Academic year : 2023-2024

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**Tutored Project Report**

Macroeconomic and structural parameters likely to influence the use of antibiotic and bacterial resistance in Humans and Animals in European countries.

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Tutored project submitted : 6th January 2024

## ACKNOWLEDGEMENTS

First and foremost, we would love to express our gratitude to Claire CHAUVIN, Epidemiology, Health, and Well-being Unit Anses Ploufragan (22), for her tremendous work and insightful contributions to this report. Thank you for your continuous support, patience, motivation, and immense knowledge in the subject.

Besides Ms. CHAUVIN, we would love to thank our scientific tutor Kenny OBERLE, BIOEPAR Joint Research Unit (Oniris/INRAE), Nantes (44), for his contribution in the completion of this report and sharing advice to complete this report.

Finally, a huge gratitude toward our coach Franck INSIGNARES, Oniris (44), for implementing appropriate communication skills during the project that allowed it to be achieved.

# ABSTRACT

The burden of Antibiotic resistance is becoming more and more important and of concern for a One Health approach. It concerns human health, animal health and the environment in the whole world, and can be influenced in many ways.

The aim of this report is to make a scoping review about the different macroeconomic parameters that can influence the use of antibiotic and bacterial resistance in humans and animals in European countries.

To conduct this review, several articles (17 selected articles) belonging to ecological study type were studied to assess the different parameters, and all the results were included in a large table to represent the article characteristics and what we can find inside.

We found that there is a positive correlation between antimicrobial use and the prevalence of antimicrobial resistance. Corruption and governance are main factors impacting resistance and environmental factors as temperature are also correlated to antibiotic resistance proportion.

This project allows us to see that there is a strong relationship between socio-economic factors and antimicrobial resistance, and the need to make further investigation in other parameters.



**KEYWORDS:** Antimicrobial resistance, Europe, socio-economics parameters, One-Health

**RÉSUMÉ**

Le fardeau de la résistance aux antibiotiques devient de plus en plus important et préoccupant dans le cadre d'une approche "Une seule santé". Il concerne la santé humaine, la santé animale et l'environnement dans le monde entier, qui peuvent être influencés de nombreuses manières.
L'objectif de ce rapport est d'effectuer une étude exploratoire des différents paramètres macroéconomiques qui influencent l'utilisation des antibiotiques et la résistance bactérienne chez l'homme et l'animal dans les pays européens.
Pour ce faire, plusieurs articles (17 articles sélectionnés) ont été étudiés afin d'évaluer les différents paramètres, et tous les résultats ont été inclus dans un grand tableau afin de représenter les caractéristiques de l'article et ce que l'on peut y trouver.
Nous avons constaté qu'il existe une corrélation positive entre l'utilisation des antimicrobiens et la prévalence de la résistance aux antimicrobiens. La corruption et la gouvernance sont les principaux facteurs ayant un impact sur la résistance et les facteurs environnementaux tels que la température sont également corrélés à la proportion de résistance aux antibiotiques.
Ce projet nous permet de constater qu'il existe une relation étroite entre les facteurs socio-économiques et la résistance aux antimicrobiens, et qu'il est nécessaire d'approfondir les recherches sur d'autres paramètres.

**Mots clés** : Antibiorésistance, Europe, paramètres socio-économiques, One-Health

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## LIST OF ABBREVIATIONS

3GCP : Third generation cephalosporins

AM: Antimicrobial.

AMC: Antimicrobial consumption.

AMR: Antimicrobial resistance.

Anses: French Agency for Food, Environmental and Occupational Health & Safety.

CRPA: carbapenem-resistant Pseudomonas aeruginosa

EU: European Union

JIACRA: Joint Interagency Antimicrobial Consumption and Resistance Analysis.

LMIC: Low - middle income countries.

WHO: World Health Organization

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## INTRODUCTION

France's agency for food, environmental and occupational health, and safety, committed to advancing knowledge and anticipating tomorrow's health and ecosystem preservation challenges. Anses' broad scope of action gives it a cross-disciplinary view of health issues, at the crossroads of human health, the health of other living organisms and ecosystems. It's a public agency that reports to the Ministries of: Health, Environment, Agriculture, Labor, and Consumer Affairs. Since 2010, it has been providing the scientific benchmarks needed to protect our health against risks linked to food, environment, and work, or which affect the health of animals and plants. With more than 1,400 employees, more than 800 independent experts mobilized, Anses has 9 laboratories across France with a budget of 140 million euros.

According to Roger Genet, general director of Anses from 2016 to 2022, in summarizing the agencies' goals and principles *" Our role is not to formulate injunctions, but to provide the means to understand, to guarantee access to as much reliable scientific knowledge as possible to enable everyone, individually or collectively, to choose or act"*. Anses is involved in various fields including food, animal welfare and health, plant health, health at work and environmental health. The main scope of this prestigious organization is to provide a cross-disciplinary overview of health issues with respect to the intersection of human health and other organisms as well as ecosystems. The organization aims to establish comprehensive approaches to risks as it has always been positioned between animals, humans, and plant health. Moreover, the agency utilizes scientific experts in their fields as well as collaboration with research stakeholders in France and across the world, that implement reference strategies and methods. Furthermore, the agency advocates transparency and independence as two valuable principles to always take into consideration. Finally, as the health issues are both a source of interest and concern for society, Anses emphasizes dialogue with society with associations, unions, elected officials, businesses, and ministries that are represented in the Anses board of directors. [1]

Dealing with the antimicrobial resistance (AMR) issue, Anses conducts a surveillance plan for certain bacteria. This surveillance is possible through the national antimicrobial resistance reference laboratory in the laboratory of Fougères and the laboratory Ploufragan-Plouzané-Niort. These laboratories develop, optimize, and validate analysis methods in response to demand of the agricultural ministry. [Anger et al. *Bilan 2014-2020*.]

Acquired expertise in the AMR domain is invested in a European interagency task called "Joint Interagency Antimicrobial Consumption and Resistance Analysis" (JIACRA), in which one an integrated analysis of national AMR and antimicrobial consumption (AMC) surveillance results in human and veterinary medicines is carried out. This group was created in 2013 following a request from the European Commission to the three agencies ECDC, EFSA, EMA to produce a joint report on antibiotic consumption and resistance. The aim is to study potential relationships between AMC in Humans, AMC in Animals, AMR in Animals & AMR in humans. In this JIACRA framework, it is planned to extend integrated analysis using new statistical models and new variables. In order to improve statistical analysis, other drivers can be considered. So, Anses asked us to create a scoping review about the macroeconomic and structural parameters that can likely influence the bacterial resistance in humans and animals in European countries.

## CONTEXT

AMR refers to micro-organisms' ability to survive or to grow in the presence of a concentration of an antimicrobial agent which is usually sufficient to inhibit or kill microorganisms of the same species. This mechanism can be natural or acquired. Resistance genes can spread, both between bacteria of the same species and between bacterial populations belonging to different bacterial genera, by horizontal gene transfer (for commensal bacteria and bacteria that are pathogenic to humans and animals) [Jian Z et al., 2021].

AMR is a crucial problem for the modern world, regardless of variations among countries. Recognized by World Health Organization (WHO) as 1 of the 10 major global public health threats, with an estimation of 5 million deaths associated with bacterial AMR worldwide. It imposes large clinical and financial burdens where resistant bacteria can develop in any country, and any region and spread tremendously. Where AMR threatens the effectiveness of treatments to treat or prevent bacterial infections in humans and animals, resulting in increased morbidity and mortality. [Murray et al., 2022]. According to WHO's global action plan on antimicrobial resistance, this notion threatens cores of modern medicine and effective approaches of global public health response to threats from infectious diseases. Without harmonized and global action on this topic, the world is heading toward a post antibiotic era where common infections will kill again.
Nowadays, this major health issue is recognized as the *One Health* problem; where it concerns humans, animals as well as the environment. Thus, it requires sector specific actions in human health, food production, animal and environmental factors and a coordinated approach across these stakeholders.

As widely reported in literature, the consumption and overuse of antibiotics are the primary drivers of AMR emergence and maintenance. For example, according to an econometric study by Ortega-Heudo *et al*. issued in 2020 dealing with data from 2006 to 2016, the misuse of 3rd generation cephalosporins and fluoroquinolones with nosocomial *E.coli*, *K.pneumoniae* and *P.aeruginosa* increases resistance by increasing AMR genes. [Ortega-Huedo et al., 2020]. Furthermore, Mc Donnell *et al*., found out, in an ecological cross-sectional in European hospitals from 2009 to 2014 that antimicrobial (AM) quality prescribing contributes to patterns of resistance as well as the volume of consumption. Where the overall AM consumption is strongly correlated to 19 different bacterial resistant strains. [Maugeri et al., 2023]

However, different reports suggest the involvement of other factors that influence the case further. According to Collignon *et al*. (2019), resistance levels don't correlate with Human Usage volumes. As seen in Figure 1, global regional groupings show an inverse aggregate relationship between antibiotic usage and percent resistance of *E. coli* to 3rd generation cephalosporins (3GCP) and fluoroquinolones.

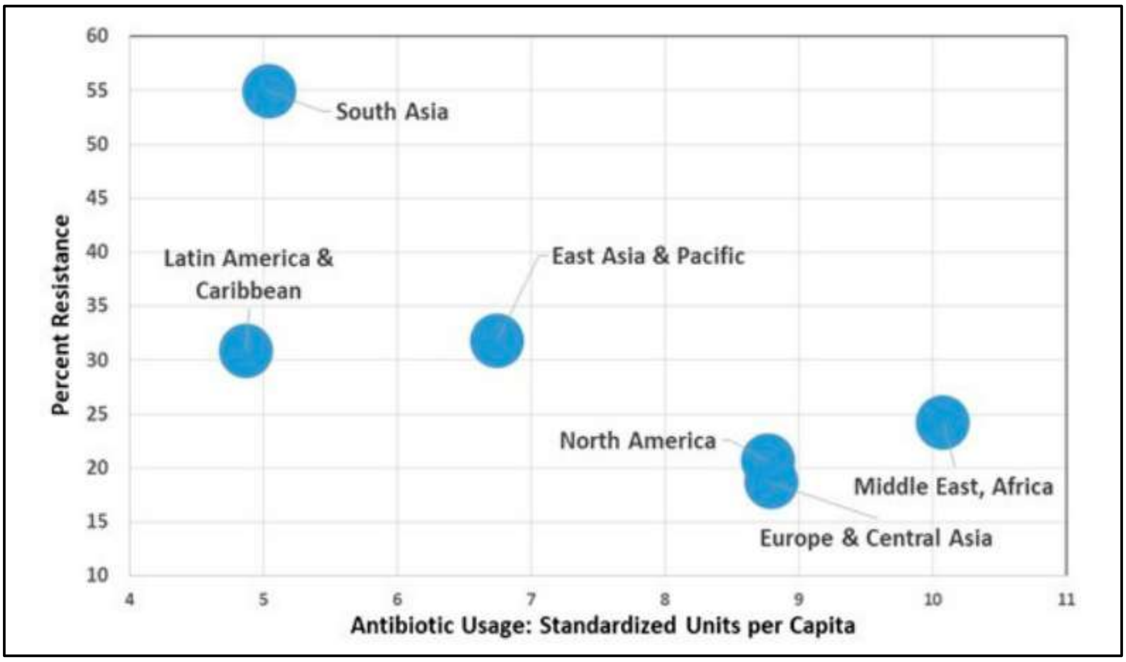



*Figure 1: Percent resistance in E.coli to 3rd generation cephalosporins and fluoroquinolones*

Nevertheless, the same researchers suggest other factors than AMC that can affect AMR. In which this can be explained by the observation of increased resistance in Low-income countries and middle-income countries (LMICs). Where per-person AMC in LMICs is far lower than that of high-income countries, as seen in Table I. Surprisingly, LMICs proceed to have higher rates of antimicrobial resistance.

*Table I: Percent of antibiotic usage and resistance of E.coli to 3GCP and Fluoroquinolones according to income*

| World Bank Income Group | Antibiotic Usage CDDEP Standardized Units | Percent Resistance *E. coli* to 3GCeph&FQ |
|---|---|---|
| High income countries | 8.5 | 18.3 |
| Upper middle-income countries | 7.2 | 31.1 |
| Lower middle-income countries | 6.9 | 42.6 |
| Grand Total | 7.9 | 25.6 |

Source: Percent resistance *E. coli* to third-generation cephalosporins (3GCeph) and fluoroquinolones (FQ). CDDEP is the Centre for Disease Dynamics, Economics and Policy. Source Data: Collignon et al. (2018) [15].

Collignon and Beggs indicated that AMR is driven by two factors; volume of AMs used as well as the spread of resistant microorganisms. Focusing on the spread, the notion is modulated by several factors, and it is supported by conditions that allow the spread of resistant microorganisms, such as poor-quality management of sanitation, poor health facilities and poor hygiene practices. [Collignon et al., 2019] With a good contribution of antimicrobial consumption and misuse, to the increased prevalence of AMR, the same entity can be affected by several parameters that are not related to consumption, but rather go far beyond.

As a "thinking outside the box" mentality overall excels in science, several researchers took AMR prevalence into another level. The article by [Kaba et al., 2020] concludes that any factor influencing transmission might play a role, and these factors can belong to diverse thematic, for example climate factors. These factors can have a relationship with the prevalence of few pair bacterial resistance, like carbapenem-resistant *Pseudomonas aeruginosa* (CRPA).[Kaba et al., 2020]

To tackle the AMR burden, a lot of laboratories are involved in Europe. A new EU One Health Action Plan against AMR is issued to provide a continued and more extensive action to reduce the emergence and spread of AMR as well as to increase availability and development of new effective antimicrobials. Different stakeholders are involved including ECDC, European Centre for Disease Prevention and Control and EMA - European medicine agency -, that gather AMR and AMC data through various networks such as EARS-net and ESVAC-net, which deal respectively with antimicrobial surveillance in eight major species and antibiotic sales in the veterinary sector, following the standardized methods for AMR monitoring set by international agencies such as the FAO and WHO. [European Commission. 2020] At a national level, as mentioned before, Anses play an important role in AMR at the French national level.

Thus, moving forward from surveillance efforts as well as analytical efforts made in Europe, going further with efforts already performed in JIACRA. We take the opportunity of indicators present in Europe to address AMR in a One Health context. However, to help this process, a preliminary step is required to identify which additional factors that might contribute to this burden in addition to the huge contribution of antimicrobial consumption... A range of these factors, addressed later in this report, include structural, socio-economic, demographic, and geographical factors.

Nevertheless, to inventory these parameters in the framework of Anses objectives : the modeling of epidemiological data; a scoping review process seemed well adapted. Essentially, a scoping review is **a type of knowledge synthesis that uses a systematic and iterative approach to identify and synthesize scientific information concerning a given topic**. It’s a way to present bibliographic research. The main reasons for writing a scoping review are to map the extent, range, and nature of the literature, as well as to determine possible gaps in the literature on a topic.

## MATERIAL & METHOD

For this project, we were asked to perform a scoping review of articles dealing with antimicrobial resistance influential factors identified through an epidemiological approach applied to ecological data (like JIACRA datasets). To this end, several steps are involved like : Identifying the Research Question, Identifying Relevant Studies, Selecting Studies to Be Included in the Review, Charting the Data, Collating, Summarizing, and Reporting the Results. [Mak, S., & Thomas, A. (2022)]

The search question we intended to address was: **Which are the influential factors considered in the scientific literature dealing with epidemiological ecological models of antimicrobial resistance?**

### *1. Identification of relevant studies*

In order to perform the literature analysis, articles had to be firstly identified through a bibliographic query. The search was performed on PubMed.
The search equation applied to PubMed database was: ((Anti*[Title]) AND (resistance[Title])) AND (econom*) AND (country OR local OR global). It was created from eight articles dealing exactly with our subject. A broad query associating “factors” “antimicrobial resistance” was providing too numerous articles, mostly out of the scope, for a manual screening. To narrow the query spectrum, frequent terms were identified from the text of the initial set of 8 articles. Their association and use were tested to ensure that a major part of this initial set could be retrieved.

### *2. Studies Selection*

Applying the query, 630 articles were found. Of these 630 articles, 33 were retained with the title and the abstract. Inclusion criterions considered were i) the publication language (English) ii) belonging to ecological epidemiological study design (with a reported statistical data analysis) iii) dealing with at least one parameter in addition to AMC to ‘explain’ an AMR outcome. Reviews were excluded, as clinical cases and clinical trials or experiments.

In a second step, articles related to these 33 ones were looked for in the Scopus database. This led to the additional inclusion of 24 articles fulfilling inclusion criterions. Applying exclusion criterions during the full text reading of these articles and paying attention to their references list to complement the database, 54 eligible articles were finally identified. Considering time constraints for the project realization, and the strong focus of our sponsor on the European context, it was decided to add a geographical inclusion criterion limiting the scope of our review to European countries and areas.

Considering the complexity involved in defining queries, implementing them, and the limitations of time, the selection step was executed in Anses, as depicted in Figure 2. [1] Finally, we only kept 17 articles for the present report (Figure 2).

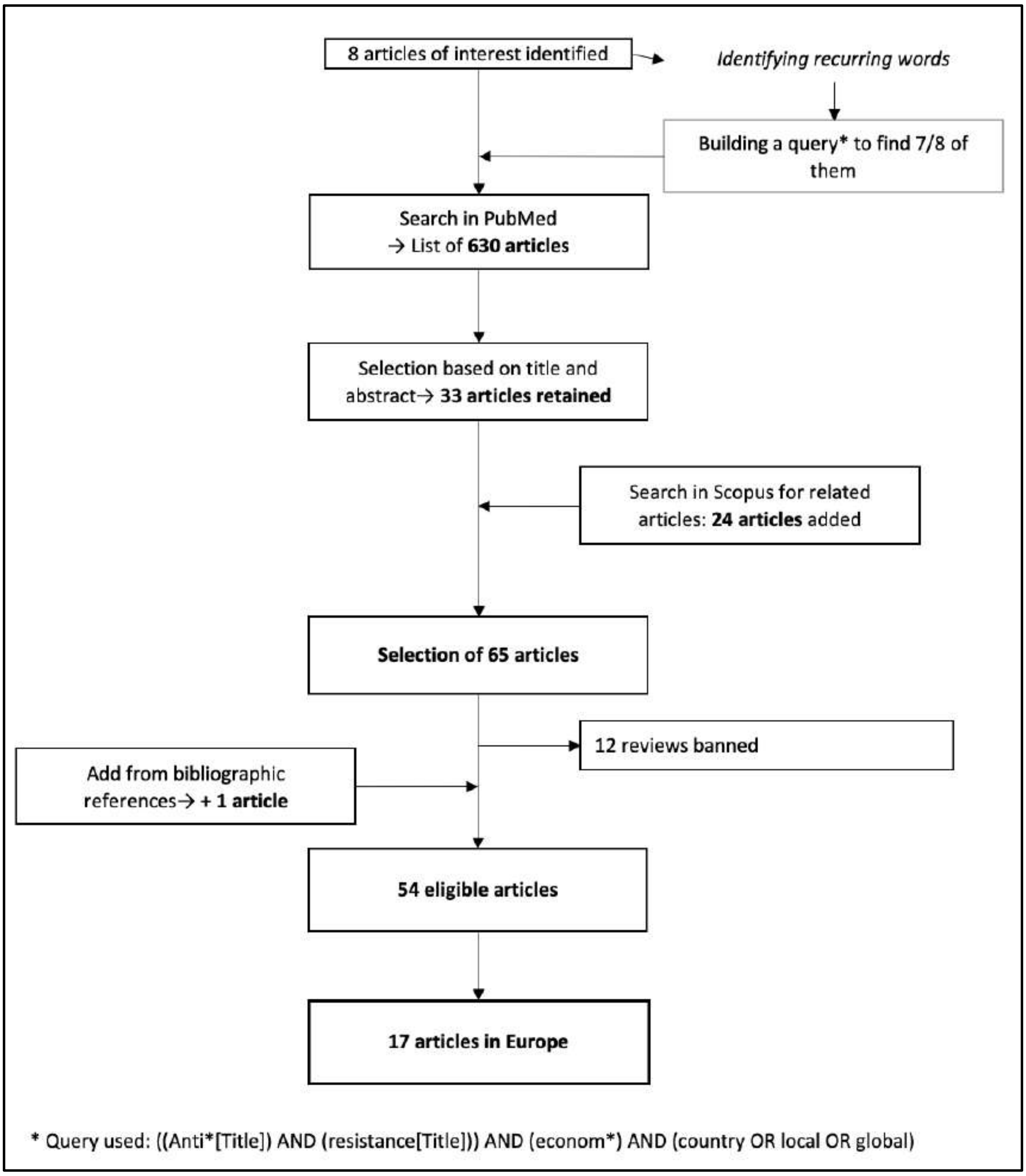



*Figure 2: Scheme of the article selection process.*

[1] Difficulties to do the selection process by ourselves because of the cyberattack at Oniris and the lack of access to web services and bibliographic resources in this context.

### 3. *Data extraction and storage*

To store the information, on the articles and factors studied, a spreadsheet had to be defined. For the purpose, we firstly carefully read four articles to be more familiar with vocabulary and diversity of items. An Excel table was thus defined, slightly amended during the other articles reading.

<u>The table is declined in five main parts, these different parts are identified with a color code:</u>

The first part in yellow, as we can see below (Table II), is for the information about the article characteristics. It's important to consider the year of publication because it provides the temporal context of this study. The column "Type" is to help us to know if the articles, whether ecological or analytical, are either cross-sectional, or longitudinal study. As we have analyzed articles with epidemiological study, the statistical model is necessary to help Anses about how the data was processed as well as to provide accuracy about the type of studies conducted with years followed.

*Table II: Characterization of the article*

| Title of article | Authors | Publication Year | Type | Statistical Model |
|---|---|---|---|---|

The second part in orange (Table III) is for spatial characteristics of a given article and the topic, to identify the characteristics of the data in the different articles. It included:

- The origin of data: to facilitate the future work of Anses regarding this topic, since Anses is highly involved in topics related to France and EU. This point is also useful to determine if results are comparable (for example, LMICs might have particularities not applying to European countries)
- Topic, variable to be explained.
- Period of data collection;

*Table III: Characterization about space and time of the article*

| Where the study/data come from | Topic, variable to be explain | Period of data collection |
|---|---|---|

The third part in red (Table IV) is for more accurate/detailed information in relation to AMR. This part is great when we are looking for information about one couple of bacteria and the resistance with antimicrobial substances. The epidemiological unit, however, is for the type of sample used in the article.

*Table IV : Information about the bacterium studied and sample used*

| Pair bacteria/resistance | Population | Epidemiological unit |
|---|---|---|

The fourth part in blue (Table V) is the largest part of this table. This part is for the different factors that can influence the AMR addressed in the articles. We have no put limitation for the choice of the parameters. Any items related to countries and populations studied are included in our purpose. For example, climate and pollution might not be considered neither structural nor socio-economic, but it can be interesting to consider these parameters' influence.

*Table V: The different target parameters*

| Usage AM | Pollution | Corruption / governance | Access to health | Geographic caracteristics | Climate | Population income | Tourism | Infrastructure | Demographic structure | Co resistance | Animals Health | Economic data /GDP | Resistance evolution / average |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|

The parameters selected can be defined in different ways, since it may not be clear for everyone, Appendix 2 contains some definitions of our different parameters. Furthermore, since the meaning of one parameter can change a little between two articles. The difference is addressed in the "Notes" column of the table. Thus, the last column of the table is just a box in green "Notes", it contains important information and comments about articles.

Articles reading and database fulfillment was performed by three readers for the four initial articles. This allowed us to check and correct data storage, to ensure harmonization between investigators. This is important for the process quality. Then, the remaining articles were screened by two readers.

# RESULTS

*1. Description of the articles included.*

To describe our database, we performed some figures showing the global repartition of articles dealing with AMR, both geographically and temporarily.

In our work, we identify 54 articles published between 2003 and 2023, although only 3% of these studies were published before 2014. In fact, the literature is mainly recent, around 55% of articles were published these last three years. Nevertheless, some are much older and date from the early 21st century (Figure 3A). Around the world, the number of studies published on AMR increased from 1 in 2003 to 14 per year in 2023. For Europe, studies are more recent and the 17 articles we deal with were written these last ten years. But this trend is also set to increase between 2014 and 2023 (Figure 3B).

Moreover, in the map representation (Figure 3C), we can see that the topic of AMR, with our specific selection, is addressed all around the world with more or less specific areas. Few (7/54) are dealing with only one country - excluding China - maybe due to the lack of detailed data, but we noticed that most of the articles (36 out of 54 articles) deal with international (19 out of 54) or European databases (*Appendix 3)*. Indeed, this will influence the results because some parameters are more contrasted between LMIC and Europe and then situations observed might not be transposed to any countries or at a limited level. We have 40% of the articles dealing with Europe or specific regions of Europe. This represents a substantial part of the complete database, knowing that 35% are dealing with the world and 25% with countries in the world.

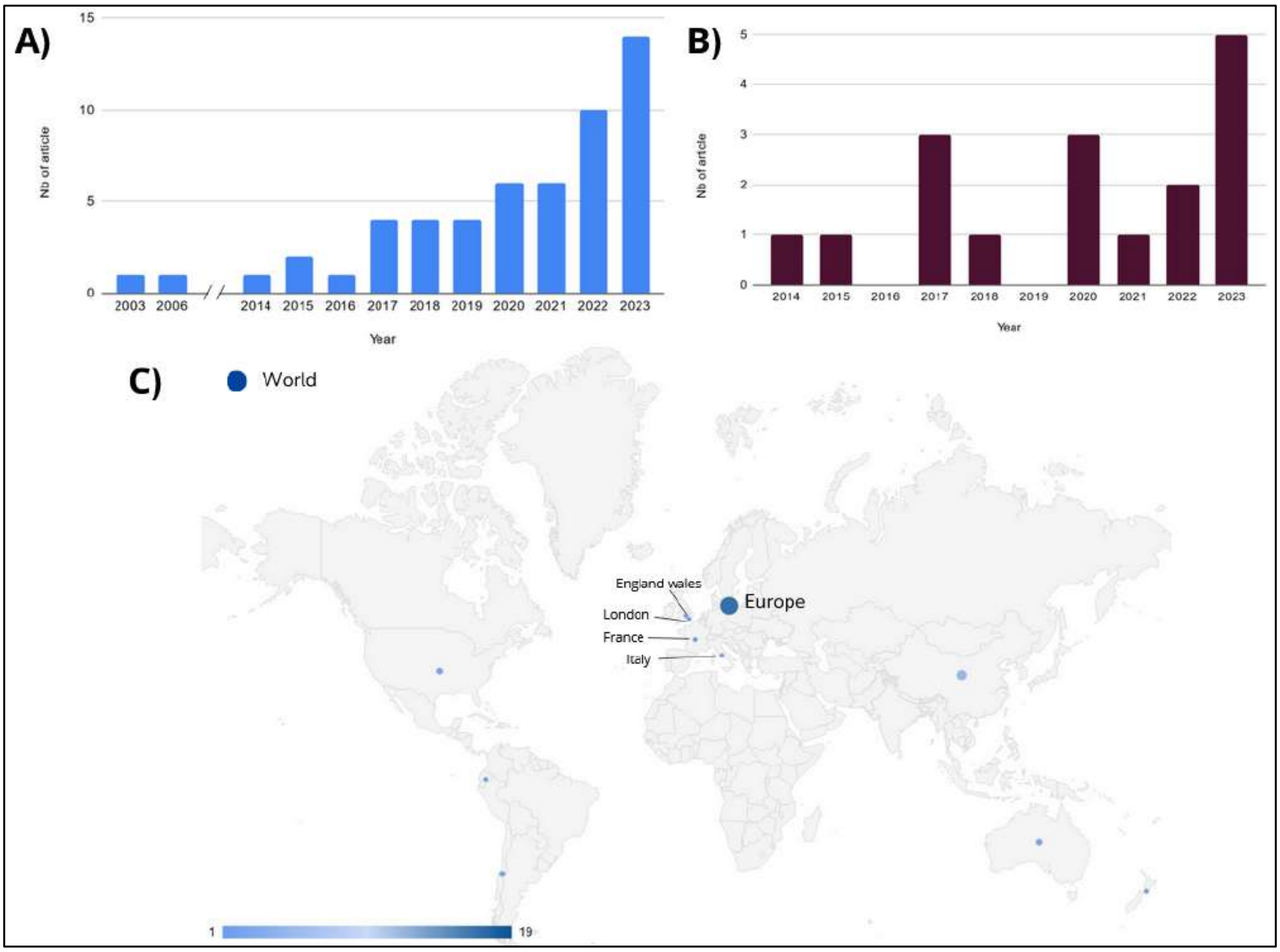



*Figure 3: Database description. A) Number of articles by year of publication for the world ; B) Number of articles by year of publication for EU ; C) Worldwide distribution of included articles*

2. *Scope of article include.*

On February 27, 2017, WHO published the list of global priority pathogens, which corresponds to a catalog of 12 bacterial species grouped into three priority levels based on their antibiotic resistance: critical (three species), high (six species) and medium (three species). [GV Asokan et al. 2019]

From these 12 species, 9 are included in our set of 17 publications in Europe. The number of studies per bacteria is highly heterogeneous. The majority of studies focused on *E. coli* (64%), followed by *P. aeruginosa* & *K. pneumoniae* (47%) and *S. aureus* (41%). (Figure 4)

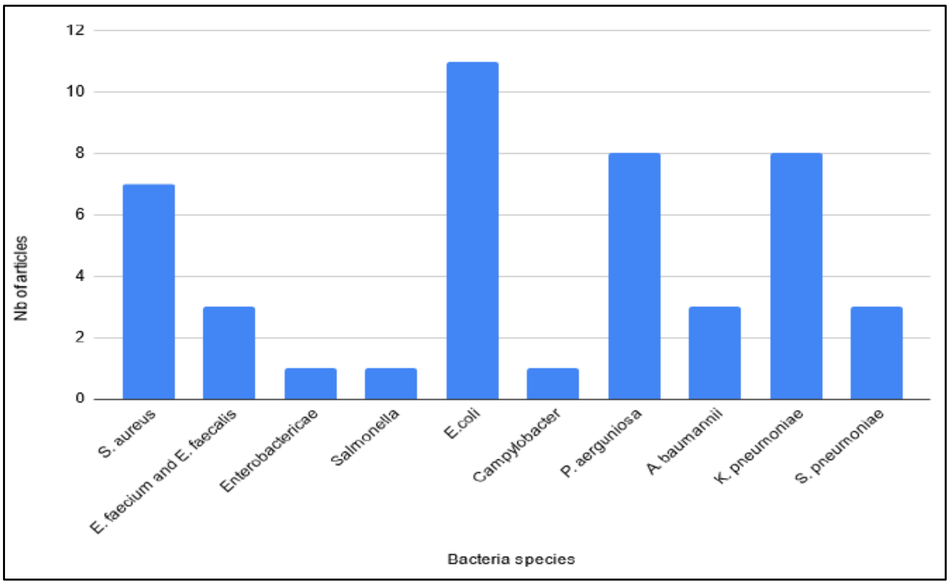



*Figure 4: Number of publications per bacteria species*

Considering the diversity of resistance, we have both the class of AM associated with each species, which vary a lot, and the various factors impacting the resistance. We can see that for *E. coli* the main concern is the resistance to 3GC (41%).

For other species, like *P. aeruginosa* the main concern is carbapenem resistance, and for *K. pneumoniae* both two precedent classes of AM are considered approximately at the same level. Finally, for *S. aureus*, the main AMR addressed is methicillin (Table 6). If we look at the classification by priority category for AMR published by the WHO, we may conclude that the bacterial/AM pairs discussed most often in the articles are those classified as critical. Except for *S. aureus*, which is classified as high.

*Table VI : AMR bacteria addressed in publications* [2]

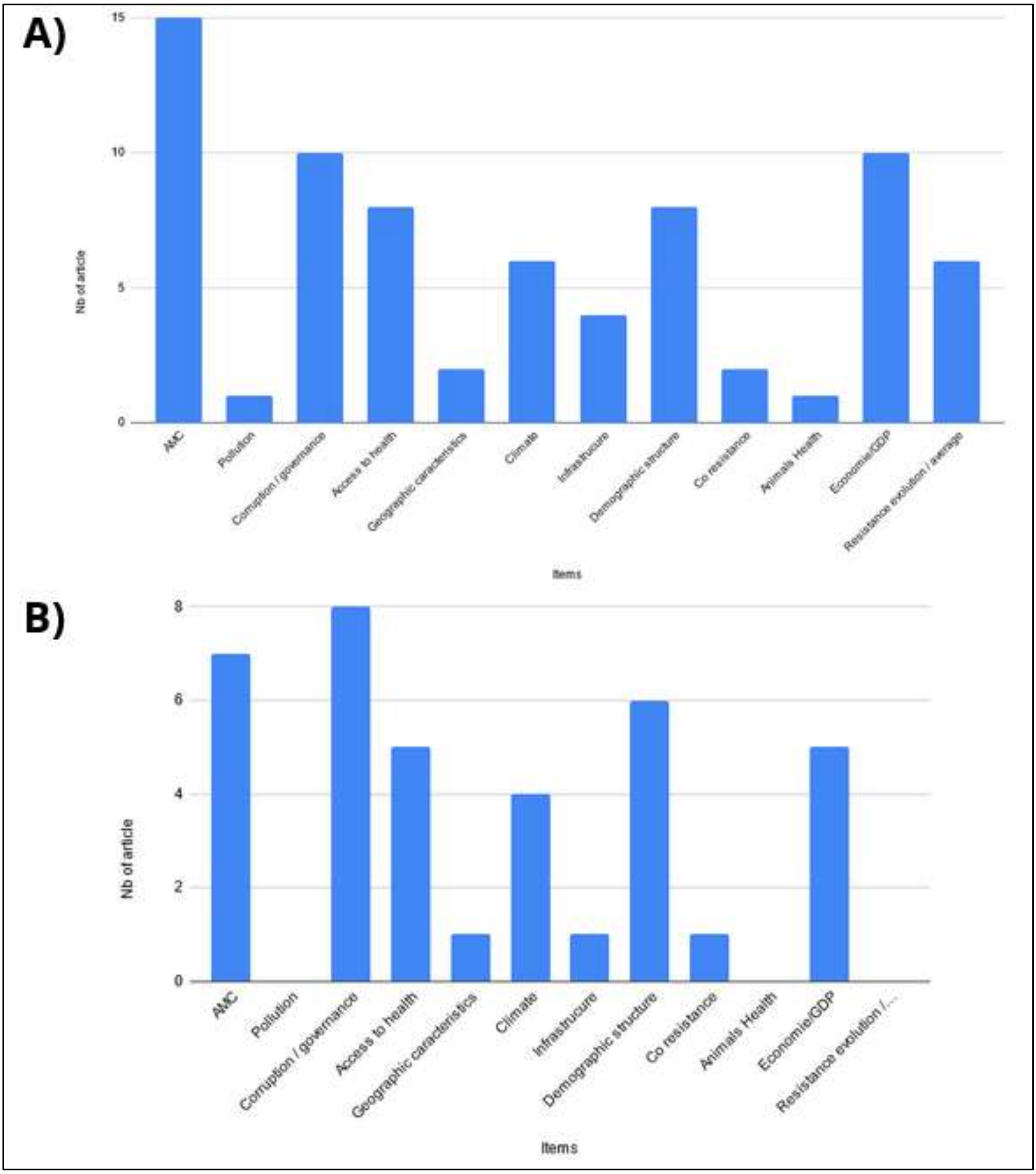
| Pathogens | | Antibiotic resistance | Nb of articles | References |
|---|---|---|---|---|
| *Acinetobacter baumannii* | | Carbapenem-resistant | 11,76% (2/17) | 1; 12 |
| *Pseudomonas aeruginosa* | | Carbapenem-resistant | 17,65% (3/17) | 1; 12; 13 |
| | | Third generation cephalosporin and fluoroquinolone-resistant | 5,88% (1/17) | 7 |
| | | Multi-resistant | 11,76% (2/17) | 3; 17 |
| *Enterobacterales* | | Carbapenem-resistant | | |
| | *E.Coli* | | 11,76% (2/17) | 12; 17 |
| | *K.pneumoniae* | | 23,53% (4/17) | 11; 12; 13; 17 |
| *Enterobacterales* | | Third generation cephalosporin-resistant | | |
| | *E.Coli* | | 41,18% (7/17) | 6; 7; 8; 10; 11; 15; 17 |
| | *K.pneumoniae* | | 29,41% (5/17)) | 7; 8; 10; 11; 17 |
| *K.pneumoniae* | | Aminoglycoside-resistant | 23,53% (4/17) | 8; 10; 11; 17 |
| *E.Coli* | | Aminopenicillin-resistant | 23,53% (4/17) | 8; 11; 15; 17 |
| | | Multi-resistant | 5,88% (1/17) | 13 |
| *Enterococcus faecium & E.faecalis* | | Vancomycin-resistant | 11,76% (2/17) | 1; 17 |
| | | Aminopenicillin-resistant | 5,88% (1/17) | 17 |
| *Staphylococcus aureus* | | Methicillin-resistant | 35,29% (6/17) | 1; 6; 8; 11; 13; 17 |
| *Staphylococcus aureus* | | Third generation cephalosporin-resistant | 5,88% (1/17) | 6 |
| *Campylobacter spp.* | | | 5,88% (1/17) | 5 |
| *Salmonella spp.* | | | 5,88% (1/17) | 5 |
| *Streptococcus pneumoniae* | | Penicillin | 11,76% (2/17) | 15; 17 |

Moreover, in our 17 articles, we also have a high diversity of design, model, and population. (Appendix 4). For example, even though we have a majority of models based on multivariate analysis (9/17), we also have a combination of methods or modeling approach (2/17). The population also varies a lot from EU global population to age range right down to clinical isolates (hospital, urinary infection…) and even the bacterial population itself.

[2] To retrieve reference from the number, refer to Appendix 1

*3. Factors included.*

As described before, we selected various factors that could be considered, based in part on a study by Collignon et al. 2018, which also serves as a reference for many other authors.



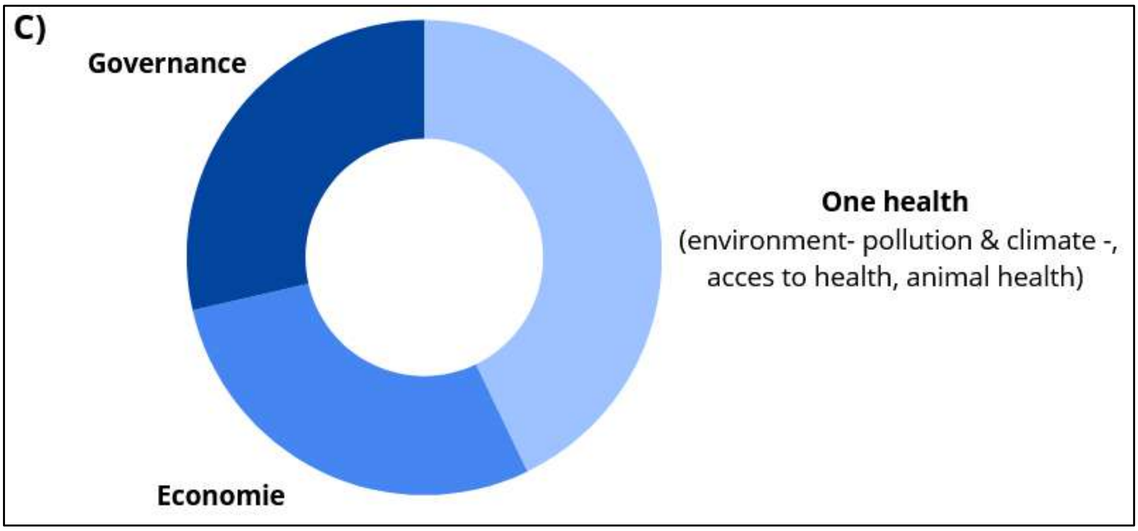



*Figure 5 : Socio-economic and other factors addressed in European countries.* ***A)*** *Percentage of articles dealing with each item;* ***B)*** *Number of articles with significant results (parameter was found as significant in the model);* ***C)****Main factors excluding AMC*

If we look at the diversity of the factors, we may note that there is a high heterogeneity. As we can see in the (figure 5A), most of the articles investigated deal with AM usage, which coincide with what has been mentioned earlier, about the consumption role in the prevalence of AMR. Which is logical since most of the literature dealt with AMC(88%), however, 12% of the articles dealt with AMR without considering AM usage that is known to be a driving factor for the burden. Afterward, the two main factors addressed are corruption and economy. If we exclude AMC of the percentage repetition, we can highlight three main categories addressed approximately at the same level, i.e. governance, economic and One Health (Figure 5C). In the latter, we group together environmental factors such as pollution and climate, human health factors (access to health) and animal health factors.

Looking more specifically at significant results (figure 5B), for AMC, only 46% of the articles dealing with it show significant results concerning the link between bacteria/AM and resistance. 80% show significant results for governance and 50% show significant results for the economy.

Trying to relate these factors with significant results to bacterial/AM pairs, we can draw the main trends for AMR (Table 7). Focusing only on the four bacteria mentioned earlier, Table 7 shows the key findings from studying how different factors affect resistance. Most articles discuss antimicrobial resistance (AMR) on a global scale, so the conclusions drawn can be applied broadly to all bacteria with resistance.

For the AMC, unsurprisingly, a positive correlation with AMR was found in articles that include it as parameters in the model. One of them also highlights the selection pressure that applies to bacteria this way and *P. aeruginosa* is particularly sensitive to this selection pressure according to Kaba et al., 2020.

*Table VII: Significant factor impacting resistance for the four main bacteria addressed in the publications.*

| Pathogens | | Antibiotic resistance | Usage AM | Corruption / governance | Access to health | Climate | Demographic structure | economie/GDP | Resistance evolution / average |
|---|---|---|---|---|---|---|---|---|---|
| *ALL* | | ALL | - AMR rate is inversely corelated with human ambulatory antimicrobial consumption<br>- 28% of ABR explain by usage<br>- ABU significantly and positively associated with AMR proportions | - 63% explain when add Corruption → corruption is the main socioeconomic factor that explains ABR<br>- corruption perception = major predictor that is negatively associated with AMR | | - Positive linear association between annual temperature change and AMR proportion across all countries, years, pathogens, and antibiotic classes<br>- Positive linear association with temperature, AMR increase faster with higher temperature | - Mean years of schooling had a significant negative relationship with Ab use<br>- Social desirability had a statistically significant correlation with Ab use | AMR rate is inversely related to the country's per capita expenditure on health, in euros | |
| *Pseudomonas aeruginosa* | | Carbapenem-resistant | P.aeruginosa quickly react to selective pressure resulting from ABU | | * | CRPA strong correlations with wm_net_warming | | | |
| | | Third generation cephalosporin and fluoroquinolone-resistant | | | | | | | Slight increase from 2006 to 2015 |
| | | Multi-resistant | | - Control of corruption negatively corelated with MDR-Pa<br>- Governance indicators as the most important determinants of MDR-Pa | | | | GDP for health negatively corelated with MDR-Pa | |
| *Enterobacterales* | *K.pneumoniae* | Carbapenem-resistant | | | * | CRKP significantly correlated with warm temperature | | | |
| | *K.pneumoniae* | Third generation cephalosporin-resistant | | | | | | | Since 2014, the AMR suffers from recession leading to stabilization in AMR rates |
| | *E.coli* | Carbapenem-resistant | | | * | | | | |
| | *E.coli* | Third generation cephalosporin-resistant | | | | positive relationship between annual temperature change and proportion of E. coli resistant to 3GC | | | Low rate in 2016, unstoppable growth until 2012, striking slope declaration in 2013, and stablized rate onwards. E.coli has smallest rates among other AMR to 3GCP |
| | E.coli | Multi-resistant | | stronger association with CPI | | - MREC correlated with wm_temp & wm_net_warming | | | |
| *Staphylococcus aureus* | | Methicillin-resistant | | - executive capacity is significantly associated with MRSA when including ABC<br>- countries adapting infeciton prevention and control practices reduce the rate of increase of healthcare associated MRSA | | warmer temperature has larger rates of DECREASE for MRSA | | | |

* a decrement of 1 practicing nursing professional per week of hospital stay of a random population individual was associated with a 0.51% [95%-CI 0.01–1.02%] increase (p=0.046) in CR Gram Negative on average

As for the impact of corruption, there are several ways of measuring it. The most common are the Corruption Perception Index (CPI) and the Governance Control Index (GCI). Although there are many ways of assessing corruption, the conclusion is the same: poor governance leads to an increase of AMR. Main results for governance impact are obtained on multi drug resistant bacteria (*E. coli* or *P. aeruginosa*). In addition, as far as human health is concerned, for carbapenem-resistant gram-negative bacteria (CRGN), average resistance increases if healthcare staff, and especially nurses, are reduced. [Kaba et al., 2022]
Moving on to climate, the authors agree that temperature is positively correlated with AMR. Indeed, warm temperatures lead to an increase in AMR proportion. Nevertheless, this correlation is reverse for S. aureus methicillin resistant. Finally, regarding the economy, expenditure on health is negatively correlated to AMR which is logical since the more money invested in health, the less likely it is that AMR will have a chance to develop.

Considering the diversity of models, populations and the heterogeneity of parameter definition (for example climate: temperature evolution is defined as a minimal, an average, etc...), we have concluded that our results are not comparable and therefore we could not perform a meta-analysis. Moreover, resistance is not assessed in the same way in all articles, the same bacterial/AMR pairs are not studied, and the aim of the articles, as mentioned above, is not the same. For these reasons, the scoping review turned out to be the most interesting way of presenting our findings.

# DISCUSSION

## *1. Limits of methods applied and critics of the process.*

An important limitation of our project is the **time limit**, which restricted our ability to analyze and interpret the data from a global perspective. The unexpected amount of data available worldwide presented a challenge, making it necessary to focus on articles dealing specifically with Europe. Given this time constraint, we made the strategic decision to focus our efforts on Europe to ensure a more thorough analysis within the time available. This therefore allowed a focused study of the complexities of AMR in the European context, but necessarily limited the scope of our study by excluding ideas and data from other regions of the world (tourism, culture…). Our study aimed to provide a picture of a global understanding of AMR in the European context, highlighting the importance of further global data to achieve a more holistic understanding of this key issue. It also allowed us to highlight the need for global research to improve understanding of AMR.

We may also have introduced a bias into the results by relying exclusively on European articles. The socio-economic factors influencing antimicrobial resistance can vary considerably from continent to continent, country to country and even region to region. This limitation could bias our conclusions, by not capturing the full range of socio-economic determinants affecting AMR in different socio-cultural contexts around the world.

The selected articles show differences in data quality, methodologies, and study designs. This diversity makes the analysis complex and could potentially affect the robustness and reliability of the study results and conclusions.

Reading complex, data-rich articles was quite complex. Most articles were challenging due to their complex nature and density of information. The amount of data presented in these articles required a longer approach to sort out the complex details. Despite these challenges, our perseverance and adaptability enabled us to successfully work our way through the complexities and extract essential information for our study of antimicrobial resistance.

Moreover, there are some selection limitations also highlighted by Anses. First, they didn't proceed as usual in restricting the query to only one unique database. Where they started in articles limited to PubMed but shortly after, they selected articles in second database Scopus. Second, the query dealt with resistance directly and therefore missed articles dealing with AMU that were out of the scope. Finally, the inclusion criteria were limited to articles written in English language, as this condition shouldn't have a great impact on the results, but it can possess some limitations.

*2. Main results*

As seen in the sections of this report, most of the articles investigated deal with AM usage which coincide with what has been mentioned earlier, about the consumption role in the prevalence of AMR. Which is logical since most of the literature worldwide has dealt with AMR as well as the countless efforts to reduce AMR through reduction of consumption. However, a good number of articles also deal with governance and corruption. This highlights the significance of this problem within the EU and for Europeans. Nevertheless, in certain countries such as Bulgaria, the corruption rates remain higher compared to other countries like Denmark, where the level of corruption, for example in the healthcare sector, is notably low.

As seen in the results methods, several socio-economic, structural parameters were reported to influence AMR. Although the outcome is scarce, parameters mentioned in our work are rarely considered together. Perhaps due to recent investigations. It is worth mentioning, however, that these parameters can in fact be linked together at some point.

Data on Tourism and people movement across borders are not represented in European studies, we have no article that deals with these parameters. This can be explained by the fact that there is no priority over other parameters; study of the impact of tourism on AMR is quite complex because need to take into account different other interdependent factors specific to each country (for instance: the prescription and regulation, behavior of traveler…) ; lack of sensibility for this potential link ; lack of data about "How many antibiotics the traveler take", "If they are sick?"...

For parameters on Animal Health and pollution, the results were not significant in AMR. Maybe because we have very few articles dealing with this subject, only 1 article in a European country deal with these parameters respectively. It could be important to investigate more about the impact of consumption of antibiotics in animal health because the restriction for the usage can be really different compared to each country. Antibiotics are also used in livestock and to treat domestic animals, as well as growth promotion in countries outside the EU. Which can heavily impact the spread of AMR.

As seen before, a diversity of 12 parameters were reported. However, we were able to observe a diversity of definitions for a specific parameter. This variability in the definition of certain parameters had a significant impact on the interpretation and analysis of our results. For example, the AMC parameter is measured in terms of either defined daily dose or antibiotic sales volume, while the climate parameter includes both annual changes and rising temperatures. The governance parameter is measured by a lot of different factors, and not always the same ones... This is also why we carried out a scoping review rather than a meta-analysis.

In addition, only the AM consumption is considered with other parameters (AMC with corruption, with demographic index…). It can be interesting to consider the other parameters with each other, for example: how the co-resistance can be influenced by the governance or the climate.

Finally, focusing on the articles we analyze in details in Europe, we notice that we have three main type of studies : i) some of them making use in their models of already published parameters “just to be in line with the current knowledge and practices” ; ii) other ones trying to check a precise hypothesis such as a link between resistance and temperature, without adjusting on other parameters; iii) other articles looking for new parameters (such as E.Rahbe et al., 2023 using ATLAS or Aarestup article).

### 3. *Parameters lacking*

Following this study, we can consider the missing parameters that may have a direct or indirect impact on antimicrobial resistance. (Appendix 2, 2nd part)

First, a potential important factor is **hygiene and biosafety**, in the healthcare field, as well as in the agri-food environment. This raises the question of quantifying the use of biocides in human environments as a potential contributor to antimicrobial resistance. Assessing the prevalence and volume of biocides used in various environments such as healthcare facilities, households and public spaces can provide an indicator of the impact of these chemicals on the development of antimicrobial resistance. Unfortunately, there is currently a lack of comprehensive data on the quantities and specific types of biocides used in different contexts. We have some Data in Europe in the point prevalence survey of hand rub.

In the context of **animals and agriculture**, the absence of **public market data** is a notable gap. Understanding the economic dimensions of antimicrobial use in the livestock industry is essential for a full evaluation of the socio-economic factors influencing AMR. Access to detailed market data, which includes the economic value attributed to the sale and use of antimicrobial in the livestock sector, could provide information on the relationship between economic incitement and antimicrobial use practices. However, the limited accessibility and transparency of these data prevent a comprehensive understanding of the economic drivers of antimicrobial use in livestock farming and their subsequent impact on antimicrobial resistance. This could explain why we have very limited information about studies concerning animal health. Furthermore, the correlation between **veterinarian density** and antimicrobial use in animal health care is key to understanding how access to veterinary services influences the development and spread of antimicrobial resistance. This data should be accessible in the same way as physician density.

Secondly, regarding **public knowledge of AMR**, we have data in Europe with the Eurobarometer survey. It's an essential resource for assessing understanding and awareness of antimicrobial use (AMC) and antimicrobial resistance (AMR) among a sample of European citizens. This survey, carried out periodically, provides data to assess the public's knowledge, attitudes and practices regarding antibiotics and antimicrobial resistance in the EU. However, despite the existence of the Eurobarometer survey, more precise data is lacking, e.g., regional specificity, global representation, or longitudinal analyses based on this database to track changes in public awareness and knowledge over time. And above all, it's not addressed at all in the studies to find out whether it would have an impact on resistance.

As far as **eating habits** are concerned, we have databases available, especially in Europe, with the database of the European Food Safety Authority (EFSA). This is an important tool for understanding dietary habits and their potential implications for AMR. This database provides information on consumption patterns and the use of antimicrobials in food production. While the EFSA database is a fundamental resource for understanding food consumption in relation to antimicrobial resistance, further exploration and detailed analysis is required to access the potential of these data. The use of EFSA data, combined with targeted research efforts, could lead to a better understanding of the impact of food choices on AMR.

Then, thinking about **Environment and Antimicrobial Resistance**, we do not have many factors in our review. However, several can have an impact, such as :

- ➢ Animals Rearing Practices and Density that can vary a lot between intensive or extensive farming.
- ➢ Sustainability of Agricultural Practices, numerous indicators related to the sustainability of agricultural practices are available, these indicators might include water usage, pesticide usage, land management techniques, crop diversity, and carbon footprint… synthesizing this information for its direct correlation with AMR is challenging.
- ➢ Landscape characteristics cover a wide range of environmental factors such as topography, soil type, vegetation cover and proximity to bodies of water. And certain landscape characteristics can influence the dissemination and persistence of antimicrobial-resistant bacteria and antimicrobial residues in the environment.

Understanding the interaction between animal farming practices, agricultural sustainability, landscape characteristics and antimicrobial resistance requires in-depth research that takes into account multifaceted environmental factors. By focusing on specific indicators and using comprehensive, interdisciplinary approaches, future studies may elucidate the complex relationship between these environmental aspects and the development of antimicrobial resistance.

Finally, we can ask whether **cultural traits** might have an impact on microbial resistance. Indeed, cultural practices and beliefs can significantly influence people's perception of health, illness, and the use of antibiotics. Some cultures may prioritize traditional remedies or self-medication over seeking professional health care. Local community practices and social norms can also influence health-related behaviors, including the way antibiotics are used and shared within communities. This can lead to antibiotic misuse and overuse. Nevertheless, culturally sensitive approaches to healthcare, education and policy formulation can play a vital role in encouraging responsible antibiotic use, while respecting diverse cultural perspectives and practices. It could therefore be interesting to focus on these factors linked to culture in the study of AMR.

Considering this set of points, we realize that current studies are potentially missing crucial factors for understanding antimicrobial resistance and its evolution. This is also why we carried out this study, to find important factors in the study of resistance which are not considered today.

Concerning the missing factors, it would be necessary to make standardized data collection and to promote interdisciplinary research collaborations between economists, public health experts, veterinarians, and sociologists to comprehensively investigate the socio-economic dynamics of antimicrobial use and its relation to AMR.

### *4. Perspectives*

In the perspective of including some of these parameters in JIACRA, we believe that several factors could be interesting. Firstly, since we have available databases on certain underrepresented parameters, it seems worthwhile to focus on these initially. For instance, utilizing the data from the Eurobarometer survey to assess the impact of public awareness concerning ABU and AMR on AMR proportion or evolution. Concerning the environment, investigating the correlation between agricultural practices (intensive vs. extensive farming) and antimicrobial usage in livestock as well as the influence of environmental pollution from agricultural runoff or pharmaceutical waste on the spread and development of antibiotic resistance could be interesting.

Moreover, making further analysis of animal health, as we have discussed in the part “Parameters lacking”, to collect more information about the economic situation of antimicrobial in this sector can be useful. For example, the cost of antimicrobial substances purchased by the veterinary sector so to have an idea of how many antimicrobial substances are used in this field.

### *5. Feedback on this experience*

The experience allowed us to make critical analysis of articles. Because we had to read several articles to get into the context and then analyze the selected articles. It was essential to have the same way of thinking to have the same interpretation because we didn't have the time to read all the articles selected by Anses. During this semester, we have planned several meetings with our sponsor Claire Chauvin from Anses, she was a real support and give us good advice for our work. So, we have conducted a file with our meeting reports with her (Appendix 5).

The project enabled us to think about how different parameters can influence the burden that is AMR. To become aware of what we can do at our level.

It also introduced us to scoping reviews, another way of writing a report based on bibliographic research. This enables us to carry out more in-depth studies on a subject. So, we learned how to write and format the content of this kind of report.

As part of this international master's program, this project has enabled us to discover different ways of working and to improve our communication skills. Yet, to identify skills and competencies we have that we need to develop further to work in the context of One Health and to be good One Health officers.

## CONCLUSION

A thorough examination of AMR and its association with socio-economic factors highlights the complex interplay between human behavior, governance structures and the rise of antimicrobial resistance. In addition to the impact of many other factors that have yet to be studied. However, the synthesis of the data collected in the 17 selected articles highlights several key findings.

Firstly, a positive correlation between antimicrobial use and the prevalence of resistance among the populations studied has been demonstrated. Over the years, data have systematically highlighted the impact of excessive antimicrobial consumption on the proliferation of resistant strains. This reaffirms the importance of measures to regulate and optimize antimicrobial use, with an emphasis on judicious prescribing practices and public education campaigns.

However, what we were mainly interested in here was the importance of factors other than antimicrobial use. In fact, taking AMU alone into account in epidemiological models is not enough to characterize and understand AMR. We may be right to try to improve JIACRA by taking other factors into account. We can therefore turn to the level of governance, which has a major influence on antimicrobial resistance. Poor governance environments have been found to have higher levels of antimicrobial resistance. Fragile health systems, inadequate regulatory frameworks and limited access to healthcare may explain this. Furthermore, the study of these governance and corruption factors also revealed a notable link between corruption and antimicrobial resistance. Regions characterized by higher levels of corruption have a concomitant increase in resistance rates. Corrupt practices often impede effective healthcare, compromise the quality of medicines, and prevent regulatory oversight, thus fostering an environment conducive to the emergence and spread of resistant pathogens. This underscores the imperative of strong governance structures and effective healthcare policies to mitigate the proliferation of antimicrobial resistance.

Regarding environmental factors, we found very few significant results, except for temperature. Indeed, for most resistant bacteria, a warmer temperature will favor their development. The only one for which the opposite has been demonstrated is *S. aureus* Methicillin-resistant. However, the complexity and heterogeneity of outcomes across the diverse studies have made comprehensive analysis challenging.

In conclusion, this scoping review highlights the multidimensional nature of the relationship between socio-economic factors and antimicrobial resistance. The results underline the need for a multidimensional approach needed as a One Health approach, incorporating new factors that have so far been unexplored, but which potentially can have an indirect impact on bacterial resistance. Future research efforts should aim to explore these complex links while including a broad spectrum of pathogens, in order to strengthen our understanding and conduct more targeted interventions in the ongoing fight against antimicrobial resistance.

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**APPENDIX**

*Appendix 1 : table for the 17 articles (n° 1-17, description of articles, factor collection)*

| N° Article | DOI | Title of articles | Authors | Year's publication |
|---|---|---|---|---|
| 1 | DOI: 10.3390/antibiotics10070834 | Determinants of Antimicrobial Resistance among the Different European Countries: More than Human and Animal Antimicrobial Consumption | Silva, A. C., Nogueira, P. J. and Paiva, J. A. | 2021 |
| 2 | DOI: 10.1016/j.healthpol.2016.12.010 | Corruption and use of antibiotics in regions of Europe | Rönnerstrand, B. and Lapuente, V. | 2017 |
| 3 | DOI: 10.3390/antibiotics11020212 | Contribution of Governance and Socioeconomic Factors to the P. aeruginosa MDR in Europe | Riaño-Moreno, J., Romero-Leiton, J. P. and Prieto, K. | 2022 |
| 4 | DOI: 10.1038/s41429-023-00601-6 | Persistence of resistance: a panel data analysis of the effect of antibiotic usage on the prevalence of resistance | Rahman, S., Kesselheim, A. S. and Hollis, A. | 2023 |
| 5 | DOI: 10.3389/fpubh.2023.1170426 | The effect of antibiotic usage on resistance in humans and food-producing animals: a longitudinal, One Health analysis using European data | Rahman, S., Hollis, A. | 2023 |
| 6 | DOI: 10.1080/13501763.2023.2255223 | The four worlds of politics and administration in the EU: how institutional arrangements shape the struggle against antimicrobial resistance | Pierre, J., Carelli, D. and Peters, B. G. | 2023 |
| 7 | DOI: 10.1016/j.ijantimicag.2019.09.004 | Econometric ARIMA methodology to elucidate the evolution of trends in nosocomial antimicrobial resistance rates in the European Union | Ortega-Huedo, R., Cuesta, M., Hoefer, A. and Gonzalez-Zorn, B. | 2020 |

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| 8 | DOI: 10.2807/1560-7917.ES.2020.25.45.1900414 | Rates of increase of antibiotic resistance and ambient temperature in Europe: A cross-national analysis of 28 countries between 2000 and 2016 | McGough, S. F., MacFadden, D. R., Hattab, M. W., Mølbak, K. and Santillana, M. | 2020 |
| 9 | DOI: 10.1093/jac/dkx248 | National disparities in the relationship between antimicrobial resistance and antimicrobial consumption in Europe: an observational study in 29 countries | McDonnell, L., Armstrong, D., Ashworth, M., Dregan, A., Malik, U. and White, P. | 2017 |
| 10 | DOI: 10.1186/s12992-023-00913-0 | Socio-economic, governance and health indicators shaping antimicrobial resistance: an ecological analysis of 30 european countries | Maugeri, A., Barchitta, M., Puglisi, F. and Agodi, A. | 2023 |
| 11 | DOI: 10.3390/antibiotics12040777 | Socioeconomic and Governance Factors Disentangle the Relationship between Temperature and Antimicrobial Resistance: A 10-Year Ecological Analysis of European Countries | Maugeri, A., Barchitta, M., Magnano San Lio, R. and Agodi, A. | 2023 |
| 12 | DOI: 10.1186/s13756-022-01076-0 | Estimating the effect of practicing nursing professionals density on cumulative carbapenem-resistance prevalence in gram-negative invasive Isolates: a 30 European country observational modeling study | Kaba, H. E. J. and Scheithauer, S. | 2022 |
| 13 | DOI: 10.1016/j.ijheh.2019.09.008 | Thinking outside the box: Association of antimicrobial resistance with climate warming in Europe - A 30 country observational study | Kaba, H. E. J., Kuhlmann, E. and Scheithauer, S. | 2020 |
| 14 | DOI: 10.1016/j.jiph.2016.11.011 | Socio-economic factors, cultural values, national personality and antibiotics use: A cross-cultural study among European countries | Gaygısız, Ü, Lajunen, T. and Gaygısız, E. | 2017 |
| 15 | DOI: 10.1093/jac/dkt377 | Determinants of between-country differences in ambulatory antibiotic use and antibiotic resistance in Europe: a longitudinal observational study | Blommaert, A., Marais, C., Hens, N., Coenen, S., Muller, A., | 2014 |

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| | | | Goossens, H. and Beutels, P. | |
| 16 | DOI: 10.1016/j.jgar.2018.05.024 | Trends and factors associated with antimicrobial resistance of Acinetobacter spp. invasive isolates in Europe: A country-level analysis | Alvarez-Uria, G. and Midde, M. | 2018 |
| 17 | DOI: 10.1371/journal.pone.0116746 | Antimicrobial resistance: the major contribution of poor governance and corruption to this growing problem | Collignon, P., Athukorala, P. C., Senanayake, S. and Khan, F. | 2015 |

*Appendix 2: Table to specify the content of the items defined, in the table and in discussion*

| Name of parameter | Definition & <u>factors included</u> | How it might influence AMR |
|---|---|---|
| Usage AM | Defined Daily Dose(DDD) - average amount of antimicrobial expected to be used by one person - per 1,000 inhabitant and per day<br><br><u>Human antibiotic consumption at ambulatory care/ hospital care,</u><br><u>Total human antibiotic consumption</u><br><u>Prescription quality</u><br><u>Country level consumption</u> | When microorganisms are repeatedly exposed to antimicrobial drugs, they can develop mechanisms to resist their effects. Over time, this exposure can lead to the survival and proliferation of resistant strains of microorganisms. |
| Pollution | Any indicators of pollution, for example emission.<br>Emission= Activity level(quantity of product producing pollution) x Emission factor (amount emitted per unit of activity<br><br><u>Smoking</u> | Pollutants can create selective pressures that favor the development and spread of resistant microorganisms. Environmental pollution can lead to the exchange of resistance genes between different bacteria, accelerating the spread of resistance. |
| Corruption/ governance | Governance: wide range of steering and rule-making related functions carried out by governments/decisions-makers [Chanturidze et al., 2016]<br>Corruption is a socio-economic factor, measuring with the corruption in different sectors (healthcare sector for instance). In “corruption” we can include the measure of bribery. | Corruption and poor governance can undermine healthcare systems and regulatory enforcement. Poor governance can hinder the implementation of effective policy, oversight and regulation, making it more difficult to combat the growing threat of antimicrobial resistance. |

| | | |
|---|---|---|
| | Quality of governance<br>Corruption perception index<br>Control of corruption<br>Rule-law | |
| Access to health | the opportunity to use appropriate services in proportion to healthcare needs. [Núñez et al., 2021]<br><br>Ratio Public/Private health expenditure<br>Physician density, Nurse density | Limited access to healthcare can lead to improper use of antibiotics and inadequate treatments, contributing to the rise of AMR |
| Geographical characteristics | Distance to the equator, Latitude, Longitude<br>Southern countries/ Western Countries<br>Neighbor countries AMC | Different climates and ecosystems can influence the spread of resistant microbes and genes through water, soil, and air, impacting the prevalence and distribution of antimicrobial resistance in various geographic areas. |
| Climate | The composite weather conditions of a region, as temperature, air pressure, humidity, precipitation, sunshine, cloudiness, and winds, throughout the year, averaged over a series of years. Indicators of warm temperature, temperature change (increase with range between min and max T°C).<br><br>Temperature average<br>Temperature change<br>Warming temperature<br>Season temperature<br>Humidity | Changes in temperature, humidity, and precipitation patterns can affect the survival, growth, and transmission of bacteria, facilitating their adaptation and potentially increasing resistance. |
| Tourism | Number of tourists arriving to a designated area in a given time frame | Tourism can spread antimicrobial resistance as travelers may carry resistant bacteria to new places, contributing to its global transmission. |
| Infrastructure | Effect of the infrastructure (if it's poor or not) of the healthcare system: toilets and wastewater treatment plants. | Affects health systems, sanitation and access to drinking water. The result can be an increase in infections, over-consumption of |

| | | |
|---|---|---|
| | School<br>Health care system<br>Sanitation | antibiotics and difficulties in implementing infection control measures. |
| Demographics | Statistics that describe populations and their characteristics (e.g., proportion of elderly).<br>Many subgroups of parameters like religiousness, mean years of schooling, social desirability… are identified in this column.<br><br>Years lost, /100,000 population, aged 75 years old.<br>Human Development Index<br>population density<br>freedom index<br>Years of schooling<br>Proportion of elderly persons | Affect how infections spread and how often antibiotics are used, influencing antimicrobial resistance. |
| Co-resistance | Effect of co-resistance on AMR abundance<br><br>Toxic substance<br>Other AB class | When bacteria, already resistant to one type of antibiotic, acquire resistance to other antibiotics through various mechanisms. Co-resistance poses a challenge in treating infections because when bacteria become resistant to multiple drugs, fewer effective treatment options remain. |
| Animal health | Antibiotic consumption in animals (veterinary, livestock, and domestic animals)<br><br>Veterinary antibiotic sales | Use of antimicrobial agents in veterinary medicine can contribute to the development of resistant bacteria in animals. Overuse or misuse of antibiotics in livestock, pets, or aquaculture can lead to the emergence and spread of resistant bacteria. Resistant bacteria from animals can be transmitted to humans |
| Economic data / GDP | Gross Domestic Product (GDP) is the economic indicator that quantifies the total value of annual "wealth production. GDP purchasing power parity by country. Include also parameters impacting the country's economy : population income, expenditure on health…<br><br>Expenditure on health per capita<br>GDP per capita | Affects healthcare resources and access to antibiotics. Countries with high GDP may benefit from better access, which can lead to overuse, while countries with lower GDP may experience difficulties in accessing appropriate healthcare, which has a different impact on antimicrobial resistance. |

| | | |
|---|---|---|
| | Gross national income | |
| Resistance evolution & average | Evolution over time of resistance for bacterial/AM pairs.<br>Ranking of resistance levels for the same antibiotic class in different bacteria<br><br>Proportion of resistance<br>Average of resistance<br>Year evolution resistance | / |

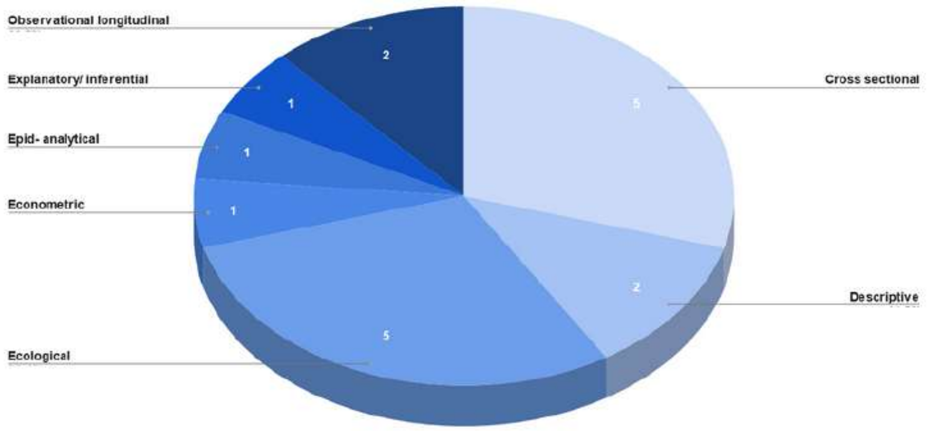
| Parameters not addressed | How they impact AMR |
|---|---|
| Hygiene and biosafety | Good hygiene practices, such as handwashing and sanitation, can help prevent infections, reducing the need for antibiotics. Appropriate biosecurity measures in healthcare facilities can prevent the transmission of resistant bacteria between patients. Conversely, poor hygiene and biosecurity practices can lead to infections, resulting in increased antibiotic use and facilitating the spread of resistant strains. |
| Animals and agriculture | Agricultural practices, especially the use of antibiotics in livestock and crops, can contribute to the development of antimicrobial resistance by promoting the emergence of resistant bacteria that can spread to humans and the environment |
| Public knowledge of AMR | Shaping behaviors related to antibiotic use. When people understand the consequences of overusing or misusing antibiotics, they are more likely to use these medications responsibly. |
| Eating habits | Through food production and consumption practices. The use of antibiotics in animal agriculture can lead to the presence of resistant bacteria in food products. When people consume these products, they may be exposed to these resistant microorganisms.<br>Poor food safety practices or inadequate cooking methods can also contribute to the transmission of resistant bacteria from food to humans. |
| Environment | Impact by acting as a reservoir for resistant bacteria and antibiotic residues. Resistant bacteria can survive and spread in various environmental media such as soil, water and air, potentially transferring resistance genes to other bacteria. |
| Cultural traits | Through behavior, beliefs and practices in society regarding healthcare and antibiotic use. Cultural attitudes towards illness, traditional remedies and perceptions of antibiotics can influence the way people use these drugs and then AMR. |

*Appendix 3 : Dataset use for data collection in the 17 article dealing with EU*

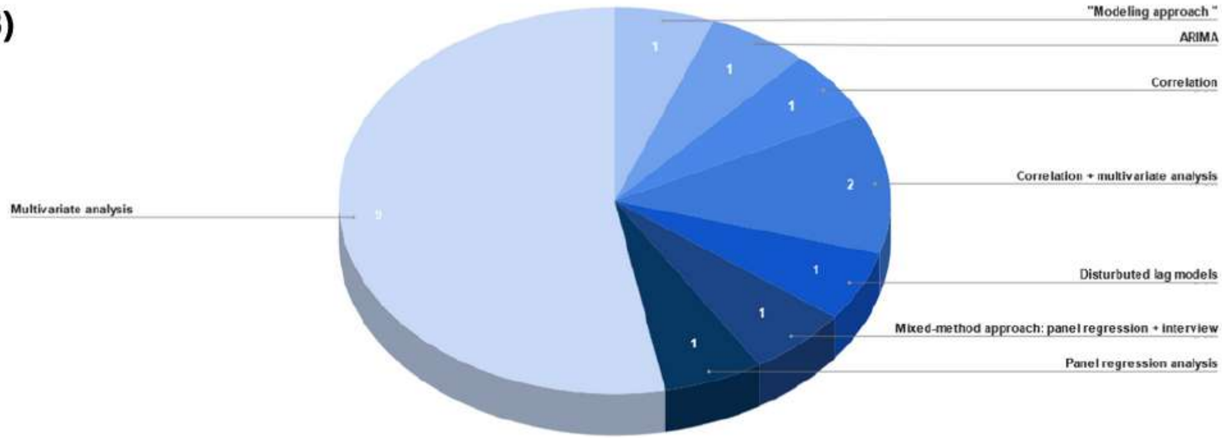
| Database set | Complete title | Information |
|---|---|---|
| **Ears-net** | European Antimicrobial Resistance Surveillance Network | Publicly funded system for antimicrobial resistance (AMR) surveillance in Europe |
| **ECDC** | European Centre for Disease Prevention and Control | Strengthening Europe's defenses against infectious diseases by collecting data |
| **OECD** | Organisation for Economic Co-operation and Development | Promote policies that will improve economic and social well-being worldwide |
| **ESVAC** | European Surveillance of Veterinary Antimicrobial Consumption | How antimicrobial medicines are used in animals across the European Union |
| **MIDAS** | Global Database of Microbes in Wastewater Treatment Systems and Anaerobic Digesters | Database containing all the microbes found in these engineered microbial ecosystems |
| **ESAC** | European Surveillance of Antimicrobial Consumption Network | Antibiotic consumption is expressed as the number of DDDs per 1 000 inhabitants per day and tonnes per year |
| **WHO** | World Health Organisation | Health for All database, European mortality database. |
| **Eurostat** | | Statistical Office of the European Union |
| **FAOSTAT** | Food and Agriculture Organization Statistical Database | Food and agriculture statistics |
| **WVS** | World Values Survey | International survey project on the evolution of values and beliefs around the world |
| **World Bank** | | Data on population and gross domestic product per capita |
| **CPI** | Transparency International's Corruption Perceptions Index | Transparency International's organisation ranks 180 countries and territories around the world by their perceived levels of public sector corruption |
| **European Union Summary Report (EFSA)** | European Food and Safety Autority | Resistance in zoonotic and indicator bacteria from humans, animals and food |

*Appendix 4: Diversity of the studies A) diversity of type; B) Diversity of models; C)Diversity of population studied*

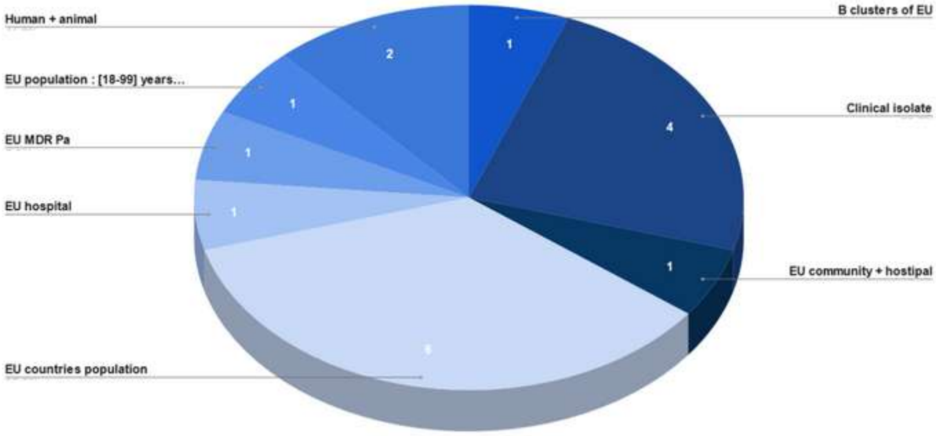
A)




B)



C)


Human + animal
EU population : [18-99] years...
EU MDR Pa
EU hospital
EU countries population
B clusters of EU
Clinical isolate
EU community + hostipal
1
4
1
1
1
1
2

*Appendix 5: The meeting reports with Claire Chauvin*

| Meeting date | Point discussed | Status |
|---|---|---|
| | **Presentation of the subject**<br>presentation of AMR, JIACRA reports, work we have to conduct …<br>6 first articles to read and resume | Terminé |
| **October 6th** | **Evaluation of our work on 6 articles + discussion**<br><br>We have to work on human and animals factors for AMR but the majority of article deals only with Human<br><br>**Did by Claire :**<br>Identified right keywords for article selection → textual analyze → words informative, combination of words select the article of interest => AMR, economics, national, global or local<br>Result : among 630 articles, selection of 30 articles<br>In addition, research on scopus & pubmed with function related result on 20 additional articles<br>All these article have various interest & similar analysis<br><br>**For next meeting :**<br>we have to define template to create a Scoping review<br><br>Scoping review → aim : inventory considering main characteristics of the subject, identify gaps, difficulties …<br>Guidelines and good template<br>We have to read article "together" to find the ways to achieve/build the template<br><br>We need to identified item to collect over all article<br><br>Different kind of various but our aim is not data analysis<br>We need to create a functional timetable to know how many studies focus on that or that factor → define the list of parameter + where the studies come from, type of studies …→ explaining everything about each article in short way<br>temperature, pollution, corruption as factor of interest<br><br>/!\ Repeat reading 2 articles by same person to be able to discuss, identify correctly sources for collecting data in | Terminé |

| Meeting date | Point discussed | Status |
|---|---|---|
| | future (by Anses) + pay attention to references → identification of other important article ?<br><br>For construction: based on a reflective study about factors | |
| **October 24th** | **Presentation of the table and discussion of points to be modified**<br><br>Add a column dealing with topic of the article —> variable to be explained when we have statistics<br>For studies dealings with animal →create 2 columns : presence + AB use<br><br>Add a final line for Conclusion on results for each parameter (number of studies with statistically correct result…)<br>Majority of ABM in human → just add columns or note if this is not on human<br><br>Create other table for descriptive article→ studies database on statistical studies<br><br>**For next meeting:** read article Hendricksen Global monitoring of AMB resistance based … and complete the new table.<br><br>For us, discussion of other factor as AB consumption<br><br>Question : minimum number of articles to be processed? Because We'll have more projects and less time. → Claire answer: look for a valid reason to reduce nb of article (geographic area, window of time …) | Terminé |
| **October 27th** | **Correction of our work on Hendricksen & al. article.**<br>- For the column type of study : precision about individual date or ecological<br>- Be synthetic in columns with key word<br>- Epidemiological unit→ search on Method section<br>- color to indicate when a case is significant or not : maybe write in green? | Terminé |

| Meeting date | Point discussed | Status |
| --- | --- | --- |
| | Claire proposes to complete the beginning of the table with the article she had found. After that we can distribute the articles between us to fulfil the table.<br>We focus on the article dealing with European countries<br><br>Meanwhile, Claire asked us to write the part of "Context and Introduction" for our report. by reading the review article she'll sent for helping us.<br>In context: Why are we looking for other variable concerning AMR?<br>Explain that statistical procedure have 2 ways : explanation with strong relation & finding relation without casualty → build a model to predict<br>We can also explain the dataset construction with a scheme. | |
| **November 23th** | **17 articles in Europe : table discussion**<br>bibliography : before starting studies, specific part of research = synthesize results : presentation of every result on one subject (scoping or metaanalysis)<br>free to write, no specific rules.<br><br>Scoping: what was already examined, plan, performed : looking at the region, the pop, the outcome… easy to present various parameters<br>→ better for us = synthetic way to present AMR in EU with a limited part of article amount article around the word (to justify in the report)<br>Maps, graph in result section to resume every result we obtain through the study<br><br>**Context 5 pages :**<br>● where we are now concerning AMR<br>● what subject is whiting this context, ecological studies, surveillance data, no need to go back in deep details to AMR = few sentences enough<br>● AMR is a burden, studies shown that usage is the main driver, but there are other drivers → main point of our subject<br><br>● Anses: do not usually carry studies on human health<br>One health way of thinking concerning AMR<br>Anses not studied human health → but AMR for | Terminé |

| Meeting date | Point discussed | Status |
|---|---|---|
| | identification of other drivers (link with environment, animal health…)<br><br>● Contex have to be enough developed → clear in mind for the reader: starting point, for understanding the next part<br><br>**Method section (area, …)**<br>- presentation of the subject : main part, selection of article : anses did it because of the internet issues at Oniris<br>Graph: start point, research queries, KeyWords, selection considering 7 articles (the more recent) to obtain kw, then selection of 360 articles, then first reading to sort by area to extract EU for us<br>- how item what define<br>95% of work<br><br>**Results**<br>figure or table,<br><br>**Discussion :**<br>● main ccl : pollution not adress very much → lack of data, not a question that address by biologist. Bio/ecological are not same searchers : maybe way to improve (example plastic pollution but no database easly accesible)<br>● even in Europe, 5 article dealing climate<br>→ Put in light the result and why (database difficult to obtain, not accessible : medecin not free exple<br><br>● in the world: what is done but only for discuss result of EU : nb of article, but some deal with specific part (asia, France…) annex : deal with fr and rest of the world - limitation of the work with EU (ask by tutor)<br><br>**20 of December we have to finish the report**<br><br>Claire will sent us 3 doc with idea :<br>- how to illustrate method section + selection of article<br>- how to present results<br><br>**deadline :**<br>next week: plan finalize + 1st part context section : end of November (main ideas)<br>method : 1 week | |

<table>
<tr><th>Meeting date</th><th>Point discussed</th><th>Status</th></tr>
<tr><td></td><td>results :<br>discussion: last week of December (extra points) : global view, limitation, critical view… propose next step, identify way of improvement …<br><br>mention that subject change : maybe the title can change a little?<br>inventory of database : annex for database with the website (Request)</td><td></td></tr>
<tr><td>December 5th</td><td>Discussion about our work<br><br>Context: write it before intro + warning : do not repeat the info in intro and context<br><br>in results: all argument we need for discussion, 2 important points: diversity of the outcome how to measure AMR (hospital, surveillance lab, proportion, couple bacteria/AMR …), vary the way of representation : histogram, maps, table…<br>Justification : we do not perform a meta analysis because the result are not comparable<br><br>Discussion : Claire sent us a doc with variable that can impact AMR in indirect ways and that are not studied :<ul><li>the case for the transmission btw people / animal : link with density of pop° / area also link to the practice and biosecurity : all the measure you can take (mask, alcohol) in farm there is a lot of biosecurity measure BUT no database storing measure for the average per country → not easy to use. We can imagine if all farms are not related to other farms. Transmission can be difficult (protective factor) => transmission + diff → biosecurity</li><li>Hygiene : biocide use in hospital … database of sale from enterprise (no access)</li><li>immunity important : no way to measure this in pop° : access to toilet… a lot of variables we don't have.</li><li>access to physician, density of physician but not density of veterinarian? Follower less strict → indirect influence (next step for a good discussion)</li></ul>…<br><br>Next week meeting for talking about the discussion</td><td>Terminé</td></tr>
</table>

| Meeting date | Point discussed | Status |
|---|---|---|
| 12/12/2023 | item : tick for item without definition<br>Definition exist?<br>discuss for the parameter that can be group or belong to some categories<br><br>stick to something understandable<br>no official def for everything example→ imagine what is the factor behind the name<br><br>1-selection article<br>2-limit eu, EU data interesting in JIACRA<br>3-<br><br>combination of items interesting<br>parameters to influence other that we have to mention<br><br>model : kind of parameters<br>new ideas<br>presentation → as a story<br><br>missing for a naive reader → Claire will read it like that for next time so we can finalize | Prévu |