for the patient's profile. Finally, PARS is a sound and stable system (as our additional analysis proved), that can suggest results that are at least equal or better than, the manual cross-checking static-text alternatives.

[22] Considered as a particular form of sensitivity analysis [61,32].

8. Limitations

Despite PARS showing promise, when compared with the textual guidelines, there are currently a number of limitations of our system that we are trying to address. regarding both its validation and its potential deployment:

- PARS does not currently tackle the problem of inappropriate prescription of antibiotics in general. Right now, the system considers only those cases where we are targeting bacterial infections. Nevertheless, we are currently generalizing our model to other cases of antibiotics usage (such as inflammations). To this end, our "Infection ontology" can become a "Clinical disease ontology", with an *Infection_Disease* being a subclass of *Clinical_Disease*. This class in turn will also be a super class of *Inflammation*. Finally, a new concept of *Pathogen* will be a super class of *Antimicrobial_Spectrum* and *Other*.
- PARS as a system covers infection diseases and sorts antibiotics according to their toxicity risk. However it does not treat drug-drug interactions and it does not consider the interactions of the recommended antibiotics with other on-going therapies for the patient. We plan to address this limitation in the future by reusing existing ontologies which cover this issue and which can be integrated into PARS. To this end, by using ATC for drug classification we are facilitating the matching of PARS knowledge structures to existing systems for drug-drug interactions like GalenOWL Doulaverakis et al. [30] and Drugs.com[23].
- Regarding our validation, we considered allergies of patients to penicillin, which where readily comparable with recommendations given by the guidelines. We did not incorporate allergies to other drugs. Nevertheless, at the patient level our system does model several different cases, such as drug intolerance and patient hypersensitivity indicators, like pregnancy and aging to evaluate antibiotics by their toxicity risk. We are in the process of integrating and adapting one of the existing ontologies like SNOMED CT[24] or the Substance Intolerance Ontology (SIO)[55], to address this issue.
- Despite the fact that PARS has a generic architecture, deploying it to new environments, such as other hospitals or clinics, requires considerable additional work in order to integrate new local characteristics and knowledge. This is particularly true for our infection

[23] http://www.drugs.com/drug_interactions.php.
[24] http://bioportal.bioontology.org/ontologies/SNOMEDCT.

ontology. We are looking into ways of automating knowledge extraction processes, from pre-existing local textual sources (such as the guidelines we used at EpiCura). This automation can reduce the time and resources needed for adjusting and validating PARS in new contexts.

- Finally, while we would optimally like to have several different alternatives evaluated for EpiCura, the most pressing issue was to assess the performance of PARS against the currently deployed method in the hospital (i.e. the textual guidelines). Given that their current solution is unable to improve prescription practices. Aspects of the system that were not directly comparable with the textual guidelines however, have been compared with data given to us by EpiCura's medical experts.

9. Conclusion

We have developed the system PARS that assesses and sorts antibiotics according to their suitability and adequacy to a patient with bacterial infection. This system is based on an innovative recommendation model using explicit knowledge and rules modeling. This model has the structure of triplets (alternative, subject and issue). It is structured around the coupling between a general MCDA sorting model and a Semantic Ontological model (specific to each domain of application). This architecture proved successful for supporting antibiotics prescription, and was able to link heterogeneous data-sources and ontologies, involving expert knowledge from a variety of fields. This was made possible through a MCDM model (MR–Sort with Veto) and structured ontological queries that respected the specific medical recommendation requirements.

Our proposal sorts antibiotics into three categories:"Recommended", "Possible" and "To Be Avoided" using a small number of generalized rules to ease the maintainability. The system can generalize to new scenarios when (for example) a new antibiotic needs to be taken into account, while being able to accommodate the particular needs of individual patients. Given our collaboration with the EpiCura hospital center [87], we were able to fine-tune the parameters of our solution and proceed with a validation, spanning several case studies. Through these case studies we were able to categorize the recommended prescriptions, given their pathogen effectiveness and side effect toxicity risk. Finally, we validated experimentally the robustness and stability of the system through sensitivity analysis under parameter variation.

At the end of our evaluation of PARS, we detailed a number of limitations of the current version, giving rise to the need for further development (regarding modeling, implementation and validation of our system). First, from the point of view of theory and methodology, the development and analysis of models of assessment for the adequacy of triplets, (*alternative, subject, issue*) similar to the one we presented here, could be generalized and transferred in other domains. Second, from the applicative perspective, we are extending our system to handle additional aspects of antibiotic prescription, such as joint prescribing of several antibiotics. In these cases, combining "insufficient" and "poorly targeted" antibiotics, could yield a new (composed) potential antibiotic (if the combination covers the suspected pathogens). For this kind of extension, we need to integrate drug-drug interactions into PARS, for determining the side effects of each combination. Finally, we aim to automate the knowledge extraction process for structuring and enriching ontologies. This automation could facilitate, the time consuming and resource intensive process of building, adjusting and validating, triplet-based decision models.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Guidelines

See Figs. A.11 and A.12 and Tables A.8 and A.9.

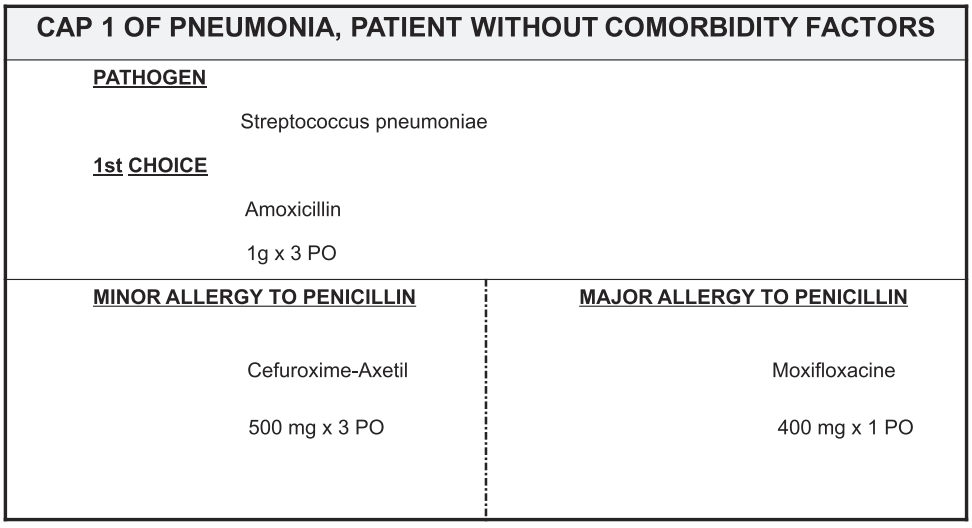

Fig. A.11. Guidelines Pneumonia CAP 1.

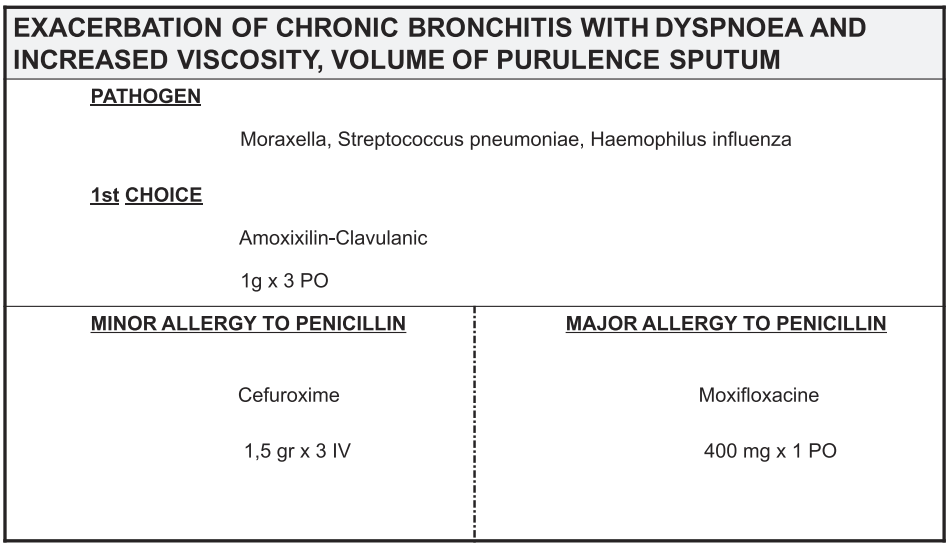

Fig. A.12. Guidelines Exacerbation of Chronic Bronchitis with dyspnoea.

Table A.8
EpiCura guidelines p. 19: Table of antibiotics indication classification for pregnant woman.

Probably safe	Only compelling indications	Contraindicated
Penicillins	Cotrimoxazole	Tetracyclines
Amoxicillin_ clavulanic	Clarithromycin	Quinolones
Piperacilline_ Tazobactam	Vancomycine	Trimethoprim
Aztreonam	Colistine	Aminoglycosides
Rifampicine	Fluconazole	Amantadine
Clindamycin	Itraconazole	
Cephalosporins	Pyrazinamide	
…	…	

Table A.9
Cases of the guidelines.

Case	Name	Germs	Recommendation (∅ allergy)	Recommendation (minor allergy)	Recommendation (major allergy)
1	EBCSDIV	S.pneumoniae Haemophilus Moraxella	Amoxicillin-clavulanate	Cefuroxim Cefuroxime-axetil	Moxifloxacin
2	CAP 1 PNEUMONIA	S.pneumoniae	Amoxicilline	Cefuroxime-axetil	Moxifloxacin
3	CAP 2 PNEUMONIA	S.pneumoniae Haemophilus	Amoxicilline-clavulanate	Cefuroxime-axetil	Moxifloxacin
4	CAP 3 PNEUMONIA	S.pneumoniae Haemophilus Klebs pneumo S.aureus	Amoxicilline-clavulanate	Cefuroxime-axetil	Moxifloxacin
5	CAP 4 PNEUMONIA	S.pneumoniae Haemophilus Klebs pneumo S.aureus Leionella SP Mycoplasme	Amoxicilline-clavulanate +Claritromycin	Cefuroxime-axetil +Claritromycin	Moxifloxacin
6	PNEUMONIA FSEH	S.pneumoniae Haemophilus S.aureus Enterobacteria	Amoxicilline-clavulanate	Cefuroxime-axetil	Moxifloxacin
7	PULMONARY AEH	Mixed flora Anaerobes	Amoxicilline-clavulanat	Moxifloxacin	Moxifloxacin
8	PEEH	Mixed flora Anaerobes	Amoxicilline-clavulanat	Moxifloxacin	Moxifloxacin
9	HAP without PA	S.pneumoniae Haemophilus S.aureus Enterobacteria		Ceftazidime	Aztreonam +Vancomycine
10	HAP with PA	S.pneumoniae Haemophilus S.aureus Enterobacteria P.aeruginosa	Cefepime	Cefepime	Aztreonam +Vancomycine

Appendix B. Formal selection model for potential antibiotics

Thus to select potential antibiotics, as shown in Fig. 6, we consider the following steps:

Requests for "Suitable" and "Excessive"

1. $\mathscr{R}_1 = \{A_i \in \mathscr{A}: \forall\ G_k \in \mathscr{G}_s: A_i$ is effective against $G_k\}$ (i.e., all antibiotics that cover at least all suspected germs).
2. For $(A_i \in \mathscr{R}_1)$,
   (a) If spectrum$(A_i) = VN$, $\Rightarrow A_i \in$ Suitable
   (b) If spectrum$(A_i) = VB$, $\Rightarrow A_i \in$ Excessive
   (c) If spectrum$(A_i) \neq VN$ and spectrum$(A_i) \neq VB$,
      i. $\mathscr{G}_i = \{G_k \in \mathscr{G}: A_i$ is effective against $G_k\}$ (i.e., the set of all the germs that are affected by the antibiotic)
      ii. $\delta_i = \text{card}(\mathscr{G}_i \setminus \mathscr{G}_s)$ (i.e., the number of germs covered in excess by the antibiotic)
      iii. If $\delta_i \leqslant \alpha \Rightarrow A_i \in$ Suitable
      Else $\Rightarrow A_i \in$ Excessive

Requests for "Insufficient" and "Poorly Targeted"

1. $\mathscr{R}_2 = \{A_i \in \mathscr{A}: \exists\ G_k \in \mathscr{G}_s: A_i$ is effective against $G_k\}$ (i.e., the set of all antibiotics that cover at least one suspected germ).
2. $\mathscr{R}_3 = \mathscr{R}_2 \setminus \mathscr{R}_1$ (i.e., the set of all antibiotics that cover at least one suspected germ but not all suspected germs).
3. For $(A_i \in \mathscr{R}_3)$
   (a) If spectrum $(A_i) = VN$, $\Rightarrow A_i \in$ Insufficient
   (b) If spectrum$(A_i) = VB$, $\Rightarrow A_i \in$ Poorly Targeted
   (c) If spectrum$(A_i) \neq VN$ and spectrum$(A_i) \neq VB$,
      i. $\mathscr{G}_i = \{G_k \in \mathscr{G}: A_i$ is effective against $G_k\}$
      ii. $\delta_i = \text{card}(\mathscr{G}_i \setminus \mathscr{G}_s)$
      iii. If $\delta_i \leqslant \alpha \Rightarrow A_i \in$ Insufficient
      Else $\Rightarrow A_i \in$ Poorly Targeted

Request for "Unjustified"

$\mathscr{A} \setminus \mathscr{R}_2 =$ Unjustified (i.e., all antibiotics that do not even cover one of the suspected germs)

Algorithm 2. Selection

```
1: procedure FIRST_CLASSIFICATION
2:   G_s ← set of Germs causes the infection
3:   R_1 ← set of antibiotics covers all G_k ∈ G_s
4:   for all A_i ∈ R_1 do
5:     if A_i: VN then
6:       A_i ∈ Suitable
7:     else if A_i: VB then
8:       A_i ∈ Excessive
9:     else
10:      R_i' ← set of germs are affected by A_i
11:      if card(R_i' − G_s) ⩽ α then
12:        A_i ∈ Suitable
13:      else
14:        A_i ∈ Excessive
15:  R_2 ← set of antibiotics cover minimum G_k ∈ G_s
16:  R_3 = R_2 − R_1
17:  for all A_i ∈ R_3 do
18:    ifA_i: VN do
19:      A_i ∈ Insufficient
20:    else if A_i: VB then
21:      A_i ∈ Poorly Targeted
22     else
23:      R_i'' ← set of germs are affected by A_i
24:      if card(R_i' − G_s) ⩽ α then
25:        A_i ∈ Insufficient
26:      else
27:        A_i ∈ Poorly Targeted
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