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Mésusage des antibiotiques : quelle évaluation du coût ?

Antibiotic misuse: how to evaluate the costs?

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Abstract

OBJECTIVE. Few studies have assessed the costs associated with the misuse of antibiotics in hospitals in France, despite the value of health economic data to inform antibiotic stewardship activities. We aimed to identify the methodological tools used to assess the cost of antibiotic misuse in hospitals.

METHODS. We performed a literature review using the major electronic medical databases. An index of relevance was developed to assess the intrinsic quality of selected articles.

RESULTS. 403 articles were retrieved, but 35 were selected for analysis. Most studies investigated the inadequate choice of the antibiotic molecule (n=17), the incorrect treatment duration (n=9), and the administration of an inappropriate dosage (n=7). Only three studies were medical/economic evaluations of specific interventions, such as prescription control by pharmacists or the implementation of a new diagnostic test. Considering our aim, the relevance of the studies was limited: few had defined the economic assessment as the primary objective or had detailed the method for calculating costs. Nevertheless, the misuse evaluation was usually better described.

CONCLUSIONS. Despite these limits, key factors for measuring antibiotic misuse (i.e., molecule choice, dosage) in relation to the costs (i.e., over/under prescription, hospital stay, staff remuneration) might serve as the basis for the development of a reference methodology to value the costs of misuse. The application of this methodology on identified situations of antibiotic misuse would help hospital decision-makers to justify resource allocation for implementing antimicrobial stewardship activities.

Résumé

OBJECTIFS. Les coûts associés au mésusage des antibiotiques à l'hôpital font l'objet de rares publications en France, malgré l'intérêt d'études médico-économiques pour éclairer la prise de décision en matière d'action de bon usage. L'objectif était d'identifier les aspects méthodologiques utilisés pour évaluer le coût engendré par le mésusage des antibiotiques en établissement de santé.

MÉTHODES. Une revue de la littérature a été réalisée à partir des principales bases de données. Un indice de pertinence a été élaboré pour l'évaluation de la qualité intrinsèque des articles retenus.

RÉSULTATS. Sur 403 articles identifiés, 35 ont été inclus dans l'analyse. La plupart étudiait le choix inadapté de la molécule (n=17), une durée d'administration inappropriée (n=9), l'administration d'une posologie inadéquate (n=7). Seules trois études constituaient des analyses médico-économiques portant sur des interventions, notamment un contrôle des prescriptions par le pharmacien et la mise en place d'un test diagnostique. La pertinence des études selon notre objectif était limitée : analyses économiques constituant des objectifs secondaires, méthode du calcul des coûts peu détaillée. L'évaluation du mésusage était généralement mieux approfondie.

CONCLUSIONS. Malgré ces limites, plusieurs éléments de mesure de type de mésusage (dans le choix de la molécule, du dosage, de la posologie) et de coûts (lié à la sur/sous prescription, au séjour hospitalier, à la rémunération du personnel) pourront servir de base pour l'élaboration d'une méthodologie de valorisation des coûts du mésusage. Son application aux situations de mésusage identifiées pourrait permettre aux décideurs hospitaliers de justifier la réallocation de ressources visant la qualité des soins.

1 Introduction

Antibiotics play a key role in the fight against infections. However, they are believed to be used inappropriately in nearly half of cases [1]. This is a genuine public health issue considering the associated deleterious consequences. Misuse of antibiotics promotes the emergence of antibiotic resistance, which is responsible for 700,000 deaths per year worldwide [2], of which 12,500 occur in France [3]. Antibiotic misuse can also lead to adverse events (e.g., antibiotic-related adverse events, *Clostridium difficile* infections, and catheter-associated infections when used for drug administration) and contribute to an increased duration of intervention by healthcare professionals (e.g., for the administration of antibiotics and treatment of adverse events) [4].

The monetary costs borne by society adds to human costs, mainly because of the extension of the hospitalization length of stay and of an increase in time off work. In 2017, the World Bank published an evaluation of the economic impact of antibiotic resistance. The report mentioned that “as antibiotic resistance spreads, health care expenditures [...] will increase in step with the rising disease burden; by 2050 the annual costs may exceed the base-case level by [...] 6 percent in high income countries” [5].

In light of the socioeconomic impact of antibiotic misuse and its consequences, analyzing methods to assess the costs associated with such misuse seems to be important.

Several studies have identified various types of antibiotic misuse in hospital settings, but the financial evaluation of such misuse remains unclear [6–9]. According to the World Health Organization (WHO), studies assessing the cost of antibiotic resistance, adverse events, and other consequences pertaining to antibiotic misuse, have proven to be of poor methodological quality [10].

The relevance of assessing the cost of antibiotic misuse was recently highlighted by a report from the European Centre for Disease Prevention and Control (ECDC) on healthcare-associated infections. The ECDC suggests a common framework that allows cost-effectiveness analysis in European hospitals [11].

Yet few studies of costs associated with the inappropriate use of antibiotics in hospitals have been published in France [12,13]. A method tailored to the French system would, therefore, be useful to assess the cost of misuse and to assist in the decision to justify investment in the implementation of measures allowing for an improved use of antibiotics in France [14–16].

The aim of this article was to undertake a literature review to identify methodological tools used to assess costs associated with antibiotic misuse in healthcare facilities.

2 Methods

2.1 Definition of the variables

The definition of the term “misuse” varies depending on authors [17]. The WHO describes “improper or excessive use” of antibiotics as a factor accelerating the emergence and spread of resistance to antimicrobials [18]. For our study purpose, we used the definition suggested by Gyssens *et al.*, namely the various situations of non-optimal use of antibiotics [19] such as an inappropriate prescription (choice of molecule, dose and dosing regimen), incorrect treatment duration, inappropriate route/dosing interval, as well as the absence of treatment when it would have been necessary.

This literature review focused on evaluating the cost associated with antibiotic misuse from the healthcare facility perspective. We selected three categories of costs according to

Drummond *et al.*: direct medical costs (related to the treatment – prescriptions, diagnostic tests – hospital stay, readmission to hospital, treatment in the emergency department), direct non-medical costs (related to various charges, particularly the remuneration of the professionals involved), and indirect costs (loss of productivity due to patients being on medical leave) [20].

2.2 Study design

The literature review was performed according to the PRISMA method [21]. The main databases in health sciences (PubMed) and in economics (EconLit and the National Health Service Economic Evaluation Database – NHSEED) were queried over a 10-year period (between February 2007 and February 2017), without limitation of location.

A combination of the following search terms was used:

- cost OR expenditure;
- unnecessary OR misuse OR overuse OR inappropriate OR underuse;
- antibacterial agent.

Articles published in a language other than French, English, Spanish, and Portuguese were excluded from the study.

2.3 Selection of studies

A two-step selection of studies was implemented: reading of titles and abstracts, followed by reading of the selected documents in their entirety.

Reading of titles and abstracts led to selecting documents that addressed one of the following criteria for inclusion: (1) evaluation of costs associated with antibiotic misuse in a healthcare facility, or (2) evaluation of costs avoided as a result of the implementation of

new practices (e.g., diagnostic tests) or recommendations for proper use (e.g., information campaigns among healthcare professionals) in healthcare facilities.

Reading of the selected articles in their entirety led to identifying methodological elements used for the valuation of resources in monetary units. The main data extracted from the documents included in the final analysis was:

- situations of misuse identified;
- main objective and study perspective;
- study methodology (i.e., data collection method, tools used);
- types of costs;
- context studied (i.e., healthcare facilities or healthcare facilities and primary care).

To ensure inclusion and exclusion criteria suitability, as well as the quality of the critical review, a sample of 10% of publications was randomly selected and subjected to verification by a second reader. Observed differences were resolved by discussion and consensus, on a case-by-case basis, with the help of a third reader.

2.4 Data analysis

Studies included in the analysis were classified according to their observational or interventional approach [22]. Interventional studies were then categorized according to the type of intervention evaluated to facilitate comparison between the various studies and to identify common measurement characteristics as a function of the type of intervention [11]:

1. Antimicrobial Stewardship Program (ASP): program for the proper use of antibiotics conducted by multidisciplinary teams, usually comprising at least one physician (an infectious disease specialist), a pharmacist, and a microbiologist [23].

2. Diagnostic tests: implementation of new diagnostic tests aimed at faster and/or more appropriate management.
3. Control by the pharmacist: the set of measures only carried out by the pharmacist.
4. New tools: implementation of recommendations, algorithms for decision-making, and computerized control systems.

The types of misuse, as well as the various costs assessed by the articles included in the review, were identified.

2.5 Qualitative evaluation

A relevance index was developed to assess the quality of articles included in the review in light of our objectives, and to identify the most relevant cost assessment methods.

This index is based on existing evaluation charts [22–24], with a degree of customization to meet our objective of identification of cost assessment methods of misuse.

The relevance index was calculated as the sum of the points attributed to various criteria identified as being necessary to address our health economic objective (Table 1): (1) the definition of the study perspective, (2) the types of costs measured, (3) the identification of misuse, and (4) potential application of the study results in France.

3 Results

A total of 403 studies were retrieved from the databases. After elimination of duplicates, 402 articles were selected. After reading the titles and abstracts, 93 articles were selected. After reading articles in their entirety, 35 were included in the final analysis (Figure 1).

A third of selected studies were performed in Asia (n=12, of which four in China) and a third in North America (n=12, of which eight in the United States). Furthermore, 70% of studies

were performed in the past five years. A single study was performed in France [25], out of eight European studies.

Six of the 35 selected studies were observational studies and 29 were interventional studies.

3.1 Observational studies

Table 2 summarizes the six observational studies according to the types of misuse evaluated and the associated costs. Five studies looked at a single type of misuse: the choice of molecule [26–30]. The economic impact of these misuse situations was identified by measurement of various costs such as those related to the number of inappropriate prescriptions and the duration of hospital stay. Only one study, performed both in hospital and community settings, measured the direct non-medical costs associated with salaries and with the time dedicated by physicians to patients [29].

On the basis of the relevance index, the average score for observational studies was 5.5. This score is close to the overall average (n=35 studies, average score=5.35). Four studies only took into account a single cost source: the over/under-prescription of antibiotic treatments [28,30,31] or the increase in hospital length of stay [26]. All studies specified where the economic data came from, and more than half of studies mentioned that the economic evaluation was the main objective.

3.2 Interventional studies

Most interventional studies consisted in evaluating the impact of the implementation of multidisciplinary programs for the proper use of antibiotics: ASP (n=11) and diagnostic tests (n=10). Table 3 presents the types of misuse evaluated and the associated costs per category of intervention for the 29 interventional studies identified.

3.2.1 Antimicrobial stewardship programs (ASP)

Eleven studies evaluated the impact of an ASP on situations of antibiotic misuse (Table 3). Seven looked at different types of misuse (e.g., the choice of molecule, dose, and dosing regimen). The two most frequent indicators of cost were the consumption of antibiotics before and after the ASP intervention [25,32–35] and the duration of hospital stay [35–37].

The four other studies focused on a single type of misuse: the choice of molecule [38,39] or the antibiotic treatment duration [40,41]. The measured cost was the cost of treatment, related to the over/under-prescription of medications.

Only two studies [25,38] measured the cost of time dedicated to the ASP by the multidisciplinary team.

On the basis of the relevance index, these 11 studies obtained an average score of 4.8, which is less than the overall average (n=35 studies, average score=5.35). This was particularly due to poorly developed economic analyses: for seven studies it was a secondary objective and only five specified the source of cost data.

3.2.2 Diagnostic tests

The 10 studies evaluating the impact of the implementation of a diagnostic test focused on three situations of antibiotic misuse: the choice of molecule [42–47], treatment duration [40,41], and the dosing interval [48]. Most studies specifically measured the treatment cost, hospitalization cost, and diagnostic test cost. Two other elements were identified as having a substantial impact on the total cost of an inadequate choice of molecule: admission to the emergency department [49] and readmission to hospital [44,49].

Overall, these studies obtained the best average score (6.2), mainly due to more comprehensive economic evaluations. Indeed, for eight studies out of ten the analysis of costs was the main objective, and the only two cost-effectiveness analyses identified were in this category. As previously mentioned, the authors [43–51] also looked at several types of costs, such as non-medical or indirect costs: related to general hospital charges (electricity, water, cleaning [48]), remuneration of staff [47], or loss of productivity [46].

3.2.3 Control by the pharmacist

Four studies [52–55] assessed the impact of greater control of antibiotic prescriptions by a pharmacist at the hospital (Table 3). Two of these studies investigated a specific type of misuse, not mentioned previously: the absence or delay in switching from intravenous to oral administration [52,53].

The four studies measured treatment cost. Two of them also measured the hospitalization cost [54,55] and one study the staff-related cost [52]. All obtained an average score (4.7) below the overall average. Indeed, for none of these studies was the economic evaluation the main objective, and only two authors specified the source of cost data [52,55].

3.2.4 New tools

Four studies [42,56–58] assessing the implementation of a new tool to optimize the use of antibiotics were identified (Table 3), such as the implementation of an algorithm to assist with decision-making [57]. These studies assessed multiple situations of misuse, such as the choice of molecule, the dosing regimen, and treatment duration. Three studies only took into account a single type of cost associated with misuse: treatment cost [57,58] or hospitalization cost [56]. Independently of hospitalization costs, the fourth study also

measured the length of time spent in the emergency department, the readmission rate 72 hours after admission to the emergency department, and the cost of diagnostic tests [42].

On average, these four studies obtained a score of 5.7, which is slightly above the overall average. The cost analysis was the main objective in three articles, and the source of cost data was clearly specified. The two studies [42,56] with the highest scores for this category mainly stood out due to the prominent role of the cost analysis and to a high feasibility in French hospital settings.

3.3 Prominence of health economic evaluations

The main costs measured by included studies were either the direct medical or the direct non-medical costs. A single study [46] quantified the loss of productivity related to the need for hospitalized patients to take sick leave. The authors provided few details regarding the calculation method and the sources of direct costs, while situations of misuse were more extensively covered. We have selected and described four studies using different approaches and quality scores, to illustrate the points identified in terms of economic evaluation.

Bao *et al.* [41] used the number of defined daily doses (DDD) per day of hospitalization, which allows precise quantification and comparison of prescribed treatments between patients. However, the sources of drug costs used during treatment remained poorly defined, as were the criteria used for calculation of the cost related to hospital stay (score of 7.75).

The study by Galar *et al.* [48] clearly mentioned how the health economic evaluation was performed (score of 6.25). The impact of a diagnostic test on the time interval between administration of the initial treatment and administration of the adequate treatment was

measured based on the treatment, the diagnostic test, and the hospital stay costs. Although the sources of costs and the components of hospital stay were clearly identified, the calculation method was not specified.

A cost-benefit analysis was undertaken as a secondary objective in the study by Zhou *et al.* [52]. The cost of intervention by a pharmacist in particular, regarding the choice of molecule, was measured according to the reduction in the rate of infection of the surgical site and the hospital stay duration. However, this analysis had a poor methodological quality, such as the absence of a definition of the perspective and a lack of detail regarding the sources of costs (score of 5.75).

Potasman *et al.* [58] provided few details regarding calculation of costs incurred due to inappropriate prescriptions (score of 4.0). However, the authors took into account confounding factors that could potentially lead to variation of spending by the pharmacy from one year to another (e.g., the price, volume, and rate of hospital admission and discharge).

4 Discussion

The main objective of this review was to identify the methodologies used in studies that evaluated antibiotic misuse and the associated costs in the past decade. Thirty-five studies that met the inclusion criteria were analyzed: six observational studies and 29 interventional studies. Only one study was performed in France (2006) [25], thus highlighting the need to perform further studies assessing the cost of misuse.

4.1 Relevance of the studies

To our knowledge, this literature review is the first to rely on an evaluation chart developed specifically to measure the quality of studies assessing the cost of antibiotic misuse. The novelty of this chart is the consideration of economic aspects associated with situations of misuse in hospital settings [59–61].

Studies included in this analysis usually did not meet the usual criteria for measuring the quality of a health economic analysis [62]. For instance, only six studies mentioned the perspective taken (hospital, payer, or society), despite the importance of this factor in the valuation of resources in monetary units [20].

Few studies mentioned segmentation of the studied population, that is to say an analysis of the cost in more restricted patient age groups. However, recommendations for dosage of antibiotics differ according to the patient's age (i.e., neonates, children, adults, or the elderly) and compliance with recommendations for the proper use of antibiotics may vary according to the population [63]. It would thus be relevant to segment the study population to allow identification of costs specific to each age group, mainly for age groups associated with the highest rates of antibiotic prescription.

The relevance of the studies related to our objective was also limited, particularly regarding the various types of costs taken into account in the economic evaluation. Approximately half of studies (n=18) only took into account one type of cost, mainly treatment cost (n=13). Thus, the cost of actions implemented to reduce misuse (e.g., recruitment of staff, redistribution of tasks, or purchase of prescription software) was rarely taken into account [62].

It is of interest to note that studies evaluating the impact of implementation of a diagnostic test obtained, on average, better relevance scores. These studies usually had a more comprehensive methodology for cost evaluation, and the only three health economic analyses identified in this review addressed this subject [44,46,47]. These studies were usually better performed in terms of economic evaluation [20], presumably to enhance the justification of initial investments in diagnostic tests. These studies may also be easier to perform.

4.2 Evaluated situations of misuse

Situations involving multiple misuses (Table 3) were most often (n=25) evaluated by various indirect indicators, such as treatment duration or hospital readmissions.

In several studies (n=15), an infectious disease specialist was in charge of evaluating each prescription to determine whether or not it was appropriate and to then classify inappropriate prescriptions by type of misuse using an accurate and objective list of the various possible situations. This is a relevant methodological process for a proper definition of misuse situations, and it allows identification of associated costs. The review of prescriptions by an infectious disease specialist as part of an antimicrobial stewardship program was indeed associated with a reduced prescription of antibiotics, without adversely affecting the clinical outcomes for patients [64].

In nearly all studies, misuse was identified indirectly by measurement of the consumption of antibiotics, which is readily quantifiable, particularly the cost of under/over-consumption. Use of the “number of Defined Daily Doses – DDD”, as a measurement tool, is recommended by the WHO as it is an internationally recognized indicator. Despite limitations inherent to its

definition [65], it allows for comparisons between facilities and between countries [66]. This is why its use, in 10 studies, was valued by the relevance index [32–35,38,39,41,53,54,56].

Despite the substantial resources involved in treating infections and colonization by multidrug-resistant bacteria [67,68], none of the studies included in this review evaluated consequences in terms of costs (e.g., antibiotic treatments and additional contact precautions in particular).

4.3 A poorly detailed cost analysis

Direct medical costs were the most frequently studied. Only two studies integrated both direct and indirect costs. However, the distinction between direct and indirect costs can vary from one author to another [24]. While indirect costs are usually defined as costs incurred by the loss of productivity, some authors, such as Galar *et al.* [48], also classified direct non-medical costs (e.g., electricity, water, general amenities, etc.) as indirect costs. Taking into account the costs incurred by the loss of productivity would be relevant when the author selects the perspective of society, but not that of the hospital as the budgetary consequences associated with being off work for the patient are not relevant to the healthcare facility [20].

Despite the mention of their sources of data for the costs of misuse (n=26), the authors rarely specified: the means used for collection or the method for identification of costs; the unitary cost of actions/medications/products studied; and the method used to perform the cost calculation. This lack of details regarding costs could be due to a poor understanding of good practices for health economic studies [20,62].

Nearly all studies included in this review (n=34) were performed abroad, where health systems and hospital rates can be quite different than those used in France [69]. Most

authors looked at the cost of hospitalization, but without specifying the content of this cost. In France, the identification of actual costs for a patient can be complex and hard to transpose from one facility to another; the daily cost of hospitalization can be calculated from the diagnosis-related group (DRG)-based fee, for which the valuation varies according to the type of procedure and treatment [70]. In the analyzed studies, the lack of accuracy in the calculation of costs could also be due to difficulty in accessing the list of procedures performed at the hospital and their valuation, leading to a need to resort to the use of hospital rates that are standardized and specific to the health system in question [71].

Modeling could be a solution to the difficulty related to accessing cost data. Eight studies used this technique, which by variation of different parameters, allows the cost and the expected outcomes of health interventions to be estimated, if need be in the long term. Thus, Andrews *et al.* only used data from the literature (clinical and costs) to compare two approaches to performing blood cultures in hospitalized children presenting with community-acquired pneumonia: a universal approach (all children) and a targeted approach (children at high risk of bacteremia) [44]. Although their model suggests that the targeted approach allows for savings, its capacity to produce results that are consistent and appropriate under real clinical conditions still needs to be verified [62].

4.4 Limitations

The initial literature analysis could have been more focused by adding the search term “*hospital*”. Nonetheless, the choice not to restrict the search in this regard allowed for identification of potentially relevant studies performed in a broader setting (community and hospital settings). Furthermore, other databases (e.g., Scopus, Embase, and NosoBase), as

well as the grey literature, could also be explored to verify the exhaustiveness of this literature review.

The lack of tools that can be used directly to evaluate the intrinsic relevance of studies in terms of economic analysis and evaluation of misuse led to the development of an assessment chart tailored to our issue and applicable in the French hospital setting. Selected criteria and their assessment may not be useable for assessing the quality of health economic studies in different settings, but it does provide a basis for further studies.

5 Conclusion

This literature review reveals that few studies have been performed in the past decade to assess the medical costs of antibiotic misuse in healthcare facilities. The methodological quality of these studies is heterogenous, with few details regarding the identification and calculation of costs associated with misuse.

Nonetheless, this review identified several items of measurement regarding the types of misuse (e.g., choice of molecule, dose/dosing regimen, treatment duration, administration interval, and route of administration) and the types of costs (e.g., medications, hospital stay – emergency department/readmission – staff remuneration, and diagnostic tests). These items could serve as the basis for developing a methodology for evaluating costs associated with identified situations of misuse, tailored to the French setting.

Undertaking such an evaluation would meet the needs of hospital decision-makers to justify the reallocation of resources to improve the proper use of antibiotics and the quality of care. In addition to the global figures regarding the “cost of antibiotic resistance”, the quantification of the “extra routine costs” specific to each healthcare facility could have a

more substantial impact: prescribers and other healthcare professionals would improve their engagement in actions to streamline the use of antibiotics.

Contribution of authors

MLS drafted the article and contributed to designing the protocol for the literature review and contributed to data analysis. CC performed the literature review and contributed to writing the article. MAG contributed to writing the article and to designing the protocol. CD contributed to writing the article, to designing the protocol, and to performing data analysis.

Disclosure of interests

The authors declare no conflict of interests.

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Figure 1. Flowchart for article selection, based on ref. [19]

Figure 1. Étapes de la revue de la littérature (adaptée de Moher *et al.*, 2010) [19]

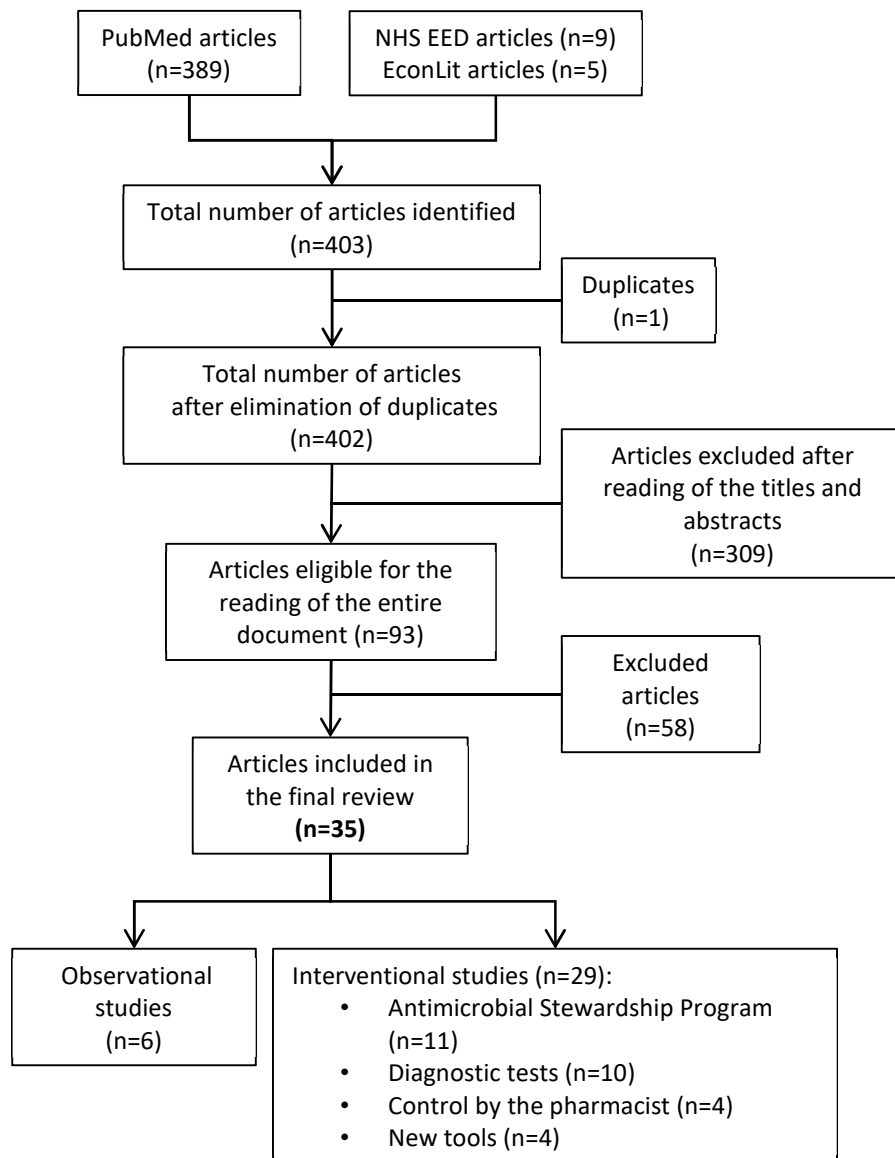


Table 1. Calculation of the relevance index for the intrinsic evaluation of studies

Tableau 1. Calcul de l'indice de pertinence pour l'évaluation intrinsèque des études

CRITERIA	SCORE			TOTAL
1. Definition of the perspective?	Yes +0.25	No 0		/0.25
2. Cost measurement				
<i>Role of the cost analysis related to the objective?</i>	Primary +2	Secondary +1		/2
<i>Definition of measured costs*?</i>	Poor +0.5	Average +1	Good +2	/2
<i>Well-established source of cost data?</i>	Yes +0.5	No 0		/0.5
<i>Method for cost calculation?</i>	Yes +1	No 0		/1
<i>Economic data?</i>	Measured +1	Estimated +0.5		/1
<i>Performance of a full economic evaluation†?</i>	Yes +1	No 0		/1
3. Measurement of the identified misuse				
<i>Clear explanation of the inadequacy evaluation?</i>	Yes +1	No 0		/1
<i>Use of the Defined Daily Dose (DDD)‡?</i>	Yes +0.25	No 0		/0.25
4. Feasibility of the study**	Easy +1	Difficult +0.5	Not feasible 0	/1
				Total: /10

* Clarification of the types of costs used in the analysis: Low = no/not accurate (i.e., only mention of treatment costs), Medium = mention of several types of direct costs, Good = mention of direct costs (medical, non-medical) and indirect costs.

† According to Drummond *et al.*, a complete health economic evaluation is defined as the comparative analysis of various options in terms of their costs and consequences [18].

‡ The WHO defines DDD as the average daily dose for a drug in its primary indication for an adult weighing 70 kg [23]. The use of the DDD allows for a better comparison between different studies.

** Feasibility characteristics: Easily feasible = data extracted from a database, non-comparative/interventional study, hospital perspective; Feasible with difficulty = real-world data field, comparative/interventional study, mixed perspective; Not feasible = undefined data source, comparative/interventional study, societal perspective.

Table 2. Types of misuse and associated costs in the six observational studies

Tableau 2. Types de mésusage et coûts associés dans les six études observationnelles

Types of misuse	Types of associated costs
Choice of molecule (n=5)	- Over/under-prescription [26–29] - Hospital stay [25,28] - Remuneration of the professionals involved [28] - Readmission to hospital [26]
Choice of molecule, dosage, treatment duration, route of administration (n=1)	- Over/under-prescription [30]

Table 3. Types of misuse and associated costs in the interventional studies according to the category of intervention

Tableau 3. Types de mésusage et coûts associés dans les études interventionnelles par catégorie d'intervention

Category	Types of misuse	Types of associated costs
Antimicrobial Stewardship Program - ASP (n=11)	Choice of molecule, dose/dosing regimen, treatment duration, dosing interval, route of administration (n=7)	- Over/under-prescription [24,31–34] - Hospital stay [34–36] - Remuneration of the professionals involved [24] - Diagnostic tests [24]
	Treatment duration (n=2)	- Over/under-prescription [39,40] - Hospital stay [40]
	Choice of molecule (n=2)	- Over/under-prescription [37,38] - Remuneration of the professionals involved [37]
Diagnostic tests (n=10)	Choice of molecule (n=7)	- Over/under-prescription [41–44] - Hospital stay [41,42,45,46] - Diagnostic tests [41,44,46] - Visit to the emergency department [41] - Readmission to hospital [41,46] - Remuneration of the professionals involved [44] - Patient's loss of productivity [43]
	Treatment duration (n=2)	- Over/under-prescription [47,48] - Hospital stay [47,48] - Diagnostic tests [47]
	Dosing interval (n=1)	- Over/under-prescription [49] - Diagnostic tests [49] - Hospital stay [49]
Control by the pharmacist (n=4)	Switch from intravenous to oral route (n=2)	- Over/under-prescription [50,51] - Hospital stay [50,51]
	Choice of molecule, treatment duration (n=2)	- Over/under-prescription [52,53] - Remuneration of the professionals involved [52]

Category	Types of misuse	Types of associated costs
New tools (n=4)	Choice of molecule, dose/dosing regimen, treatment duration (n=4)	<ul style="list-style-type: none"> - Over/under-prescription [54,55] - Hospital stay [56,57] - Diagnostic tests [57] - Visit to the emergency department [57]