ISTANBUL TECHNICAL UNIVERSITY ★ FACULTY OF MANAGEMENT

INDUSTRIAL ENGINEERING DESIGN PROJECT II

DESIGN OF A DATA-DRIVEN DECISION SUPPORT SYSTEM FOR COMBATING THE SPREAD OF ANTIBIOTIC RESISTANCE

Hasan Ali ÖZDEMIR
Aleyna Begüm ORMAN
Ayça KAYA

Department of Industrial Engineering

Burhaneddin Sandıkçı

January 2026

To our families,

FOREWORD

We would like to express our gratitude to Professor Dr. Burhaneddin Sandıkçı for serving as our thesis advisor and for continuously sharing his knowledge and skills with us.

November 2025

Hasan Ali Özdemir
Aleyna Begüm Orman
Ayça Kaya

TABLE OF CONTENTS

PAGE

LIST OF FIGURES

LIST OF TABLES

DESIGN OF A DATA-DRIVEN DECISION SUPPORT SYSTEM FOR COMBATING THE SPREAD OF ANTIBIOTIC RESISTANCE

SUMMARY

This study centers on the creation of a decision support system aimed at fostering the formulation of data-driven, sustainable health policies in the combat against antibiotic resistance, an escalating threat to global public health. The proposed design seeks to furnish health decision-makers with a comprehensive perspective by amalgamating health data from various sources, encompassing antibiotic usage statistics, resistance rates, patient profiles, and genomic information.

The system's design is based on a multi-layered methodological structure. The first stage involved defining the system's scope, its main stakeholders and their needs, constraints and performance metrics. Following this, 13 different policy scenarios were determined based on literature reviews and expert opinions. These scenarios include risk-based antibiotic prescription, a usage model based on the WHO's AWaRe classification, personalised information support systems, machine learning-supported prescribing, and genomic data-driven antibiotic selection.

Each policy proposal has been structured in a way that is suitable for modelling within the system using agent-based simulations (e.g. the SIER model) and machine learning algorithms. Although it has not yet been implemented, the design developed has been conceived in such a way as to enable each policy to be tested under different conditions, the results to be analysed comparatively, and proactive recommendations to be made to decision-makers. The data sets to be used in this context include national resistance surveillance data, patient and prescription information, antibiogram results, clinical and demographic data, and genome sequences.

The architecture of the developed system has been designed based on principles such as a user-friendly interface, modular structure, and easy integration with different health systems. In addition, compliance with data privacy and ethical standards such as KVKK, GDPR, and HIPAA has been ensured to safeguard the security of personal health data. The current design process is creating a robust, flexible, and scalable infrastructure for future applications. In this regard, the system has the potential to be used not only in the fight against antibiotic resistance but also against similar public health threats.

ANTİBİYOTİK DİRENCİNİN YAYILMASIYLA MÜCADELE İÇİN VERİ ODAKLI KARAR DESTEK SİSTEMİNİN TASARIMI

ÖZET

Bu çalışma, dünya genelinde giderek büyüyen bir halk sağlığı tehdidi olan antibiyotik direnciyle mücadelede, veri temelli ve sürdürülebilir sağlık politikalarının geliştirilmesini desteklemek amacıyla bir karar destek sistemi tasarımını ele almaktadır. Bu bağlamda, önerilen sistem; antibiyotik kullanım verileri, direnç oranları, hasta profilleri ve genomik bilgiler gibi çok kaynaklı sağlık verilerini entegre ederek, sağlık karar vericilerine daha bütüncül bir bakış açısı sunmayı hedeflemektedir.

Sistem tasarımı, çok katmanlı bir metodolojik yapı üzerine inşa edilmiştir. İlk aşamada sistemin sınırları, ana paydaşları, ihtiyaçları, kısıtları ve performans ölçütleri tanımlanmıştır. Bunu takiben, literatür taramaları ve uzman görüşleri doğrultusunda 13 farklı politika senaryosu belirlenmiştir. Bu senaryolar arasında risk bazlı antibiyotik reçetelendirme, WHO'nun AWaRe sınıflamasına dayalı kullanım modeli, kişiselleştirilmiş bilgi destek sistemleri, makine öğrenmesi destekli reçetelendirme, genomik veriye dayalı antibiyotik seçimi gibi teknolojik yaklaşımların yanı sıra; antibiyotik abonelik modeli, katkı payı bazlı finansal sistemler ve geri ödeme esaslı ekonomik modeller gibi yenilikçi politikalar da yer almaktadır.

Her bir politika önerisi, ajan tabanlı simülasyonlar (örneğin SIER modeli) ve makine öğrenmesi algoritmaları ile sistem içerisinde modellenmeye uygun biçimde yapılandırılmıştır. Henüz uygulama aşamasına geçilmemiş olmakla birlikte, geliştirilen tasarım; her politikanın farklı koşullarda test edilmesine, sonuçlarının karşılaştırmalı olarak analiz edilmesine ve karar vericilere proaktif öneriler sunulmasına olanak tanıyacak şekilde kurgulanmıştır. Bu çerçevede kullanılacak veri setleri arasında ulusal direnç gözetim verileri, hasta ve reçete bilgileri, antibiogram sonuçları, klinik ve demografik veriler ile genom dizilimleri yer almaktadır.

Geliştirilen sistemin mimarisi, kullanıcı dostu arayüz, modüler yapı ve farklı sağlık sistemlerine kolay entegrasyon gibi prensiplerle tasarlanmıştır. Ayrıca, kişisel sağlık verilerinin güvenliğini sağlamak adına KVKK, GDPR ve HIPAA gibi veri gizliliği ve etik standartlara uyum gözetilmiştir. Mevcut tasarım süreci, ileride yapılacak uygulamalar için sağlam, esnek ve ölçeklenebilir bir altyapı oluşturmaktadır. Bu yönüyle, sistem yalnızca antibiyotik direnciyle değil, benzer halk sağlığı tehditleriyle mücadelede de kullanılabilecek potansiyele sahiptir

.

1. INTRODUCTION

Antibiotics have played an important role in the treatment of bacterial infections since their development. However, in recent years, the misuse and unnecessary use of antibiotics has started to turn this success into a threat. This threat poses a risk to both individual treatment and public health on a global scale. According to the World Health Organization, 10 million people are expected to die by 2050 due to antibiotic resistance. This shows the seriousness of the problem and the need for solutions to the problem. Resistant infections not only prolong the duration of treatment, but also lead to significant increases in healthcare costs. This shows that AMR (antimicrobial resistance) is not only a medical issue, but also an economic, social and environmental problem. In this engineering design project, our aim is to use our data-driven decision-making system to analyze the spread of antibiotic resistance, predict future risks and develop engineering-based policies in a multidisciplinary way. The system aims to provide effective, sustainable and proactive solutions to health authorities, hospitals and clinical decision makers.

1.1 Methods To Be Covered By The Project

The system to be developed under this project has a multi-component structure and includes various methods and technologies in an integrated manner. Firstly, a comprehensive data collection and management infrastructure will be established to securely collect, clean and make available for analysis multidimensional health data such as historical antibiotic usage records, resistance rates, infection types and patient profiles. Using these data, models will be developed to predict antibiotic resistance trends using machine learning algorithms (e.g. Random Forest, LSTM). In addition, the impact of different policy scenarios will be analysed by modelling the dynamics of the spread of infections in the community with agent-based simulation methods that take into account the interaction between individuals. The outputs of these analyses will be included in an optimisation process in which intervention strategies will be compared in terms of cost and effectiveness, and the most appropriate implementation

options will be presented to decision-makers. Finally, in order for healthcare institutions and public authorities to use the system effectively, a user-friendly decision support interface will be designed to provide access to both visual analyses of historical data and future policy recommendations.

Compared to the approaches used in existing researches to produce and prevent strategies to combat antibiotic resistance, the system to be designed aims to provide a decision support system that will make health policies more innovative, effective and sustainable by using multiple industrial engineering techniqu

2. SYSTEM ANALYSIS

2.1 System Definition

This system is a data-driven decision support system designed to develop effective policies to combat antibiotic resistance, prevent its spread and optimize the use of antibiotics in health systems. The most important feature of this system is to provide decision support with a holistic and comprehensive system perspective and engineering design in the problem of antibiotic resistance, which has many parameters and it is difficult to reveal effective combating methods from a single perspective. The system aims to predict the regional trends of antibiotic resistance, model transmission dynamics and optimize combat strategies in terms of cost and success with the outputs from these studies.

2.1.1 System limits

The scope of the system is limited to the management of antibiotic use within health systems and the monitoring of antibiotic resistance. The system is to be designed for deployment within hospitals, clinics and public health organizations, with a general function as a decision support tool for health authorities and hospital managers. The system's recommendations will be based on interventions at this level only; they will not directly influence individual patient decisions. Nevertheless, it will provide a higher dimensional perspective, which may influence individual orientation towards antibiotic use. The policies proffered by the system may not be applicable to the health systems of every country, which are subject to regulatory and bureaucratic barriers. This may have a bearing on the decisions and practices of policy makers.

2.1.2 System stakeholders

Health authorities represent the most significant stakeholders within the system. The ability to visually and comprehensively observe and monitor the effects of antibiotic resistance, a global problem impacting all aspects of public health, the spread trend, and the utilization of antibiotics, will serve as a pivotal guide in every decision made.

In this context, more precise measures can be implemented, with the relevant determinations to be made within the scope of the hospital or health institution, with the possibility of further development in the future. Countries and regions that currently do not possess or maintain data on this subject will be able to integrate into the system with their own data, provided that said data is stored in the format utilised by the system. This flexibility will provide health authorities with new ideas to tackle the problem and opportunities for both local and global benchmarking. Since hospitals and clinics are health authorities in small regions, they will be able to see all these benefits as well. Moreover, if the hospital integrates its patients' data into the system, once the necessary personal rights are defined, it can see the state of resistance in its small ecosystem and use the system as an early warning mechanism. Hospitals can develop general policies as well as hospital-specific prevention and intervention policies. Doctors and healthcare professionals will be able to make antibiotic choices through this system, and public health experts and epidemiologists will be able to analyze the effects of the spread of antibiotic use throughout the population and develop health policies accordingly. Pharmacists and the pharmaceutical industry will be able to contribute to the development of strategies to combat antibiotic resistance by providing data on drug use and antibiotic prescriptions.

2.1.3 Possible opportunities

2.1.3.1 Data integration and detailed health document sharing

The system can monitor the spread of antibiotic resistance more comprehensively and in specific breakdowns (age, region, disease history, etc.) by ensuring regular collection and integration of data from different health institutions such as hospitals, clinics, public health organizations. This allows for more data sharing on antibiotic use and resistance and can create a strong collaborative environment between health systems. This can lead to more efficient and tailored decision-making across the healthcare sector. In addition, disease spread and resistance rates in different regions can be monitored more accurately. National data sharing can also provide an important opportunity to understand the societal impact of antibiotics and to tailor policies.

2.1.3.2 Policy development and improvement

Health authorities can holistically view and test their current policies and the steps they intend to implement. In addition, with the diversification of data sources, policies in different countries can be adapted and supported each other. This, in turn, can create a global struggle environment and bring this problem, which is defined as a silent pandemic, under control. In addition, long-term solutions can be found by testing the effectiveness of strategies such as education programmes and antibiotic sales audits with the data of the system. Thus, decision support can be obtained from the system for continuous improvement of health policies.

2.1.3.3 Early intervention and prevention methods

The system monitors antibiotic resistance both regionally and in cases where it is customised, it can turn into specific alarm mechanisms. Here, by monitoring the spread of antibiotic resistance on the basis of hospitals, districts, provinces and even countries, measures can be taken by early detection of threats to public health when above certain threshold values. An important step can be taken to protect public health with early detection and treatment. Accurate simulation of infection dynamics and data-based early warning systems enable health professionals to intervene proactively and effectively. Thanks to the early detection of resistant infections, the spread of these infections can be prevented.

2.1.4 Possible threats in the environment:

2.1.4.1 Data security and privacy

Health data are data that we can distinguish individuals and are in the sensitive data category. For this reason, if non-open source data is used, it is necessary to clean the data and use the necessary additional hiding methods. If the measures in this regard are not clearly stated, there may be mistrust in the system and problems may arise in data sharing. In addition, mismanaged data security can jeopardise patients' personal information. A serious threat here is data leaks, hacking attacks and misuse of personal

data. These problems can cause serious reputational losses and legal problems. Healthcare organisations may be concerned about data security and the widespread use of the system may be prevented.

2.1.4.2 Data inadequacy and quality problems

The amount of data required by the system is large for an accurate analysis. However, it can be difficult to find institutions or organisations willing to share health data, especially information whose existence creates a negative image, such as resistance. In addition, in some regions, data on antibiotic resistance or drug use are not available in a good quality and complete format. Incomplete data and low quality data may lead to wrong decisions and reduce the effectiveness of intervention strategies. The important thing here is to use data sources in a number and format suitable for generalisations to represent the region being studied and to process them correctly. In the next system development steps, this pilot application can be transferred to local organisations such as entire regions, countries or hospitals.

2.1.4.3 Policy applicability and legal barriers

All the policies we will test in our system are within the bounds of the law. This requires us to narrow our scope and sacrifice certain benefits. It is important to get them right and, if not, inaccurate recommendations may result, reducing the credibility of the system. Due to the obstacles encountered in implementation, effective intervention may not be achieved and the effectiveness of the system may be misinterpreted.

2.1.4.4 Lack of technological infrastructure

Problems such as lack of technological infrastructure and internet access may prevent widespread use of the system, especially in developing countries or rural areas. It may make data transfer and real-time monitoring difficult and limit the overall success of the system. In addition, since the health systems used in each country are different, there may be problems in integrating the system into these platforms.

2.1.5 Important elements of the system

2.1.5.1 Data collection and management module

The data of the system consists of open-source data shared from health systems, institutions such as WHO, infection and antibiotic usage data, AMR clinical microbial research data and AMR-induced death data. Obtaining, cleaning and formatting all these data into a format that can be given to the model and transforming the data without violating personal information constitute the data management module.

2.1.5.2 Machine learning and data analytics

With the collected data, resistance trends and predictions are created with machine learning algorithms. These data are used to predict the future effects of antibiotic resistance.

2.1.5.3 Simulation and scenario modelling

Multi-agent simulations aim to model the transmission dynamics and resistance development of resistant bacteria, so that policies can be tested in areas and at speeds that would be difficult to observe in reality.

2.1.5.4 Policy optimization:

In addition to different antibiotic use strategies, policies that are currently used in the world and considered useful, new solutions and measures can be tested with the information learned from the system and the response of the system can be measured.

2.1.5.5 User interface and decision support module:

Enables healthcare professionals to track antibiotic resistance, make the right treatment decisions and optimize antibiotic use. The interface provides an effective tool for long-term policy development, data-driven strategies and effective intervention decisions. Hospital administrators and health authorities can use this interface for data-driven, inclusive and proactive solutions.

2.1.6 System constants

2.1.6.1 Limit values for antibiotic resistance

Certain levels of resistance to antibiotics are known as fixed. These are the limit values that determine how much resistance resistant bacteria show to which antibiotics. These constants define the effectiveness of antibiotics and what levels of resistance are clinically relevant. When deciding whether the antibiotic is effective, it is checked whether the level of resistance exceeds this constant value.

2.1.6.2 Data standards and forms

International health informatics standards such as HL7 and FHIR are considered fixed. Data should be collected in these formats and integrated into the system. These constants are necessary for the system to work in harmony with different health information systems.

2.1.6.3 Antibiotic and bacteria relationship

It has been determined which antibiotic is resistant to which bacteria. These constants will affect the antibiotic selection and antibiotic dosage to be applied while setting up the system.

2.1.6.4 Antibiotic treatment periods and instructions for use

These are the general standards for the use of antibiotics determined by health institutions. The system works based on fixed standards that determine which antibiotic will be used against which bacteria and under which conditions. Antibiotic treatment times are set as a standard in a way to get the most efficiency, and the policies that our system will recommend should be determined by considering these. There are also restrictions and limits on the use of certain antibiotics. Antibiotics are also categorised and some of them can be restricted except for infections with a high risk of developing resistance, and these can be set as constants for the system.

2.1.7 Parameters

2.1.7.1 Resistance rate

Resistance rates refer to the rate of development of resistance to each antibiotic. This is a critical parameter used when analyzing the impact of antibiotics.

2.1.7.2 Infection rate

It is the parameter that shows the rate of spread of resistant bacteria. This rate varies depending on factors such as community structure and access to health services.

2.1.7.3 Intensity of antibiotic use

The intensity, duration and consumption amount of antibiotic use in the region where the system will be implemented.

2.1.7.4 Bacterial Species and Prevalence:

The prevalence of bacterial species is the distribution of bacterial species analyzed by the system, and the prevalence of these bacteria in hospitals depends on this parameter.

2.1.7.5 Policy implement ability

This is a measure of the applicability of the policies proposed by the system in the sector and in society. This parameter is used to analyze the effectiveness of the system.

2.1.8 Performance indicators

2.1.8.1 Spread prediction accuracy

Measures how well the system's predictions match actual resistance rates.

2.1.8.2 Policy effectiveness

The reduction in resistance rates can be measured by indicators such as the change in the rate of spread of resistant infections.

2.1.8.3 User satisfaction

The parameters of this indicator are user-friendliness of the interface, short training times and the decision support system producing accurate results. The trust of patients and doctors in the system can be evaluated within the scope of user satisfaction.

2.1.8.4 Process Time Efficiency

The indicator shows how well the optimization is done regarding the calculation time.

2.1.8.5 Compatibility Rate of Simulation Results with Real Data

It is to measure how compatible the simulation results are with real data.

2.2 Stakeholders of The System

2.2.1 Hospitals and health institutions

They are the main data sources and application areas of the system. They will directly use the system to develop antibiotic use policies, optimize infection control strategies and manage health resources more efficiently.

2.2.2 Health professionals (physicians, clinical teams)

This is another main stakeholder group that will directly benefit from the system outputs. It will be possible to make more accurate and faster decisions with antibiotic treatment strategies recommended in line with clinical data, patient history and antibiogram results. Optimizing the decision-making processes of these stakeholders will ease the psychological burden of their work. Since they can directly observe the effects in the system, they will increase optimization with feedback.

2.2.3 Public health authorities and the ministry of health

These stakeholders, who are responsible for formulating national policies to combat antibiotic resistance, will be able to develop more proactive and science-based strategies through regional resistance analyses and intervention simulations provided

by the system. A beneficial impact on public health will reduce costs and increase public trust in health systems. This directly serves the objectives of decision-makers.

2.2.4 Epidemiologists and academics

The simulation and modeling modules within the system will provide valuable inputs for academic analysis and scientific studies, and will constitute an important resource, especially in terms of spread modeling. Since the system serves an active problem, it can be reworked with changing conditions. This system can be adapted for different pandemics when desired.

2.2.5 Society and patients (indirect stakeholders)

The system will provide access to safer and more effective healthcare services, shorten treatment processes and reduce the burden on the healthcare system, thanks to the correct use of antibiotics and the reduction of resistant infections. This will reduce the loss of time and both psychological and physiological wear and tear faced by patients.

2.2.6 Pharmacists and the pharmaceutical industry

The pharmaceutical industry is a stakeholder that can both affect and be affected by the system. The system will be able to provide much more comprehensive results when drug sales and utilization data are added to the system from pharmaceutical companies. In addition, in line with the recommendations and outputs of the system, it can support antibiotic development studies and clinical research in the pharmaceutical industry.

2.2.7 Purpose of the study and contributions to stakeholders

The main objective of this study for stakeholders is to design a data-driven decision support system that will enable early detection of antibiotic resistance spread, test intervention strategies and support decisions. The system offers not only an analysis of the current situation, but also the possibility to predict future risks and optimize alternative scenarios. The main benefits to stakeholders include the ability of clinical staff to make safer and more accurate treatment decisions, hospitals to reduce costs by optimizing antibiotic use, and public authorities to develop more effective public

health policies. At the society level, there will be indirect but important public health improvements, such as increased treatment success, reduced rates of resistant infections and improved quality of access to healthcare services.

2.2.8 Success criteria of the designed system

The success of the designed system will be evaluated according to both technical and operational performance criteria. Technical success criteria include the predictions of the machine learning models are in a pattern compatible with historical data, the scenario reliability and realism of the simulation module, and the cost/effectiveness ratios of the optimization outputs. In addition, the computational and time efficiency of these models and algorithms will be measured and will be an important component in the success of the system. Operational success will be measured by user satisfaction, applicability of the system, level of contribution to decision makers and tangible improvements achieved in the health system. In addition, the level of integration of the system with existing health information systems and its active use by different stakeholders can also be evaluated among the success criteria.

2.2.9 Product and service description to be designed

The system will be designed in such a way that hospitals can access it from their computers, integrated into their health systems. There will be an interface where they can view diffusion maps, statistics and dashboards to facilitate the decision-making process and monitor diffusion. Algorithms that provide recommendations to determine antibiotic use on a regional group basis will be integrated into the system. The results of each policy will be visible in the system and its effects will be analyzed in detail. Due to its flexible, modular and expandable structure, clinical researchers will be able to easily use the system in their research.

2.3 System Requirements

The growing threat of antibiotic resistance on public health and health systems emphasizes the need for more analytical, predictive and systematic tools for decision-making.

2.3.1 Needs to be met

- **Data-driven clinical decision guidance:** Supporting physicians to make the right choice of antibiotics.
- **Effective planning and evaluation of health policies:** Enabling public authorities to plan interventions based on resistance trends.
- **Optimizing resource allocation and infection control:** Ensure rational use of antibiotics in hospitals.
- **Develop early warning mechanisms:** Detect increasing trends of resistant infections in advance and intervene in a timely manner.

2.3.2 Design requirements

- **Data analysis capacity:** Accurate processing and modeling of large and multi-dimensional health data.
- **Forecasting capability:** Future predictions of resistance levels and transmission risks.
- **Simulation module:** A parametric and flexible model for testing intervention scenarios.
- **Optimization component:** Comparison of intervention strategies in terms of cost, effectiveness and feasibility.
- **User-friendly interface:** An intuitive, understandable and interactive system experience for clinical users and decision makers.
- **Privacy and ethical compliance:** Anonymization and processing of patient data and compliance with relevant legal regulations.

In order for the designed system to work effectively and sustainably, some basic requirements, both technical and user-oriented, need to be met. First, the success of the system depends on its ability to reliably aggregate and manage very large datasets from different sources in the healthcare domain, which often contain irregular and personal data. Therefore, a strong technical infrastructure is needed. The system is expected to bring together different types of data and make them analyzable in the same module. In the prediction module, machine learning algorithms that can predict regional and temporal trends of antibiotic resistance based on historical data should be run. Accordingly, the system should have a structure where different machine learning methods can be tested. Future prediction based on past data will also be made. For this purpose, an agent-based simulation infrastructure to model transmission dynamics will be one of the important components of the system. Above all, considering that the system will work with patient data, utmost care must be taken in terms of data security. Therefore, it should be configured in accordance with both local (KVKK) and international (GDPR, HIPAA) data protection standards.

2.4 Constraints Directing Design

Full compliance with ethical and legal regulations on the processing, storage and analysis of patient data is expected. Accordingly, anonymization techniques and access restrictions should be integrated into the system design. It is also anticipated that problems such as incomplete records, lack of standards and access restrictions may exist in health data. It should be taken into account that this may affect the accuracy of the prediction algorithms. From a technical point of view, since running simulation and optimization modules may require high computational power, it is recommended that the algorithms to be developed should be designed considering computational efficiency.

Considering that end users may have limited technical background knowledge, the interface should be designed to be easy to understand and usable with little training. In addition, it is aimed to create a parametric and modular software architecture for the

model to be adaptable in different geographical regions or health systems. In order for the outputs of the system to be developed to be integrated with health information systems used in different countries (e.g. EHR - Electronic Health Records), it is important to comply with international health informatics standards (e.g. HL7, FHIR). Finally, it should be recognized as a fundamental requirement that system outputs should not generate false alarms and should be disclosable, auditable and transparent in order to avoid the risk of misdirection.

2.5 Professional standards to which the design is related

Professional standards and legal regulations that are directly related to the design project are listed below. These standards specify requirements in critical areas such as system security, user privacy and data management.

2.5.1 HIPAA (health insurance portability and accountability act)

HIPAA, a regulation of the United States of America, is the reference for the protection of patient data. This law aims to ensure the security and privacy of individual health information. If the system works with personal data, it must be configured in compliance with HIPAA.

2.5.2 GDPR (general data protection regulation)

The General Data Protection Regulation (GDPR) set by the European Union establishes the legal framework for the processing and storage of personal data. This regulation sets standards that must be complied with in all processes related to the protection of personal data and the privacy of individuals.

2.5.3 ISO/IEC 27001 - Information security management system standard

ISO/IEC 27001 is a globally recognized standard for ensuring information security. This standard specifies the necessary management procedures to ensure the security of all data flows.

2.5.4 ISO 9241 - Human-Computer interaction standard

ISO 9241 is a standard for human-computer interaction and ergonomic interface design. According to this standard, an ergonomic and interactive interface should be designed so that users can easily use the system.

2.5.5 IEEE Code of ethics

The IEEE Code of Ethics includes principles such as engineering ethics, benefiting society, reliability, integrity and user safety. This code of ethics will be considered during the system development process.

2.5.6 WHO - Global Action Plan to Combat Antimicrobial Resistance

The World Health Organization's (WHO) Global Plan of Action against antibiotic resistance will be used as a reference for the system to develop policies and provide recommendations to combat antibiotic resistance.

2.5.7 Personal Data Protection Authority (KVKK)

KVKK is a law that includes legal regulations for the protection of personal data in Turkey. This law provides the necessary measures for the protection and privacy of individuals' personal data.

3. LITERATURE REVIEW

3.1 What is an Antibiotic?

“An antibiotic is a chemical substance, produced by micro-organisms, which has the capacity to inhibit the growth of and even to destroy bacteria and other micro-organisms.” (Waksman, 1947, p. 565). By its very nature, an antibiotic affects some micro-organisms and others not at all or in a limited way. Each antibiotic is therefore characterized by a unique antimicrobial spectrum.

3.2 What is Antibiotic Resistance?

Antibiotic resistance occurs when a bacterium develops the ability to resist an antibiotic that is expected to harm it. Antibiotics can no longer kill the bacteria or stop their growth. This leads to untreatable infections and increases the risk of death. Antibiotic resistance can occur in three forms:

- Intrinsic (Natural) Resistance: This is when some bacteria are naturally resistant to some antibiotics.
- Resistance due to environmental conditions: Although antibiotics seem to be effective in the clinical setting, they may not be effective depending on environmental factors in the human body. Some of these factors include low oxygen, pH change or inability to cross the blood-brain barrier.
- Acquired Resistance: This is currently the most common form of resistance that can be fought. Bacteria acquire resistance through DNA mutations or by acquiring genes from outside. Acquired resistance mechanisms are also divided into four groups. These are preventing the drug from working by changing its target, inactivating the drug by degrading it with enzymes, preventing the entry of the drug into cells by reducing membrane permeability, and inactivating the drug by overproduction of target structures.

Antibiotic resistance is usually treated with drugs that are more expensive, more toxic and less accessible than antibiotics normally prescribed. This leads to an increase in

side effects and makes treatment longer and more costly. Despite all this, in some cases, none of the new drugs work.

3.3 Causes of Antibiotic Resistance

There are many reasons for antibiotic resistance. These include uncontrolled drug use, which is frequently mentioned in articles, financial-oriented drug policies of the pharmaceutical industry and widespread use of antibiotics in the food industry. In addition, unconscious and non-prescription use of antibiotics also causes antibiotic resistance to spread rapidly. It is also known that resistance rates are higher especially in areas where antibiotic use is high, such as hospitals. Therefore, hospitals are one of the most critical components in system design. Not only medical measures but also awareness raising and measures in the food sector play a critical role in combating antibiotic resistance. This is the reason why a holistic perspective, data-driven approach, multidisciplinary and sustainable practices are included in system design.

3.4 Why Combating Antibiotic Resistance is Critical?

In September 2016, heads of state and government gathered at the UN in New York adopted a groundbreaking Political Declaration on Antimicrobial Resistance (AMR), recognizing that antibiotic resistance is the “greatest and most urgent global risk” and that many achievements of the 20th century, particularly the reduction of morbidity and mortality from infectious diseases, are seriously threatened by AMR (Khor, 2018). In addition, recent studies and extensive research emphasize that antibiotic resistance is not only a medical issue but also an economic, social and environmental problem. It is also explained that this resistance has become the biggest public health threat worldwide, as it is accelerating day by day and solutions are difficult. As Khor (2018) states in his book, especially developing countries have become more susceptible to this crisis due to the lack of regulatory structure, uncontrolled prescription systems and inadequate public health investments.

Bacterial AMR is estimated to be directly responsible for 1.27 million global deaths and contributed to 4.95 million deaths in 2019, according to the World Health

Organization. Furthermore, the World Bank estimates that AMR could lead to additional healthcare costs of US€1 trillion by 2050 and gross domestic product (GDP) losses of US€1 trillion to US€3.4 trillion per year by 2030. This shows that the economic and social dimensions of antibiotic resistance can also be very severe and the importance of combating it in these areas. The cost- and feasibility-optimized control and prevention policies in system design also serve to solve this important problem.

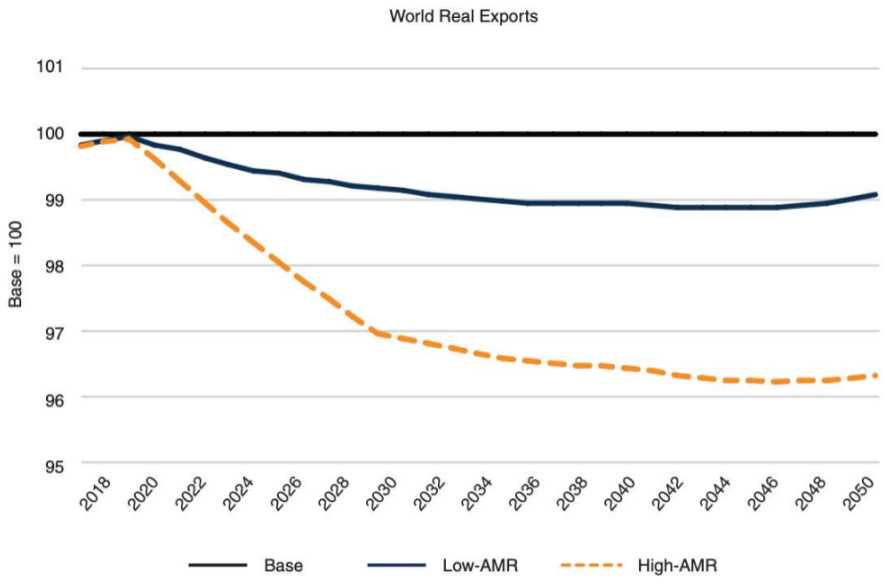


Figure 3.4.1 Projected global trade loss under high-AMR scenarios. Adapted from Drug-resistant infections: A threat to our economic future (World Bank, 2017).

As seen in the graph, it shows the long-term impact of antimicrobial resistance (AMR) on global trade. In the high AMR scenario, world exports decline by more than 3% by 2050, while in the low AMR scenario the decline is limited. This shows that fighting antibiotic resistance is important for both health and the economy.

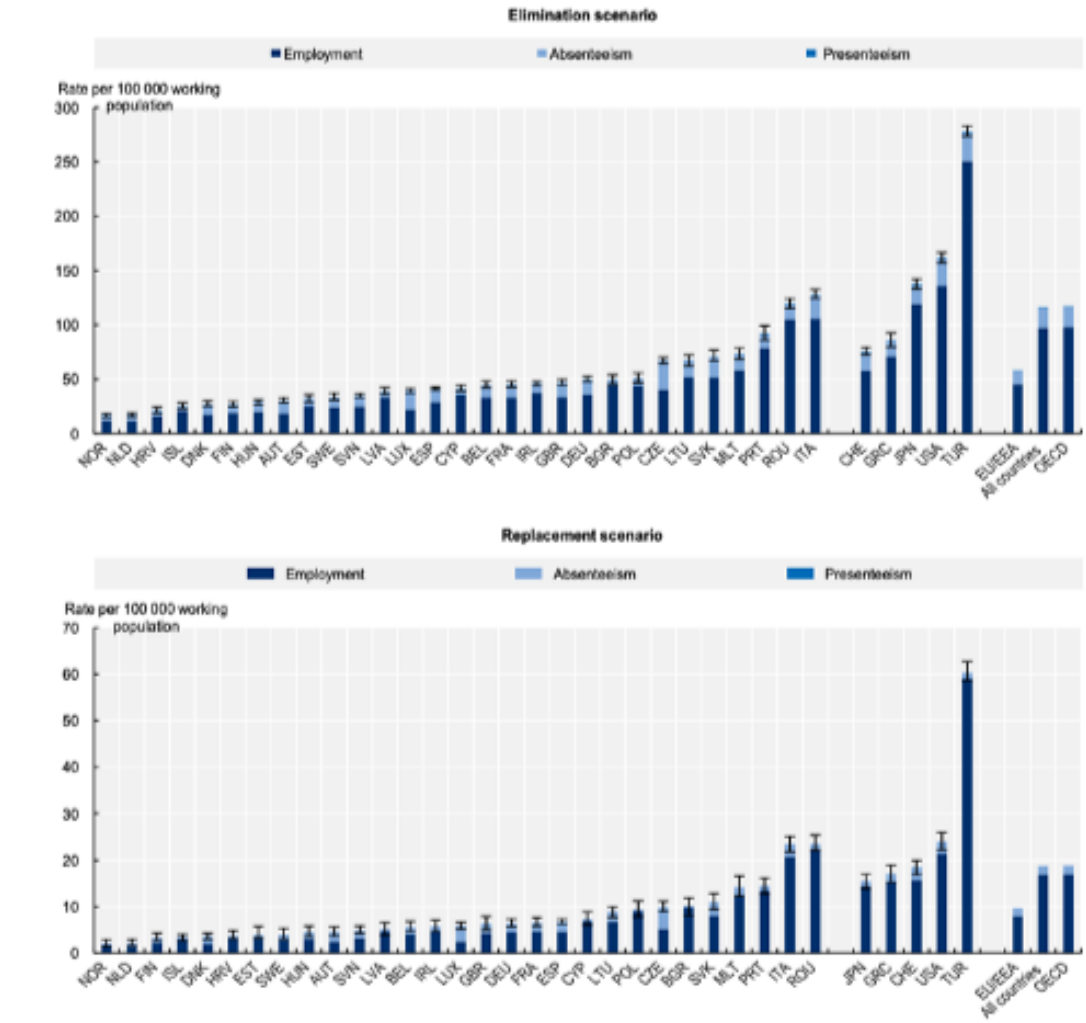
The effect of AMR on livestock production is even more important. In low-income countries, livestock production is expected to drop by as much as 11%. This will put millions of people's lives at risk, as they depend on livestock for their livelihoods.

(World Bank, 2017)

The OECD's 2023 report also says that resistant infections kill about 79,000 people each year in OECD and EU/EEA countries. This number is 2.4 times the total number of deaths from tuberculosis, influenza, and HIV/AIDS in 2020. The majority of these deaths are caused by resistant infections acquired during healthcare and account for 60% of all AMR-related deaths.

The treatment of resistant infections results in an additional annual cost of US€28.9 billion (adjusted for purchasing power parity) to healthcare systems. In particular, the additional 32.5 million days spent in hospital each year due to these infections is equivalent to a country (such as Spain) having its entire acute bed capacity fully occupied for a year.

The impact on the workforce is also significant. AMR causes annual losses in workforce participation and productivity amounting to 36.9 billion US dollars. This is roughly equivalent to one-fifth of Portugal's gross domestic product in 2020. On average, 734,000 full-time equivalent jobs are lost each year, 84% of which are due to reduced labor force participation. (OECD, 2023)



Note: Results for Greece are presented on the right-hand side of the panel because data for *S. pneumoniae* are not available. Results are presented based on the sources of input data, with data for countries in the group on the left that are all from the same source and calculated with a comparable methodology. Results are not directly comparable for countries on the left- and right-hand sides of the panel due to the methodological differences in data collection and data extraction practices.
Source: OECD analysis based on the OECD SPHeP-AMR model.

Figure 3.4.2 Annual job losses, absenteeism and presenteeism up to 2050.

The “replacement” and “elimination” scenarios shown in the figure represent different outcomes in the fight against antimicrobial resistance (AMR). The replacement

3.5 Smart Antibiotic Use in Combating Antibiotic Resistance

One of the most important elements of combating antibiotic resistance is rational drug use. Health authorities use policies such as prohibition of over-the-counter drug sales,

national action plans, awareness-raising guides for healthcare professionals, setting up antibiotic committees within hospitals and public education campaigns for rational drug use.

3.6 Key Data for Antibiotic Resistance Modeling

Some of the data required for the detection and control of antibiotic resistance that can be used in system design and modules were identified through literature reviews. These are:

- Medical data: Antibiogram data (bacterial species, antibiotics, sensitivity status), patient data, clinical data
- Environmental and Social Data: Regional resistance rates and social factors, data on food production and consumption, current laws and regulations on antibiotic use.

3.7 Trend Forecasting of the Spread of Antibiotic Resistance

Studies on predicting antibiotic resistance have gained significant momentum, especially in recent years, thanks to the opportunities offered by machine learning techniques. Many studies in the literature show that highly accurate prediction models can be developed using both clinical and genetic data (e.g. whole genome sequencing, k-mer profiles). In this way, antimicrobial resistance trends can be predicted in a way that not only analyzes the current situation but also contributes to the formulation of proactive health policies for the future.

Wang et al. (2023) stated that the models they made for Acinetobacter baumannii isolates had an average prediction accuracy of 94–97% for different antibiotics. In this research, k-mer-based feature extraction was integrated with algorithms like Random Forest, yielding results in a shorter timeframe than conventional resistance tests. In another study, Ren et al. (2022) evaluated four different algorithms developed for E. coli isolates and found that Random Forest and deep learning methods were generally

more successful. In addition, the fact that these models can work without depending only on known resistance genes shows the potential to reveal previously unidentified resistance mechanisms.

3.8 Use of Markov-Type Cohort Model and Dynamic Compartmental Model

In the health literature, simulation-based approaches are frequently used to assess the long-term effects of infectious disease policies under conditions of uncertainty. In this project, we adopted a hybrid modeling framework that combines a Markov-type cohort model with a Dynamic Compartment Model (DCM) to comprehensively evaluate antimicrobial resistance (AMR) policies, allowing us to observe two different model outcomes. This dual approach allows the model to capture both population-level epidemiological transitions and the fundamental biological mechanisms driving resistance dynamics.

The Markov-type cohort model represents long-term transitions between health states over separate annual cycles. Using incidence rates, resistance rates, mortality rates, and annual cost and benefit values, it derives aggregate outcomes such as total number of infections, number of deaths, annual QALYs, and total costs under each policy scenario. This model is compatible with standard health economics evaluation practices and facilitates comparisons between countries through adaptable AMR burden categories. The Markov approach is particularly suitable for long-term cost-effectiveness analysis and clearly quantifies increasing costs, increasing QALYs, and ICER values for policy decisions.

In contrast, the Dynamic Compartment Model (DCM) captures the biological and epidemiological mechanisms underlying AMR transmission using a continuous-time differential equation system. The model simulates colonization, progression of infection, resistance selection, recovery, and mortality on a daily time scale, producing mechanical trajectories for susceptible and resistant infections. Unlike Markov models that summarize annual transitions, DCM also reflects short-term fluctuations in pathogen dynamics and antibiotic-related selection pressure. DCM outputs can also be

converted into economic metrics; these calculations rely on a separate set of state-based benefit and cost parameters specific to the dynamic model.

The coexistence of these two independent models enhances the analytical flexibility of the study and allows decision-makers to evaluate AMR policies using a biologically grounded dynamic transmission model.

3.9 Industrial engineering techniques used in the design

3.9.1 Operations research (OR)

Operations Research (OR) is critical in addressing multifaceted problems such as antibiotic resistance and in the development of decision support systems. Since factors such as antibiotic use, resistance development and health policies are interlinked, effective planning becomes important. Therefore, cost and effectiveness analysis becomes an important tool to guide health authorities towards optimal antibiotic strategies. OR provides mathematical models that facilitate the efficient allocation of system resources. These models provide assessments to identify strategies that not only reduce antibiotic use but also reduce resistance rates. When dealing with complex and branching problems such as antibiotic resistance, OR techniques offer a significant advantage in identifying optimal solutions from both an economic and public health perspective. OR can thus be used to improve policy optimization and resource management.

3.9.2 System simulation

Systems simulation is used to analyse transmission dynamics and assess the possible outcomes of many different intervention scenarios. Due to the time-varying, multidimensional and complex nature of antibiotic resistance, simulation enables understanding the effects of policy changes and the spread of resistant bacteria over time. This approach allows stakeholders to observe and test the possible outcomes of planned interventions before they are implemented. Furthermore, simulation helps to

understand the interaction between the behaviour of individuals and antibiotic resistance, providing a valuable asset for predictive modelling and strategic planning.

3.9.3 Machine learning

Machine learning and data analytics are essential components of the design. These models can generate predictive insights into antibiotic resistance patterns by analyzing large and complex datasets. These models can identify which antibiotics are associated with resistance in particular bacterial strains, offering a clearer understanding of the current landscape. This predictive models empowers health systems to respond proactively to emerging threats.

3.9.4 Data visualization

Data visualization is essential for communicating the outcomes of analytical models. Complex data related to antibiotic resistance can be presented accessibly and visually by using tools such as graphs, maps, and interactive dashboards. These visualization techniques improves the intelligibility of analytical findings, enabling stakeholders to interpret results quickly and act accordingly.

3.9.5 System dynamics

In managing antibiotic resistance and shaping health policies, it is insufficient to rely solely on static data. A system dynamics perspective, which incorporates feedback loops, actor interactions, and temporal changes, is essential for developing realistic and sustainable policy interventions. System dynamics approach improves a deeper understanding of not only the medical aspects but also the social, environmental, and governance dimensions of the healthcare system. By analyzing the dynamic and nature of antibiotic resistance, system dynamics contributes to the formulation of more holistic and long-term solutions.

4. METHODOLOGY

This chapter describes the methodology for developing a data-driven decision support system to reduce the spread of antibiotic resistance. The decision support system assists health authorities in evaluating effective policy options and is designed to simulate and compare different intervention strategies using industrial engineering techniques.

4.1 General Methodological Framework

The development process was built on four main methodological layers:

- Problem Definition and Stakeholder Analysis
- Determination and Operationalization of Policy Set
- Model Design and Tool Integration
- Scenario Simulation and Evaluation

Figure 4.1 shows the preliminary preparation phases before starting the modeling process. In this phase, the scope of the system and key stakeholders were first defined. Then, data provided by health authorities were collected and preprocessed to make them suitable for modeling. Following the data cleaning and standardization process, feasible policy scenarios were pre-selected based on literature review and expert opinions. In the final step, data sources were organized by matching them with policies so that the selected policies could be used in the modeling. This structure ensures that the decision support system to be developed in the following chapters is based on a data-driven and consistent foundation.

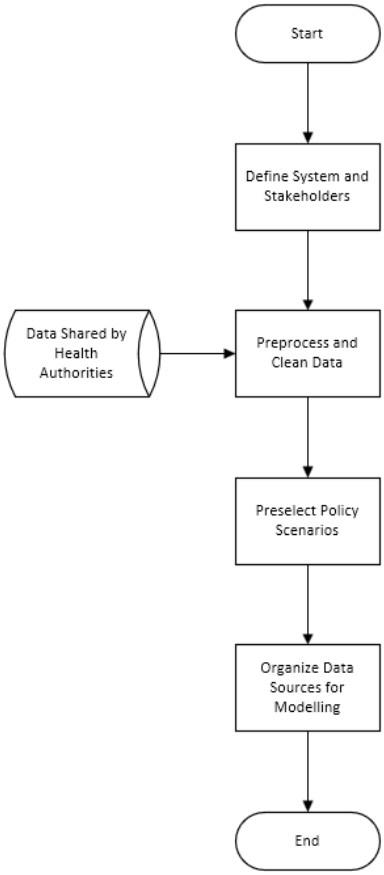


Figure 4.1.1 Flowchart of pre-modelling the system.

4.2 Policy Scope and Rationale for Selection

The project focused on policies that could be integrated into the system modeling, as well as those that have applicability and clinical validity in the field. Certain criteria were taken into account in the policy pre-selection process. First, policies with demonstrated clinical efficacy in the literature and recommended by institutions (WHO, CDC, etc.) were preferred. The ability to integrate the selected policies into the system model in a data-driven manner was taken into consideration. In addition, policies that are compatible with technological and organizational infrastructures, which can be integrated into the Turkish health system or similar structures, were prioritized.

In this context, the following seven policy proposals were selected and considered for scenario- based testing in the system model:

4.2.1 Risk-Based Antibiotic Prescribing Protocols

These are protocols that guide antibiotic prescribing based on patient-specific risk factors such as age, immune status and hospital history. This approach encourages more controlled intervention in high-risk individuals and non-antibiotic solutions in low-risk individuals.

4.2.2 Personalized Knowledge Support Systems (KSS)

Digital systems that support physicians' decision-making processes and provide prescription recommendations by combining patient data and local resistance data. It aims to provide a fast and standardized decision process in line with clinical guidelines.

4.2.3 Prescribing Based on WHO AWaRe Classification

Based on the AWaRe (Access-Watch-Reserve) antibiotic classification developed by the WHO, it encourages the use of antibiotics primarily in the 'Access' group. Uncontrolled spread is reduced by keeping resistant antibiotics in the 'Reserve' group.

4.2.4 Personalized Antibiograms and ML-Assisted Prescribing

By analyzing the antibiograms generated according to the source of infection of each patient with machine learning algorithms, the most appropriate antibiotic is selected for each patient. This model provides fast decision making and high accuracy.

4.2.5 Combined Use of ML and Physician Decisions

It is based on the principle that machine learning systems only provide suggestions to the decision maker and the physician makes the final decision. This way, both data-based recommendations are utilized and human intuition is kept in the loop.

4.2.6 Antibiotic Resistance Prediction with ML

Proactive prescribing can be achieved by developing ML models that predict whether bacteria will develop resistance to certain antibiotics in specific regions. This is particularly useful in regions where access to rapid testing is limited.

4.2.7 ML Based Prescribing with Genomic Data

By analyzing the genetic sequences of bacteria to detect resistance genes and interpreting these data with ML algorithms, antibiotic selection can be made with high precision. It is an advanced and future-oriented strategy for advanced systems.

4.2.8 Antibiotics Subscription Model like Netflix

To support the development of new antibiotics, the National Health Service (NHS) in England proposes a subscription-based payment methodology. This is a method where payment is independent of the amount of use. Just as Netflix offers access to all content for a fixed monthly fee, in this model governments or health systems pay pharmaceutical companies a fixed fee (subscription) to develop and provide access to antibiotics. This raises a number of beneficial issues. First, the use of antibiotics may decrease because companies do not make much money when they sell more, so they do not try to sell more than is needed. Second, the main reason why firms are afraid to do R&D on new antibiotics is that they think that these special antibiotics are mostly unused and they cannot recoup their investment in the development process through sales. The other is that the company feels more secure with this method because they know the money they will receive and it will be easier for them to make investment decisions and control their budget.

4.2.9 Innovation and Conservation Fee Model

This model applies to all sectors that use antibiotics for humans and animals. For example, hospitals, farms, animal clinics, agricultural companies, etc. The fee depends on the amount of antibiotic use. So the goal is to reduce antibiotic use because the more antibiotics you use, the more you pay. The aim is to use 75% of the fee income

for the development of new antibiotics and 25% for public health and awareness-raising activities.

4.2.10 Reimbursement Model for Narrow Spectrum Antibiotic Development

This model aims to incentivize the development of antibiotics. There are two different payment types in the model:

- **Fixed Reimbursement:** If the antibiotic is approved, the developer of the antibiotic receives this reimbursement. This is for R&D costs coverage.
- **Variable Payback:** This variable payback is approximately 2 parameters.
    - Bonus for Use Against Resistance: Payment is increased only when the antibiotic is used against resistant pathogens.
    - Inappropriate Use Deduction: Payment is reduced if the drug is used in susceptible (non-resistant) cases.

4.2.11 Intervention Model for Reducing CRKP Spread at Hospital Level

CRKP (Carbapenem-resistant Klebsiella pneumoniae bacteria).

This model simulates the spread of infection by looking at the interaction between healthcare workers and patients. It addresses it on 3 different bases:

- Reduce contact between health workers (e.g., shift arrangements)
- Improving hand hygiene compliance,
- Increasing patient isolation rates.

The importance of testing this model is that it can be used to test the effectiveness of non-antibiotic measures against antibiotic resistance in the World Health Organization's critical priority threat list. This could be a preventive strategy that indirectly contributes to reducing antibiotic use.

4.2.12 The One Health Approach and the Use of an Environmental AMR Tracking System

AMR is not only a clinical problem. Antibiotic residues can cause resistance to be carried into the environment. Likewise, animals, waste and plants can transmit resistant bacteria to humans. This policy recommends collecting and tracking data from the environment through samples and starting to control from there.

4.2.13 A Nonprofit Drug Development Model:

In this model, it is argued that the development of new antibiotics in non-profit organizations would be beneficial for public health. Nonprofit organizations such as the Global Antibiotic Research and Development Partnership (GARDP) are thought to be able to develop drugs that may not be commercially profitable but may provide treatment for resistant bacteria.

4.3 Plan of Tools and Methods Used

The following industrial engineering techniques were used in the realization of the project:

· **Stakeholder Analysis**: Identify and prioritize system actors.

· **Simulation Modeling (Python)**: Modeling the dynamic effects of intervention scenarios.

· **Decision Trees**: Representing individualized treatment pathways.

· **Machine Learning (Python, Scikit-Learn, XGBoost)**: Supporting resistance prediction and treatment decisions.

· **Multi-Criteria Decision Analysis (MCDA)**: Policy prioritization

· **Sensitivity and Scenario Analysis**: Test the robustness of proposals in different conditions.

· **Optimization**: Choosing the most effective policy mix with limited resources.

4.4 Data Sources and Preprocessing

One of the main data sources of the study is national resistance surveillance data. These data are critical for policy scenarios such as AWaRe classification-based prescribing and risk-based protocols, as they show the rates of antibiotic resistance in specific regions. It has also been used to generate regional risk distribution in antibiotic resistance prediction models with ML.

In addition, hospital-based infection and prescription data directly informs patient transactions. Information such as which antibiotics are prescribed, how often they are prescribed and against which types of infections is the building block of personalized information support systems (ISS), ML-assisted prescribing, physician-decision support integrations and risk-based prescribing models.

Microbiological antibiogram records are detailed laboratory data that show, on a patient-by-patient basis, to which antibiotics the bacteria causing the infection are susceptible or resistant. Such data is used as direct model input, especially for policies such as personalized antibiograms, resistance prediction with ML and physician-decision support collaboration.

Demographic and clinical metadata is also an important component. Patient information such as age, gender, hospitalization history, immune status are used in risk classification for risk-based prescribing, CSR and individual-based machine learning models. This data enables decision models to differentiate patient-specific decision models.

Finally, genomic sequence data enables the direct detection of resistance genes based on DNA analysis of bacteria. Especially in the ML-based prescribing scenario with genomic data, these data are used to provide highly accurate antibiotic recommendations based on diagnosis. It also serves as supporting data for training resistance prediction models with laboratory-based genomic analysis.

All these data sources form the basis of the decision support system developed within the project and are subjected to pre-processing steps in accordance with the data structure required by each selected policy scenario.

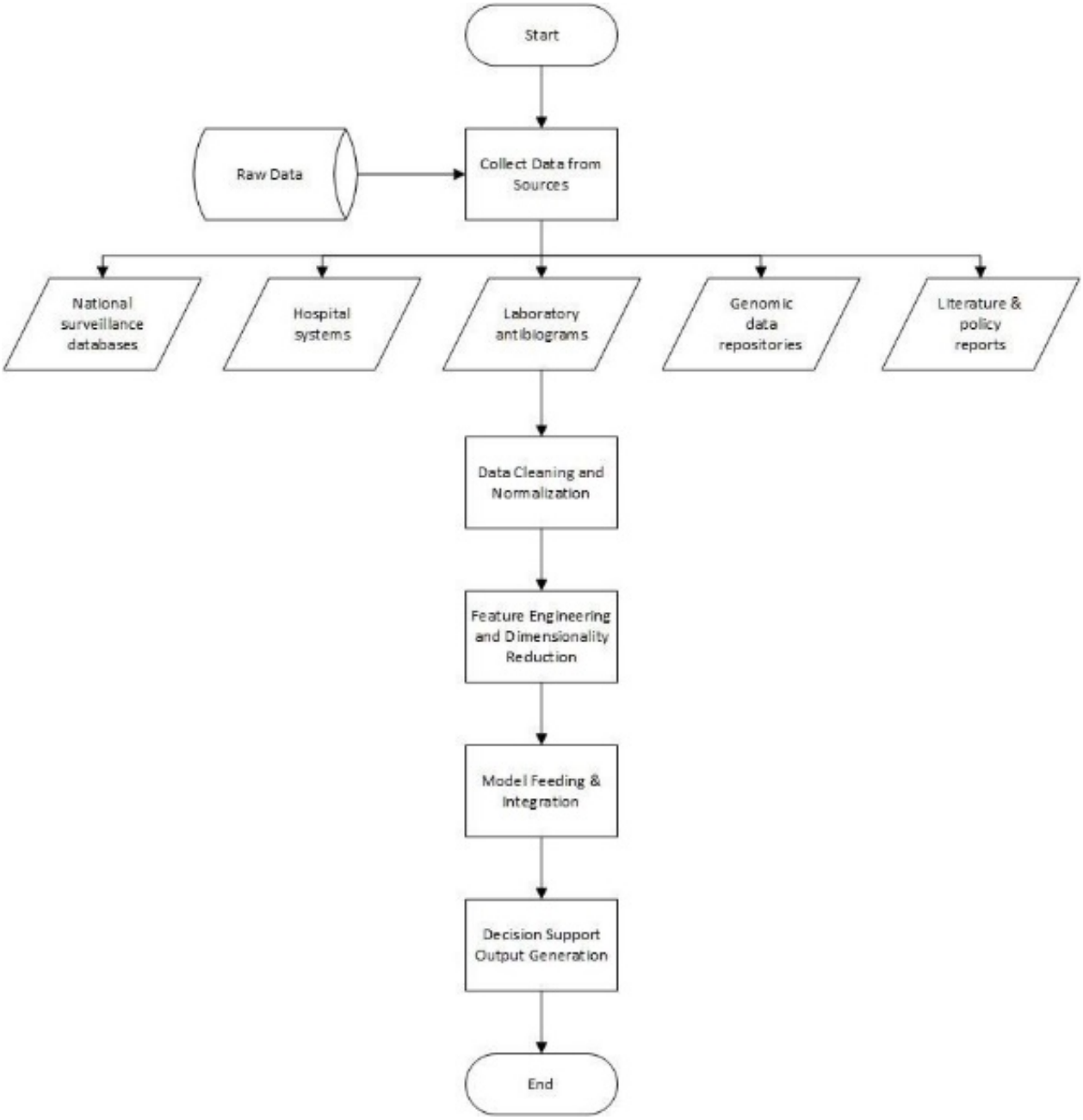


Figure 4.4.1 Flowchart of the Data Processing Pipeline.

4.5 Scenario Development and Simulation Application

4.5.1 Markov-Type Cohort Model for AMR Policy Evaluation

When examining studies involving policy simulation in the health sector, we observed that the effects of the Markov model were evaluated based on life expectancy and cost. Studies in this field were developed for AMR. The parameters, the steady-state conditions, and the transitions were also defined specifically for this problem.

The model estimates the effects of different policy packages over a specific time horizon on:

- bloodstream infection (BSI) incidence
- the proportion of resistant infections
- the number of sepsis-related deaths
- health system costs
- quality-adjusted life years (QALY)

The primary objective of the model is to compare the “no intervention” scenario with various antibiotic usage and infection control policies in the adult population and to calculate the additional cost, additional QALY (Quality-Adjusted Life Year) gain, and number of deaths prevented for each policy. A QALY is 1 year of life lived in perfect health.

The model is divided into three categories for adaptivity to different countries. Based on EDCD reports, each country will be able to categorize itself. Thus, there are three categories: Low AMR for relatively low resistance burden, Mid AMR for moderate resistance burden, High AMR for high resistance and mortality burden. The model can also be simulated with different parameters for each different group.

A time horizon of short term selects as 1 year and long term is 10 years. But user have a chance to change term in 1, 5, 10 and 20 years. In compliance with economic evaluation standards, an annual discount rate of 3% was used for future costs and QALYs, as in other literature models about health. Since death counts were reported

as absolute event numbers, no discount was applied. The model's cycle length is 1 year, consistent with global parameter reporting.

Conceptually, individuals may be in one of the following health states:

- Infection-free (healthy individual at risk)
- BSI with susceptible strain
- BSI with resistant strain
- Death

Transition probabilities in the model are provided by parameters that can be obtained from reports. Thus, the numbers for transitions from one state to another can be calculated using these formulas.

The following values are calculated for each year:

- N_t: number of individuals alive at the beginning of the year
- λ_{inf}: annual sepsis/BSI incidence (by person): The probability of a person developing sepsis/bloodstream infection within a year
- p_{res}: resistant infection rate
- CFR_S: case fatality rate for susceptible infections
- CFR_R: case fatality rate for resistant infections

Total number of infections:

$$\text{inf\_cases}_t = N_t \cdot \lambda_{\text{inf}} \quad (1)$$

Resistant/sensitive distribution of these cases:

$$R_t = \text{inf\_cases}_t \cdot p_{\text{res}} \quad S_t = \text{inf\_cases}_t - R_t \quad (2)$$

R_t: Number of resistant infections

S_t: Number of susceptible infections

Number of deaths:

$$\text{deaths}_t = S_t \cdot CFR_S + R_t \cdot CFR_R \quad (3)$$

Population living the following year:

$$N_{t+1} = \max(N_t - deaths_t, 0) \quad (4)$$

Total Cost:

The total cost for each year consists of the following components:

- Case costs
- Sensitive infection case cost: c_S
- Resistant infection case cost: c_r
- Policy/program cost

Annual fixed cost for implementing the relevant policy:

$$\text{cost}_t = S_t \cdot c_S + R_t \cdot c_R + C_{\text{fixed}}^{(\text{policy})} \quad (5)$$

Annual quality of life for infection-free adults: u_{base}

Additional QALY losses for susceptible/resistant infections:

- Δu_S: QALY loss per susceptible BSI
- Δu_R: QALY loss per resistant BSI

QALYs gained in one year:

$$\text{QALY}_t = (N_t - \text{deaths}_t) \cdot u_{\text{base}} - S_t \cdot \Delta u_S - R_t \cdot \Delta u_R \quad (6)$$

Integration of Policies into the Model

Each policy is defined using multipliers with model parameters.

- m_{inc}: factor reducing the incidence of infection
- $m_{p_{\text{res}}}$: factor reducing the proportion of resistant cases
- m_{CFR_R}: factor reducing the case fatality rate of resistant cases

- m_{c_S}, m_{c_R}: factors increasing/decreasing costs per case
- C_{fixed}: policy-specific annual fixed cost

When the policy is implemented, the effective parameters are updated as follows:

$$\lambda_{\text{inf}}^{(\text{policy})} = \lambda_{\text{inf}}^{(\text{base})} \cdot m_{\text{inc}} \tag{7}$$

$$p_{\text{res}}^{(\text{policy})} = p_{\text{res}}^{(\text{base})} \cdot m_{p_{\text{res}}} \tag{8}$$

$$CFR_R^{(\text{policy})} = CFR_R^{(\text{base})} \cdot m_{CFR_R} \tag{9}$$

$$c_S^{(\text{policy})} = c_S^{(\text{base})} \cdot m_{c_S}, c_R^{(\text{policy})} = c_R^{(\text{base})} \cdot m_{c_R} \tag{10}$$

Risk-based + AWaRe Policies:

The WHO's AWaRe classification divides antibiotics into three groups:

Access: Narrow-spectrum antibiotics commonly used in primary care with a lower risk of resistance

Watch: Broader-spectrum antibiotics that have a higher risk of resistance development

Reserve: Drugs that should be saved as a last option for highly resistant pathogens.

The WHO emphasizes that the Access group should dominate national consumption as follows: “Access group antibiotics should be at least 60% of overall national antibiotic consumption.” Thus, when this policy is used, it reduces inappropriate/broad-spectrum prescriptions and reports an approximately 10–30% decrease in total broad-spectrum use. This also reduces the proportion of resistant cases in the model. Thus, $m_{p_{\text{res}}} < 1$. More accurate prescriptions reduce hospital-acquired infections to some extent. And $m_{\text{inc}} < 1$. Since these policies will also have a cost, the fixed cost increases. Based on the literature, we can use in our model that

there will be about 10–20% fewer resistant cases and about 5–10% lower total incidence.

KSS / ML Decision Support Policies:

It significantly reduces inappropriate initial treatment. $m_{p_{\text{res}}}$ is lower. It reduces mortality in resistant cases. m_{CFR_R}<1, but it results in higher fixed cost or additional case costs due to IT investment and test usage. In Ribers & Ullrich's (2019) ML study for primary care: “Machine learning can reduce antibiotic use by 7.42 percent without reducing the number of treated bacterial infections.” Other studies like this generally report 5–15 percent less antibiotic use and higher appropriateness rates. Therefore, in the model, we adjusted the KSS/ML policy to be one level more effective than Risk+AWaRe.

Infection control Policies:

Hand hygiene, isolation, contact prevention measures are the policies that most strongly reduce infection rates. m_{inc}< is smallest, secondary decrease in resistance rate $m_{p_{\text{res}}} \leq 1$. Studies report a 30% to 50% reduction in incidence during CRE/CRKP epidemics. Particularly in cases of intense infection control packages, a dramatic decrease in the number of new cases has been shown. Therefore, using the sharpest m_{inc}< (0.6–0.7 band) in the model for the infection control package is consistent with the high effect sizes in the literature.

One Health + Environmental monitoring Policies:

Human, animal, environment holistic approach both $\lambda_{\text{inf}}$and $m_{p_{\text{res}}}$ decrease, but fixed costs are high due to environmental monitoring and laboratory infrastructure. ECDC and WHO emphasize that resistant bacteria are transmitted to humans through animal farming, the food chain, and water/waste, and that restricting antibiotic use in these areas also reduces human infections. This policy demonstrates that incidence and resistance rates can be reduced over time.

Netflix-like subscription model:

Revenue decreases based on usage volume, motivation for excessive usage weakens. $m_{p_{\text{res}}} < 1$ and faced high fixed subscription cost. In contrast, there may be a slight decrease in the unit cost of drugs. The subscription approach introduced by the UK's NHS aims to prevent companies from trying to sell more drugs by offering a fixed payment independent of volume. WHO and OECD reports also show that this model could support a more reasonable usage volume in terms of resistance development while promoting R&D. However, the fact that it creates a significant fixed cost on the budget in the short term is also an important parameter for the model.

Innovation & narrow spectrum & nonprofit R&D:

Narrow spectrum and targeted new agents reduced resistance development and reduced mortality in resistant cases. ($m_{p_{\text{res}}} <1$, $m_{CFR_R} <1$). High cost and Cr due to R&D and new drug costs. Nonprofit models such as GARDP and pull incentives are proposed in the literature to boost the development of new agents against critical pathogens, while also using these agents in a targeted and controlled manner to maintain long term effectiveness. Therefore, in the model, Innovation & nonprofit policy is assigned a strong long term health gain but a high-cost profile.

Population in the following year:

$$N_{t+1} = \max(N_t - deaths_t, 0) \tag{11}$$

The basic cost-effectiveness measure is the incremental cost-effectiveness ratio (ICER):

$$ICER = \frac{\Delta\text{Cost}}{\Delta\text{QALY}} \tag{12}$$

ΔCost= Policy – Status quo cost difference

ΔQALY= Policy – Status quo QALY difference.

Δ“QALY” >0, the policy is considered both cheaper and more effective

If the ICER value is positive, it can be interpreted by comparing it with acceptable threshold values for the health system (e.g., 20,000–50,000 €/QALY).

Net Monetary Benefit (NMB) :

$$\text{NMB} = (\text{WTP} \times \Delta\text{QALY}) - \Delta\text{Cost} \quad (13)$$

4.5.2 Dynamic Compartmental Model (DCM) for AMR Simulation

In this study, a Dynamic Compartmental Model (DCM) was developed to mechanistically represent the spread of antimicrobial resistance (AMR)-associated infections within a population, their changes over time, and resistance selection. The DCM aims to directly capture the biological and epidemiological dynamics of AMR by modeling infection and colonization processes through a continuous-time differential equation system. This structure allows for a more accurate assessment of the effects of factors driving the emergence of resistant pathogens, infection burden, and antibiotic use pressure on the population.

DCM is designed to mechanistically model the following components:

- acquisition of susceptible and resistant colonization
- antibiotic-associated resistance selection
- progression from colonization to active infection
- clinical course differences between resistant and susceptible infections
- recovery and transient immunity
- infection-related mortality

The total population ensures the following with the formula:

$$N(t) = S(t) + C_S(t) + C_R(t) + I_S(t) + I_R(t) + R(t) \quad (14)$$

Model Structure and Compartments

The DCM divides the adult population into seven mutually exclusive compartments representing colonization, infection, recovery, and mortality states. Individuals move between these states according to biologically motivated transition rates:

- S: Susceptible (uncolonized, healthy)
- C_S: Colonized with susceptible strains
- C_R: Colonized with resistant strains
- I_S: Active bloodstream infection (susceptible strain)
- I_R: Active bloodstream infection (resistant strain)
- R: Recovered from infection (temporary immunity)
- D: Death (absorbing state)

The total population at any time satisfies:

$$N(t) = S + C_S + C_R + I_S + I_R + R \quad (15)$$

Transition Dynamics

Transitions between compartments occur continuously and are governed by rate parameters obtained from clinical and epidemiological literature. Key rates include:

- κ_S, κ_R – acquisition of susceptible/resistant colonization
- α_C – conversion from susceptible-colonized to resistant-colonized (selection pressure)
- ρ_S, ρ_R – progression from colonization to infection
- α_I – conversion from susceptible infection to resistant infection
- γ_S, γ_R – recovery rates
- μ_S, μ_R – mortality rates
- ω – waning immunity / return to susceptibility

The full system of ODEs is:

$$\frac{dS}{dt} = -(\kappa S + \kappa R) \cdot S + \omega \cdot R \tag{16}$$

$$\frac{dC_S}{dt} = \kappa S \cdot S - (\rho S + \alpha C) \cdot C_S \tag{17}$$

$$\frac{dC_R}{dt} = \kappa R \cdot S + \alpha C \cdot C_S - \rho R \cdot C_R \tag{18}$$

$$\frac{dI_S}{dt} = \rho S \cdot C_S - (\gamma S + \mu S + \alpha I) \cdot I_S \tag{19}$$

$$\frac{dI_R}{dt} = \rho R \cdot C_R + \alpha I \cdot I_S - (\gamma R + \mu R) \cdot I_R \tag{20}$$

$$\frac{dR}{dt} = \gamma S \cdot I_S + \gamma R \cdot I_R - \omega \cdot R \tag{21}$$

$$\frac{dD}{dt} = \mu S \cdot I_S + \mu R \cdot I_R \tag{22}$$

Numerical Analysis

The model was solved numerically using the Euler method with a daily time step to make the continuous-time differential equations solvable:

$$X(t + \Delta t) = X(t) + \frac{dX}{dt}\,\Delta t \tag{23}$$

$$\Delta t = \frac{1}{365} \tag{24}$$

This analysis allows for detailed monitoring of changes in resistance dynamics throughout the year.

Integration of Policy Effects into the Model

The effect of policies aimed at reducing antibiotic use on resistance dynamics has been applied to three key parameters associated with reduced antibiotic pressure:

$$\kappa_R^{policy} = \kappa_R(1 - r) \tag{25}$$

$$\alpha_C^{policy} = \alpha_C(1 - r) \tag{26}$$

$$\alpha_I^{policy} = \alpha_I(1 - r) \tag{27}$$

where *r* is the percentage reduction in antibiotic exposure.

Model Outputs

At each simulation step, the model produces:

- Incidence of susceptible and resistant infections
- Cumulative resistant burden
- Sepsis-related mortality
- Recovered population size
- Total population over time

These dynamic outputs feed directly into the economic model to compute:

- total cost
- total QALYs
- incremental cost-effectiveness ratio (ICER)
- number of deaths prevented

Thus, the DCM provides mechanistic epidemiological realism, which strengthens the validity of the cost-effectiveness results.

Integration of DCM Outputs into the Economic Model

The infection, colonization, and mortality flows obtained from the dynamic model are then transferred to the cost-effectiveness analysis (CEA). At this stage:

- unit costs for each infection type,
- utility values for each health state,
- program costs

are used to calculate total cost, total QALY, and ICER.

This structure allows epidemiological processes to be directly integrated with economic outputs.

QALY calculation:

$$Q(t) = u_S S(t) + u_{CS} C_S(t) + u_{CR} C_R(t) + u_{IS} I_S(t) + u_{IR} I_R(t) + u_R R(t) \qquad (28)$$

Total discounted QALY:

$$QALY = \sum_{t=0}^{T} Q(t)\ e^{-rt}\ \Delta t \qquad (29)$$

Cost Calculation:

Cost function at the time step:

$$Cost(t) = I_S(t)\, C_{IS} + I_R(t)\, C_{IR} + C_{prog}\, \Delta t \qquad (30)$$

Total Cost:

$$TotalCost = \sum_{t=0}^{T} Cost(t)\ e^{-rt}\ \Delta t \tag{31}$$

4.6 Limitations and Ethical Considerations

Although the decision support system developed in this study aims to integrate current data science techniques into the healthcare system, it has some structural and operational limitations. First of all, genomics-based prescribing, which is one of the proposed policies, is not yet widely implemented in many countries. In terms of both cost and laboratory infrastructure, it is possible that such systems can only be implemented in a limited number of health institutions in the short term.

In addition, the use of machine learning-based decision recommendation systems alone in clinical settings poses various risks. In particular, effects such as automation bias may carry the risk of clouding physician judgment. Therefore, the systems developed must be configured to work under the approval and supervision of a physician. The "supporting role" of clinical decision support tools is important in terms of ethical responsibility.

Also, sensitive data types such as patient-based health data, microbiological results and genomic information will be used in this study. In the processing of these data, personal data security will be prioritized and techniques such as anonymization and encryption will be used. The system will be designed in full compliance with national and international data protection regulations, especially GDPR (General Data Protection Regulation). Ethical consent, data access permissions and stakeholder notification processes will be meticulously carried out throughout the project.

4.7 Overall Evaluation of the Method

The methodology proposed in this study provides a systematic and data-driven basis for combating antibiotic resistance by creating a multi-layered decision support structure. By combining simulation techniques, machine learning algorithms and

optimization methods, the impact of health policies on the field can be evaluated multidimensionally. One of the most important advantages of the model is that it takes into account real world constraints and variables. Many theoretically proposed policies in the literature have been scenarized and tested in this study, taking into account factors such as resource limitations of the health system, patient profile diversity and data accessibility. In that regard, the system created serves as both a useful tool that may guide decision makers and an academic model.

In addition, the model's modular design makes it simple to adapt to various governments' health infrastructures, institutional efforts, or new data types. This adaptability helps the system's scalability and sustainability and offers a solid basis for upcoming studies and the formulation of new policies.

5. IMPLEMENTATION

5.1 Markov-Type Cohort Model

The Markov model designed in the methodology section was modelled using Python. Here, the parameters are set to be input by the user, allowing for more comprehensive and scalable use. Users will be able to enter the parameters of their models and access the policies we have defined within the methodology as defaults. Users select the pathogenes, country/AMR category, and policy, or enter their own parameter values. The interface send these inputs to the Python model. It returns total costs, QALYs, and death counts as output, as additionally ICER values. This allows us to examine the model both in the short and long term and according to required population ranges. Furthermore, experts and organizations can evaluate their policies within their desired scope after entering their own data as parameters. Moreover, users who do not have clear data can use Google Scholar and PubMed to search for keywords on the web page. If they want to look at organizations that share reports directly, WHO GLASS, ECDC AMR, and OECD AMR web pages are available as ready links in the interface. Thus, users are supported in knowing where to conduct literature searches and, if they have their own data, can input it into the model.

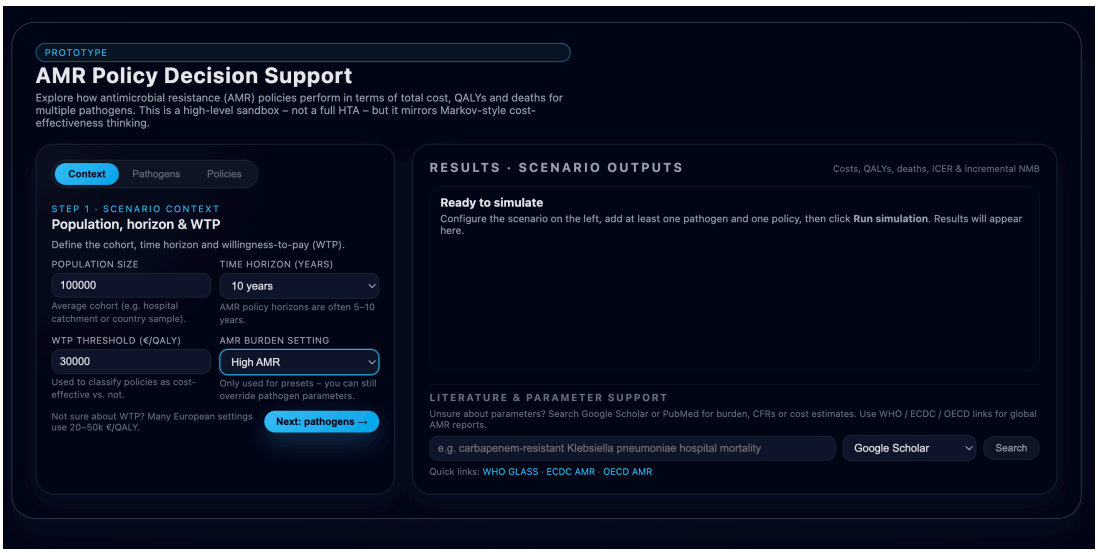


Figure 5.1.1 Prototype Main Page.

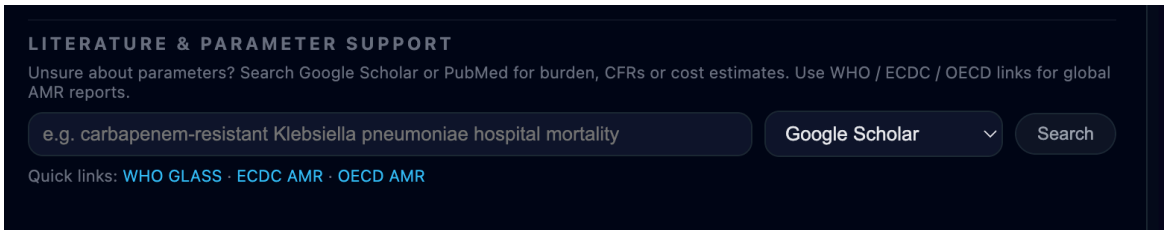


Figure 5.1.2 Parameter Support.

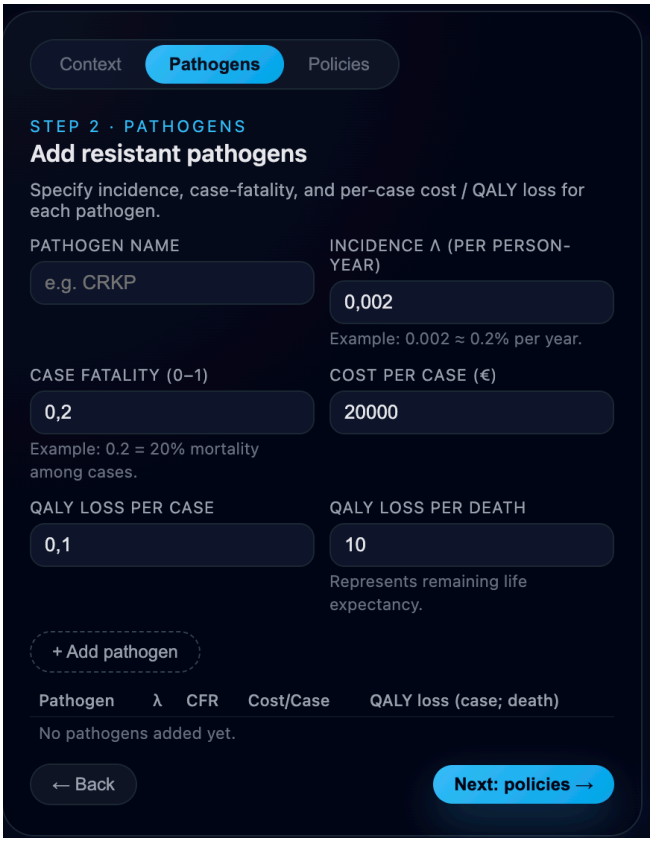


Figure 5.1.3 Pathogens Parameters.

Figure 5.1.4 Policy Parameters.

A sample application has been prepared using the interface. This implementation is for:

• E. coli (third-generation cephalosporin resistant – 3GC-R)

5.1.1 General Framework for Implementation:

Population: 100,000 adults

Pathology focus: Third-generation cephalosporin-resistant E. coli BSI

Horizon: 10 years

Perspective: Health system

Threshold value (WTP): €30,000/QALY

The maximum price deemed reasonable to spend for one year of quality life.

Figure 5.1.5 Scenario Results from User Interface.

According to the user interface scenario results presented in Figure 5.1.5 in a 10-year simulation for 3GC-R E. coli bacteria, different policy sets were compared with the "no intervention" in a cohort of 100,000 people. The results show that the infection control package and rapid diagnosis + ML-supported decision systems both reduce costs and provide significant QALY gains and reductions in mortality. The infection control package provided the highest net benefit of €88.5 million, with approximately

€10.35 million in cost savings, 2,605 QALY gains, and 175 deaths prevented, making it the most advantageous policy in the model. Risk-based + AWaRe-compliant antibiotic management and rapid diagnosis/ML solutions also emerged as dominant, that is, both cheaper and more effective. Subscription models and innovation-focused R&D policies, on the other hand, require additional costs. If evaluated below the €30,000/QALY threshold, they look cost-effective based on ICER values. In other words, they are effective but investment-demanding strategies. Users testing the policy can evaluate these policies by entering their own threshold values into the model.

5.1.2 Simulation Implemantation & Results for Different Cases

In addition to this basic example, the model compared the short-term (1 year) and long-term (10 years) economic and clinical impacts of various policy packages across different Antimicrobial Resistance (AMR) burden categories (Low, Medium, High AMR). The analyses show that policy effectiveness increases in direct rate to the level of AMR and that Infection Control and Digital Decision Support Systems provide the strongest economic benefits in most scenarios.

5.1.2.1 Annual Results

In countries with low AMR rates, the most effective short-term policies are traditional public health policies. Especially the Infection Control and One Health packages have produced net dominant results with approximately €120,000 savings and a €2.3 QALY gain. The Risk-based + AWaRe program is also dominant, but its impact is more limited. KSS/ML decision support systems, despite an additional cost of €40,000, were found to be cost-effective near the threshold due to a QALY gain of 1.4. In contrast, high-cost models such as Subscription and Innovation & R&D did not provide a return in the short term. When the resistance rate reached the medium AMR level, both clinical and economic gains increased significantly. Infection Control/One Health packages €380,000 savings and 4.9 QALY and KSS/ML systems €76,000 savings and 3+ QALY have clearly become dominant. In this category, policies now both save

lives and ease the cost burden on the health budget. In countries with a high AMR burden, almost every policy provides economic support. The Infection Control package produced very strong dominant results, with annual savings of €0.9 million and a QALY gain of €12. Even the normally expensive Subscription model has become quite cost-effective in the short term, thanks to the significant cost-QALY gain from preventing each resistant case under high resistance burden. The Innovation & R&D policy was also found to be cost-effective with an ICER value of €16,000.

5.1.2.2 10 Year Results

In the long term, all effects grow exponentially. Even at a low AMR level, Infection Control saves €1 million and yields a QALY gain of €92, while the KSS/ML system achieves strong cost-effectiveness with a QALY gain of €53 despite an additional cost of €356,000. At the mid AMR level, gains have reached millions. Infection Control saved €3 million, while KSS/ML remained dominant with savings of €664,000 and a QALY gain of 115. At this level, even Innovation & R&D, which initially appeared to be weak, became reasonable for mid-high-income countries with a QALY gain of 124, despite an additional cost of 2.19 million €. Long term results are most impressive at the High AMR level. Infection Control provides savings of €8.2 million and a QALY gain of 450, while KSS/ML is a very attractive dominant policy with savings of €3.36 million. Even the subscription model demonstrated very strong cost-effectiveness, achieving a QALY gain of €103 at a nearly neutral cost of €27,000 with an ICER of approximately €267 per QALY. This shows that even advanced R&D and financing models can be economically justified under high resistance burdens.

5.1.2.3 Sensitivity Analysis

Sensitivity analyses conducted by defining specific ranges instead of net values for parameters showed that as the resistance rate or incidence value increased, the cost-effectiveness of core policies such as Infection Control, One Health, KSS/ML, and Risk-based + AWaRe became even stronger, and their ICERs decreased or became

negative. In addition, in high AMR scenarios, even Innovation & R&D policies that provide long-term benefits have been observed to become economically rational.

5.2 Application of the Dynamic Compartment Model (DCM) Simulation

In this study, the Dynamic Compartment Model (DCM) developed in the methodology section has been converted into a user-interactive policy simulation tool. The primary objective of this application is to translate the continuous-time epidemiological model into a practical, decision-maker-oriented environment, enabling users to test antimicrobial resistance (AMR) policies under different epidemiological and economic conditions.

The developed interface combines dynamic infection modeling with cost-effectiveness analysis on a single platform. Users can determine all variables themselves, such as population size, simulation duration, clinical parameters, health outcomes, policy impact, and program cost. This structure offers both researchers and policymakers the opportunity to examine short- and long-term outcomes: total infections, resistant infection burden, death counts, QALYs, and total costs can be calculated simultaneously.

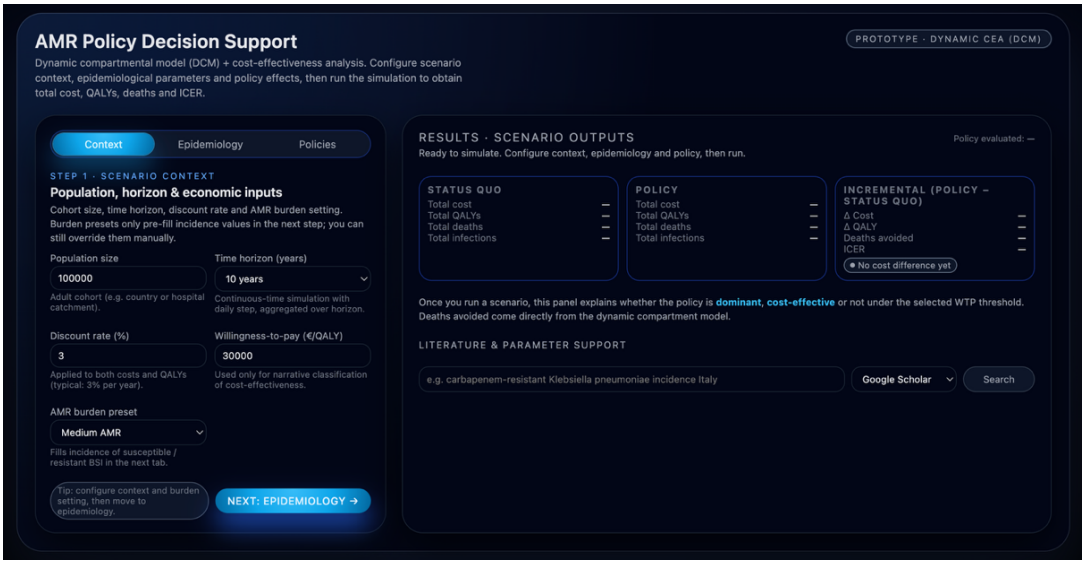


Figure 5.2.1 Prototype Main Page.

The interface consists of three main steps: Context, Epidemiology, and Policies.
In the first step, the user selects the cohort size, time horizon, discount rate, willingness to pay (WTP) per QALY, and AMR burden level.

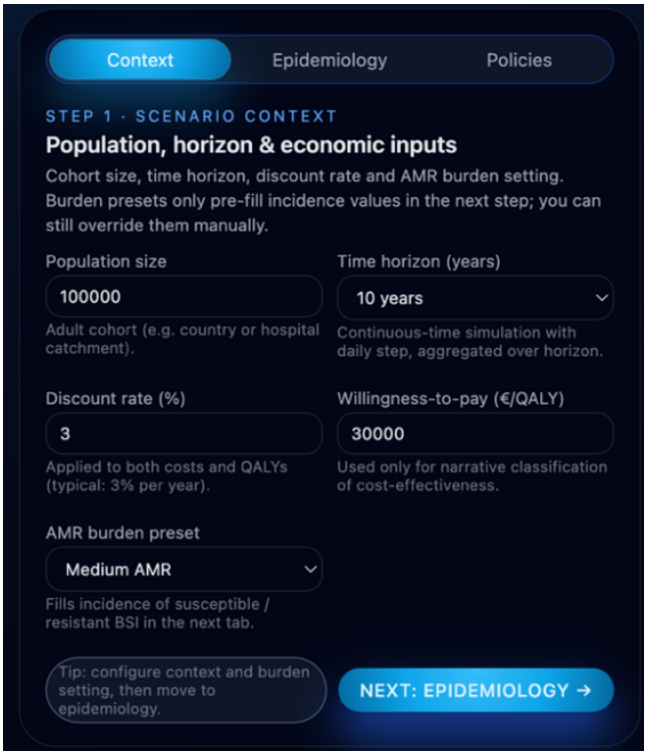


Figure 5.2.2 Scenario Context.

In the second step, the epidemiological and clinical parameters that determine the model's dynamics are entered: susceptible and resistant infection incidence, length of stay, mortality rates, QALY weights, and costs per infection episode.

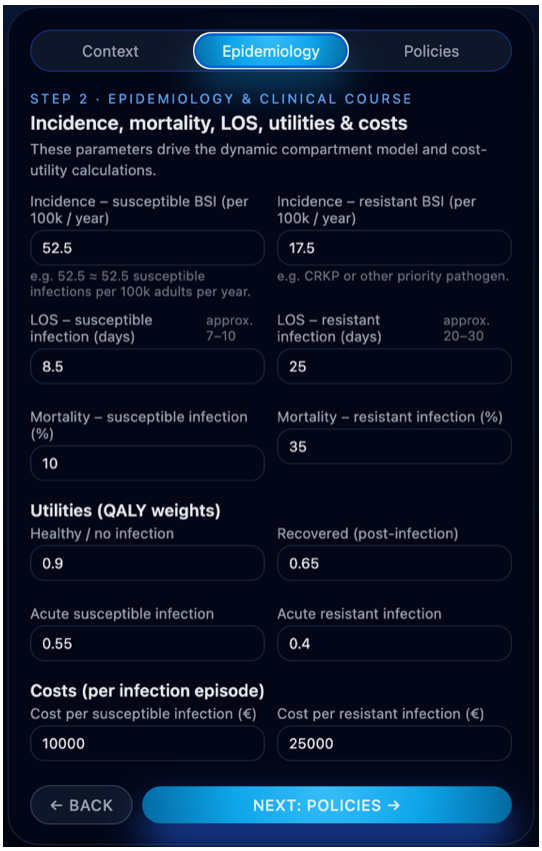


Figure 5.2.3 Epidemology Section.

In the third step, the policy to be tested is defined. The user can either define their own policy or select one of the ready-made policy sets commonly used in the literature

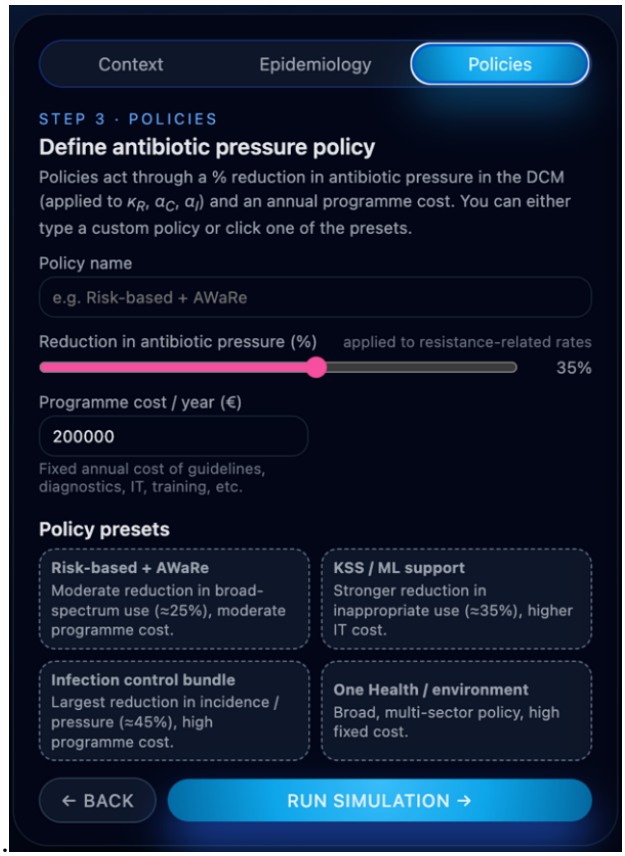


Figure 5.2.4 Policy Section.

5.2.1 Simulation Implemantation & Results for Different Cases

5.2.1.1 Annual Results

When evaluated annually, as the AMR burden increases, the clinical and economic impacts of policies become significantly stronger. In settings with low AMR levels, Infection Control and One Health interventions yield the most advantageous outcomes; they become dominant strategies, providing approximately €120,000 in cost savings and a 2-3 QALY gain. Risk-based + AWaRe antibiotic stewardship offers more limited improvement, while Digital/ML decision support applications are cost-effective despite their low additional costs, thanks to an increase of approximately 1.4 QALYs. At moderate AMR levels, both economic and clinical impacts are further amplified; Infection Control and One Health approaches remain among the most

effective policies, yielding approximately €380,000 in savings and 5 QALY gains. Digital/ML systems also provide significant benefits in this environment, generating approximately €76,000 in savings and becoming one of the most powerful interventions. At high AMR levels, nearly all policies are economically advantageous. In particular, the Infection Control policy demonstrates an extremely strong impact, saving approximately €900,000 and gaining 10-12 QALYs, while even higher-cost subscription models or innovation/R&D policies become cost-effective thanks to the significant reduction in resistant infections.

5.2.1.2 10 Year Results

Ten-year simulation results show that the effects of policies increase exponentially over time. At low AMR levels, Infection Control policies resulted in total cost savings of approximately €1 million and provided over 90 QALY gains, making them the dominant strategy in the long term. Digital/ML decision support systems, despite their implementation costs, provided over 50 QALY gains, demonstrating high cost-effectiveness. At medium AMR levels, policy effects become more pronounced; Infection Control provides approximately €3 million in long-term savings, while Digital/ML systems again deliver dominant results with €664,000 in savings and 115 QALY gains. Although innovation and R&D-focused policies impose a higher cost burden, they still achieve an acceptable level of cost-effectiveness by providing over 120 QALY gains. The high AMR category is the scope where the strongest effects are seen. Infection Control interventions are extremely effective, with savings of approximately €8.2 million and a QALY gain of around 450, while Digital/ML systems also produce dominant results, saving €3.36 million. Even costly subscription models become quite attractive in this environment, generating over 100 QALY gains while keeping total costs at a nearly neutral level, suggesting that such investment-intensive policies may be an economically rational option in countries with high resistance burdens.

5.3 AMR Forecasting with ML

Objective: Estimate antimicrobial resistance (AMR) percentages for key pathogens across European countries for 2025–2030 and derive a weighted "General AMR" score to support policy discussions.

Input data: Country-level AMR metrics across years with multiple measurement units and pathogen categories.

Steps:

- Data Cleaning, Normalization, and Feature Engineering
- Per country–organism combination, trained a polynomial regression model (degree 2) on historical `Time` vs. resistance `%`.
- Generated forecasts for each year from 2025 to 2030.
- Post-processed predictions by bounding values to the feasible range [0, 100] (%).

5.3.1 Data Cleaning, Normalization, and Feature Engineering

We performed a number of preliminary procedures in order to analyze the data consistently across nations and organisms. In order to focus on combined resistance patterns rather than individual cases, we first cleaned up additional information and filtered out only the records that demonstrated resistance to multiple drugs. We treated time as a flowing variable in our analyses and limited the results to fall between 0% and 100% to prevent illogical predictions; thus, through all these cleaning and organizing steps, we transformed the messy raw data into a structured format suitable for examining trends and making cross-country comparisons.

5.3.2 Model Selection

In this study, the second-degree polynomial regression method was chosen for antibiotic resistance predictions because it strikes the best balance between simplicity and realism. Unlike methods that assume change occurs at a constant rate, this model can successfully capture the slopes of increases or decreases in resistance rates, i.e., the fluctuations observed in real life. Given the limited amount of data available, this method avoids the risk of error associated with highly complex models, producing reliable and understandable results for decision-makers by clearly showing the trend without unnecessary deviations.

5.3.3 How General AMR calculated?

The most recent, and population-weighted data on pathogen frequency comes from the European Centre for Disease Prevention and Control (ECDC), which operates multiple surveillance networks.

Data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) provides the 2024 estimated incidence of invasive isolates (e.g., from blood) per 100,000 population for the EU/EEA. This is a clear measure of general, population-level frequency:

E. coli: 73.9 per 100,000

K. pneumoniae: 25.3 per 100,000

P. aeruginosa: 11.1 per 100,000

Acinetobacter spp.: 4.5 per 100,000

To visualize this discrepancy, Table 5.1 normalizes the EARS-Net incidence data to create a "pure frequency" weighting and compares it to the composite score.

Table 5.3.1 Normalizing EARS-Net Data.

Pathogen	EARS-Net 2024 Incidence (per 100,000)	Frequency-Normalized Weight (EARS-Net) (%)
E. coli	73.9	64.4%
K. pneumoniae	25.3	22.0%
P. aeruginosa	11.1	9.7%
Acinetobacter spp.	4.5	3.9%
Total	114.8	100.0%

5.3.4 Forecast Results and Key Findings

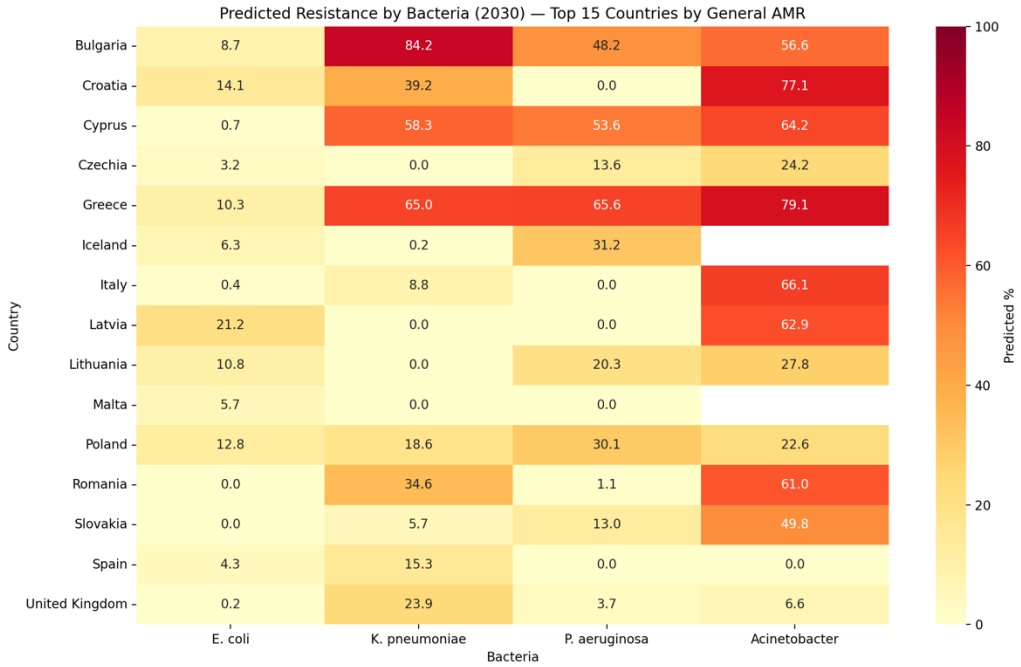


Figure 5.3.1 Antimicrobial Resistance Heatmap.

This graph (Figure 5.3.1) details the resistance levels of the top 15 countries selected based on the “General AMR” rate for 2030 against 4 different bacterial species (E. coli, K. pneumoniae, P. aeruginosa, Acinetobacter).

Yellow represents low resistance (favorable situation), while red and dark red represent very high resistance (dangerous situation).

5.3.4.1 Most At-Risk Countries (Dark Red):

Greece: Stands out as the most “red” country in the table. Acinetobacter (79.1%), P. aeruginosa (65.6%), and K. pneumoniae (65.0%) bacteria are expected to have particularly high resistance rates.

Bulgaria: Has one of the highest resistance rates in the table, at 84.2% against K. pneumoniae bacteria. Acinetobacter resistance is also above 50%.

5.3.4.2 Bacteria-Based Analysis:

Acinetobacter: Appears to be the most problematic bacterial species. Resistance rates are very high (red zone) in many countries, including Croatia (77.1%), Italy (66.1%), Latvia (62.9%), and Romania (61.0%).

E. coli: It appears more “controllable” compared to other bacteria in the table. Most countries are yellow (low resistance). Only Latvia (21.2%) and Poland (12.8%) have relatively high values.

5.3.4.3 Countries in a Better Position:

United Kingdom, Spain, Czechia: They are generally yellow, meaning their resistance rates are estimated to be lower. However, Spain and the United Kingdom show a medium level of risk for K. pneumoniae.

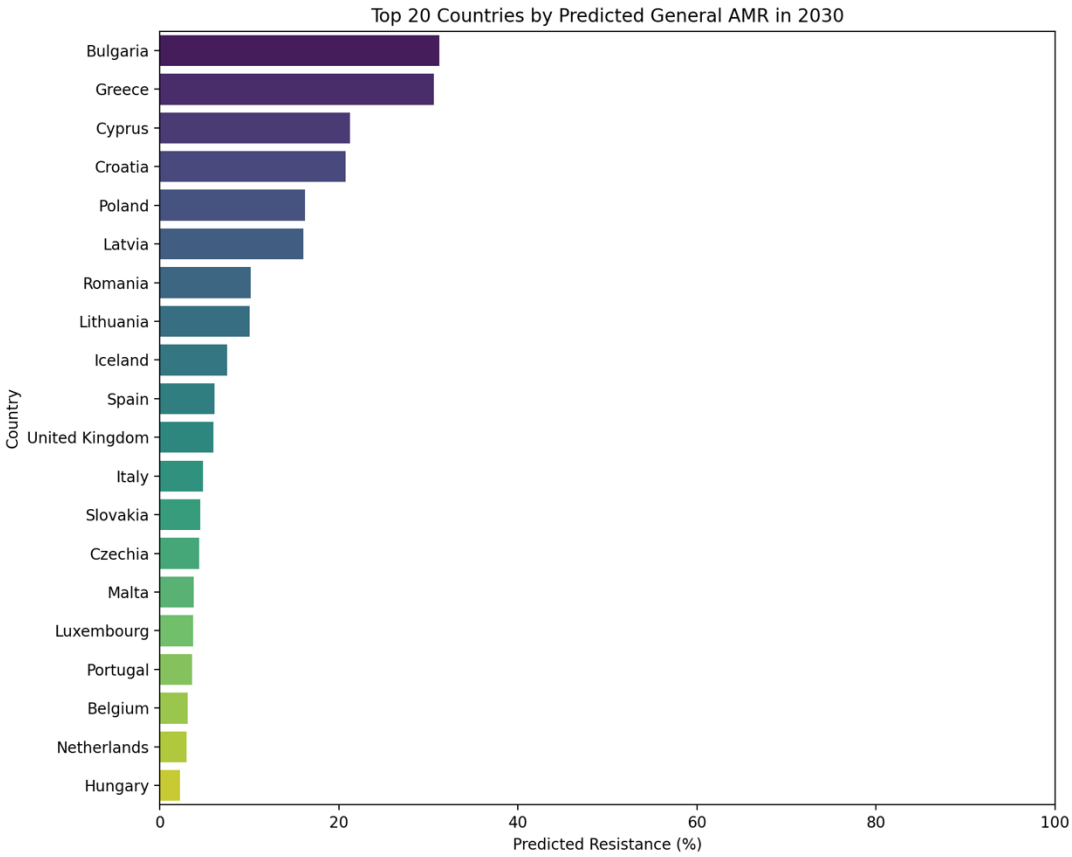


Figure 5.3.2 General AMR Rates.

This graph (Figure 5.3.2) ranks the top 20 countries based on the projected "General AMR" rates for 2030. It serves as a summary of the first visual but covers more countries.

Bulgaria and Greece stand at the top of the list with estimated overall resistance rates exceeding 30%, indicating a very high probability of antibiotic treatment failure, followed closely by Cyprus and Croatia. As the rankings progress downward, resistance rates drop rapidly, placing Poland, Latvia, Romania, and Lithuania in the medium-risk group. Meanwhile, Western European countries such as Italy, Spain, and the United Kingdom occupy the lower end of the list, with Hungary, the Netherlands, and Belgium specifically projected to have the lowest resistance estimates.

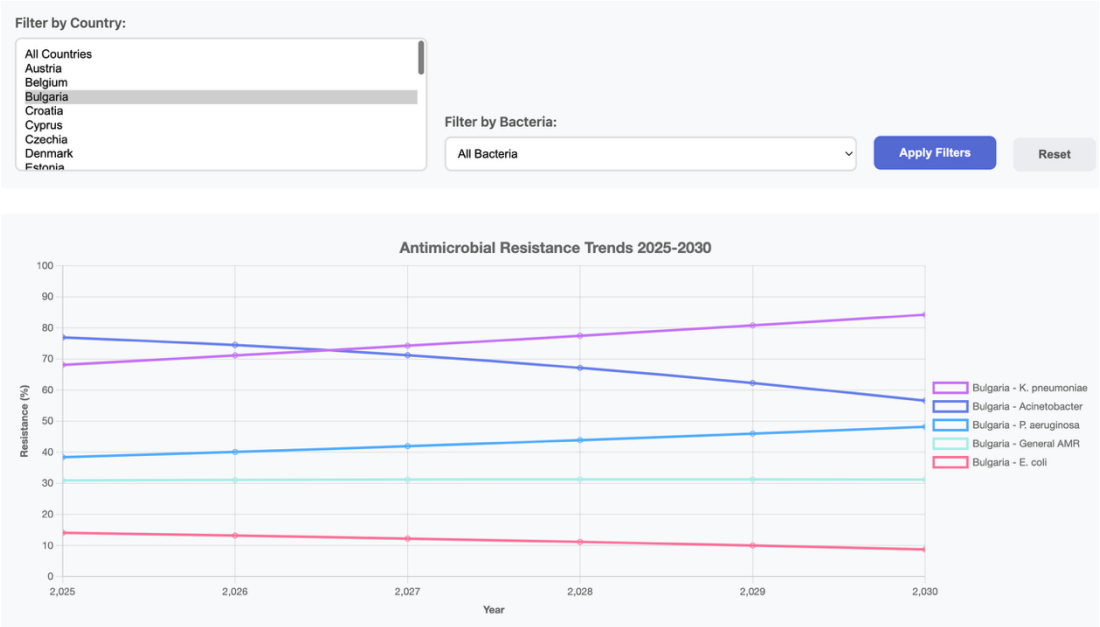


Figure 5.3.3 AMR Trends.

Detailed Data

COUNTRY	BACTERIA	2025	2026	2027	2028	2029	2030
Bulgaria	K. pneumoniae	68.14%	71.16%	74.27%	77.49%	80.81%	84.24%
Bulgaria	Acinetobacter	76.96%	74.50%	71.23%	67.16%	62.28%	56.61%
Bulgaria	P. aeruginosa	38.40%	40.11%	41.95%	43.91%	46.00%	48.21%
Bulgaria	General AMR	30.93%	31.10%	31.22%	31.27%	31.26%	31.21%
Bulgaria	E. coli	14.09%	13.21%	12.24%	11.16%	9.99%	8.73%

Figure 5.3.4 Yearly Details of Bacterias.

These projections (Figure 5.3.3 – Figure 5.3.4) provide a specific forecast for antimicrobial resistance in Bulgaria between 2025 and 2030, highlighting a mix of improving and worsening trends. The data predicts a positive decline in Acinetobacter (falling from approximately 77% to 56%) and E. coli resistance, while a worrying increase is seen in K. pneumoniae resistance, which is expected to rise sharply from 68.14% to 84.24%. Interestingly, despite these variable changes among individual bacteria, Bulgaria's overall “General AMR” level is expected to remain remarkably stable at around 31% throughout the five-year period.

5.4 Generating and Evaluating Design Solution Alternatives

Three levels of solution alternatives were implemented and evaluated in this study: machine learning prediction models, policy packages, and simulation models. Two distinct structures that represented the same AMR issue were created on the simulation side. A dynamic compartment model that captures transmission dynamics over time and a Markov-type cohort model that prioritizes cost-effectiveness were developed. As a result, the decision-maker is given two different analytical frameworks that examine the same set of policies from the perspectives of epidemiological dynamics and economic burden. For comparison with the current situation scenario, a number of different policy alternatives have been defined in both models, including Risk-based + AWaRe, Infection Control, One Health, Digital/ML decision support, Subscription, and Innovation & R&D. These policies have been compared under various AMR burden, time horizon, and willingness-to-pay (WTP) thresholds in terms of total cost, quality-adjusted life years (QALY), deaths, incremental cost-effectiveness ratio (ICER), and net monetary benefit indicators. The second-degree polynomial regression method was chosen as the best prediction model based on data quantity, error values, and interpretability criteria after various predictive approaches were tested on the machine learning side to forecast countries' future resistance rates. The overall AMR score and policy prioritization were then determined using the model's output. As a result, the design methodically generated both the policy and prediction components and the simulation architecture. Then, alternative scenarios were compared using various performance metrics.

6. CONCLUSION AND RECOMMENDATIONS

Brief Summary of the Design and Development Steps

In this study, a data-driven Decision Support System was designed and implemented to support decision-makers in the fight against antibiotic resistance. The main objective of the study is to comprehensively address antibiotic use, resistance rates, patient and prescription information, antibiogram data, and epidemiological parameters based on the literature, and to test different policy alternatives. It also aims to systematically evaluate the health and economic impacts of these candidate policies.

The design process began with problem definition, determination of the system's scope, and stakeholder analysis. At this stage, the clinical and economic burden of AMR on the healthcare system was assessed, and the types of outputs or comparisons needed by decision-makers were clarified. Subsequently, alternative policies such as infection control, risk-based prescribing, WHO AWaRe-based policies, rapid diagnostic systems, and digital/ML-supported decision mechanisms were defined based on the literature.

In the next step, two complementary modelling approaches were used to quantitatively assess the effects of these policies. First, a Markov-based cohort model was used to calculate costs, quality-adjusted life years (QALYs), averted deaths, incremental cost-effectiveness ratios (ICERs), and net monetary benefits (NMB) at different time horizons. The other model, the Dynamic Compartment Model (DCM), modelled the evolution of susceptible and resistant bacterial populations over time. The processes of infection spread, and resistance selection were represented.

Following the modelling phase, the epidemiological and economic outputs obtained have been integrated into the decision support section. Thanks to the interface prototype developed in this layer, users can define parameters such as population

size, time horizon, discount rate and willingness to pay (WTP) and compare the results of the selected policy alternatives. Thus, the system demonstrates which policies are dominant or cost-effective under different scenarios.

Finally, the findings obtained during the implementation phase revealed that infection control and ML-supported policy packages provided health gains and reduced total costs in many scenarios. These results demonstrate that the developed decision support system can provide evidence-based, comparative, and actionable policy assessments in the fight against AMR.

6.1 Applicability of the Design and Managerial Contributions

The data-driven decision support system developed within the scope of this study has been designed to be used in strategic decision-making processes in the fight against antibiotic resistance. The system offers an applicable and scalable structure in different country, region and institutional contexts, thanks to the fact that the data requirements largely consist of antibiotic consumption data, resistance rates, patient profiles and clinical cost information already produced within healthcare systems.

From a management perspective, the developed system provides significant value by offering a comparative analysis of alternative policy packages rather than presenting only a single policy outcome. In particular, the joint reporting of indicators such as ICER, net monetary benefit (NMB), QALY gain, and number of deaths prevented enables managers to make more informed, predictable choices, considering budget constraints and willingness-to-pay (WTP) thresholds. This allows for evidence-based resource allocation and performance evaluation.

The system's user-interactive interface allows policy and health managers to quickly evaluate different scenarios. They can change factors such as population size, time horizon, epidemiological characteristics, and policy scope on a scenario basis. This ensures that the system is not just an academic model but a management tool that can be applied to real decision-making processes.

However, the combined use of the Markov model and the Dynamic Compartment Model offers a significant advantage in terms of decision-making. Evaluating long-term cost-effectiveness outcomes alongside short- and medium-term epidemiological dynamics enables managers to see the effects of both rapidly implementable policies and long-term sustainable strategies simultaneously.

In summary, this study evaluates interventions for antibiotic resistance not only in terms of their effectiveness but also under specific resource constraints and within a specific time frame. Thus, the developed framework contributes to the creation of a more rational, transparent, and accountable decision-making mechanism in the design and implementation of health policies.

6.2 Assessment of Environmental, Social, and Economic Impacts of the Design

Environmental Impacts

Antibiotic resistance is not just a clinical problem; it is also a systemic problem with environmental dimensions. The excessive and inappropriate use of antibiotics can accelerate the spread of resistant microorganisms through wastewater and environmental residues. This process not only affects human health but also directly impacts animal health through livestock and natural ecosystems. Antibiotics used in livestock farming can pollute the environment and facilitate the spread of resistance genes among animals and from animals to humans.

The decision support system developed in this study aims to indirectly reduce the environmental pressure of antibiotic resistance by promoting policy packages that encourage reduced antibiotic use and more targeted prescribing approaches, thereby reducing both human and animal-derived antibiotic consumption. Infection control limits unnecessary antibiotic use and enables a reduction in the amount of antibiotics released into the environment. In this respect, the design is consistent with the ‘One

Health’ approach and can be considered a complementary tool for limiting the spread of resistance genes within ecosystems in the long term.

6.2.1 Social Impacts

Antibiotic resistance directly affects not only health indicators at the societal level, but also individuals' daily lives and their perception of the healthcare system. The prolongation of treatment processes due to resistant infections and the failure to achieve the desired outcome in some cases lead to both increased mortality rates and longer hospital stays. This situation can have particularly severe consequences for chronically ill patients, the elderly, and socioeconomically disadvantaged groups.

On the other hand, repeated treatments and uncertainties in the recovery process place a significant psychological and financial burden on patients and their families. The failure to achieve the expected benefits from treatment can, over time, lead to a decline in public confidence in the healthcare system. In this context, antibiotic resistance is considered not only a clinical problem but also a multidimensional social issue that affects individuals' quality of life, social welfare, and confidence in healthcare services.

In this context, antibiotic resistance emerges as a significant public health issue, not only due to its clinical consequences but also because of its impact on individuals' social well-being and society's perception of health. Furthermore, the scenario-based structure of the system allows for the examination of policy performance under different population groups and resistance levels. This ensures that decision-makers consider not only average outcomes but also the effects on high-risk or disadvantaged groups. Therefore, the design offers an analytical framework that can contribute to the development of more equitable and inclusive health policies.

6.2.2 Economic Impacts

AMR poses a significant burden on public budgets through increased costs on healthcare systems. The need for more expensive drugs to treat resistant infections, longer hospital stays, and additional diagnostic/treatment processes increase per capita healthcare expenditures and cause healthcare budgets to be depleted more quickly. This situation makes the long-term sustainability of healthcare systems difficult, especially in countries with limited resources.

Furthermore, the rise in antibiotic resistance has indirect but lasting effects on the national economy through labour losses and reduced productivity. The temporary or permanent withdrawal of the working-age population from the workforce due to illness, premature deaths, and long-term health problems negatively impact total production and economic growth.

The system developed in this study contributes to the more rational and efficient use of public resources by evaluating policy alternatives that can be implemented in the fight against antibiotic resistance in terms of cost and effectiveness.

6.3 Ethical Evaluation of the Design

Policies aimed at combating antibiotic resistance should be evaluated not only in terms of their technical effectiveness but also in terms of their long-term effects on society and the ethical responsibilities inherent in decision-making processes. The decision support system developed in this study enables more ethically conscious decisions to be made by making the outcomes of different policy options visible and comparable.

From the justice principle perspective, the consequences of antibiotic resistance are not distributed equally within society. Resistant infections often affect groups with limited access to healthcare or chronic diseases more severely. The developed decision support system allows for the analysis of policy impacts under different scenarios, enabling resource allocation to consider not only average outcomes but also the effects on different segments of society. This approach supports more equitable and needs-based decision-making in healthcare.

When evaluated within the framework of duty ethics, the fundamental responsibility of health authorities is to protect public health and ensure the continued availability of effective treatment options in the future. Limiting the excessive and inappropriate use of antibiotics is an important part of this responsibility.

The system supports decision-makers make decisions that set long-term social obligations ahead of immediate profits.

From an economic point of view, the system makes it possible to identify interventions that, given limited resources, will result in the greatest overall health benefit. Decisions intended to maximize health gains throughout society are supported by assessments based on QALY gains, prevented deaths, and cost-effectiveness indicators.

From a virtue ethics perspective, transparency, prudence and accountability come to the fore. The developed system enables reasoned decisions to be made instead of intuitive ones by presenting policy outcomes in a clear and traceable manner. This approach allows decision-makers to take an ethical stance that encompasses the reasoning and decision-making process in addition to the chosen ultimate outcomes.

Overall, this study shows that a system can offer a thorough and organized framework for assessing antimicrobial resistance policies from social, ethical, clinical, economic, and environmental viewpoints. The suggested system facilitates more transparent, consistent, and accountable decision-making under uncertainty by combining epidemiological modeling with cost-effectiveness analysis and scenario-based evaluation. The results show that successful AMR interventions should be evaluated in terms of their wider societal effects and ethical ramifications in addition to health outcomes and expenses. In this way, the suggested framework aids in the creation of health policies that are more ethically sound, evidence-based, and sustainable in the fight against antibiotic resistance.

REFERENCES

Angermueller, C., Pfreundschuh, M., & Stegle, O. (2022). Predicting antimicrobial resistance from bacterial genome sequences using machine learning. Nature Communications, 13(1), 2951. https://doi.org/10.1038/s41467-022-30684-0

Callahan, A. (2011, April 18). Resistance: What works? *WIRED*. https://www.wired.com/2011/04/resistance-what-works/

European Centre for Disease Prevention and Control. (2023). *Antimicrobial consumption in the EU/EEA (ESAC-Net) - Annual Epidemiological Report 2022*. Stockholm: ECDC. https://www.ecdc.europa.eu/sites/default/files/documents/AER-antimicrobial-consumption.pdf

European Centre for Disease Prevention and Control, & World Health Organization Regional Office for Europe. (2025). *Surveillance of antimicrobial resistance in Europe, 2024 data*. European Centre for Disease Prevention and Control. https://www.ecdc.europa.eu/sites/default/files/documents/antimicrobial-resistance-surveillance-Europe-2024-data.pdf

Ghani, A. C., Donnelly, C. A., & Ferguson, N. M. (2021). Pandemic policy modeling and assessment using individual-level simulation. *Clinical Infectious Diseases, 73*(Supplement_2), S174–S180. https://doi.org/10.1093/cid/ciab887

Hutton, D. W., Tan, D., So, S. K., & Brandeau, M. L. (2010). *Cost-effectiveness of screening and vaccinating Asian and Pacific Islander adults for hepatitis B*. Annals of Internal Medicine, 153(12), 796–808. 10.7326/0003-4819-147-7-200710020-00004

Khor, M. (2018). *Antimicrobial resistance: A global epidemic*. Third World Network.

Love, J. (2023, July 11). NHS doubles down on 'Netflix-style' antibiotic subscription model. *Pharmaceutical Technology*. https://www.pharmaceutical-technology.com/news/nhs-doubles-down-on-netflix-style-antibiotic-subscription-model/

McKenna, M. (2011, April 7). *World Health Day update: Use an antibiotic, pay a fee?* Wired. https://www.wired.com/2011/04/resistance-what-works/

Murray, C. J. L., Ikuta, K. S., Sharara, F., Swetschinski, L., Aguilar, G. R., Gray, A., ... & Hay, S. I. (2024). Global burden of bacterial antimicrobial resistance, 1990–2021, with projections to 2050: A systematic analysis. *The Lancet, 403*(10428), 1287–1308. https://doi.org/10.1016/S0140-6736(24)00043-5

OECD. (2023). *Embracing a One Health Framework to Fight Antimicrobial Resistance*. OECD Health Policy Studies. https://doi.org/10.1787/ce44c755-en

Paltiel, A. D., Schwartz, J. L., & Salzman, B. (2020). Clinical and economic effects of screening for pandemic influenza with rapid testing and antiviral treatment. *arXiv*. https://arxiv.org/abs/2007.06468

Pharmaceutical Technology. (2024, May 21). *NHS doubles down on Netflix-style antibiotic subscription model*. https://www.pharmaceutical-technology.com/news/nhs-doubles-down-on-netflix-style-antibiotic-subscription-model/

Ren, Y., Chakraborty, T., Doijad, S., Falgenhauer, L., Falgenhauer, J., Goesmann, A., ... & Heider, D. (2022). Prediction of antimicrobial resistance based on whole-genome sequencing and machine learning. *Bioinformatics, 38*(2), 325–334. https://doi.org/10.1093/bioinformatics/btab681

Rodrigues, L. C., Costa, P. M., & Monteiro, A. P. (2023). Influence of antibiotic consumption on the environment: A review and update. *Environmental Research, 231*, 116118. https://doi.org/10.1016/j.envres.2023.116118

Tang, Z., Yan, K., Sun, L., Zhan, W., & Liu, C. (2023). A microscopic pandemic simulator for pandemic forecasting using scalable million-agent deep reinforcement learning. *Proceedings of the AAAI Conference on Artificial Intelligence, 37*(11), 13341–13349. https://doi.org/10.1609/aaai.v37i11.26705

Zaric, G. S., Barnett, P. G., & Brandeau, M. L. (2000). *HIV transmission and the cost-effectiveness of methadone maintenance*. American Journal of Public Health, 90(7), 1100–1111. 10.2105/ajph.90.7.1100

Waksman, S. A. (1947). What is an antibiotic or an antibiotic substance? *Mycologia, 39*(5), 565–569. https://doi.org/10.2307/3755195

Wang, Y., Li, H., Zhao, C., Li, S., Yin, G., & Wang, H. (2023). Machine learning and feature extraction for rapid antimicrobial resistance prediction of *Acinetobacter baumannii* from whole-genome sequencing data. *Frontiers in Microbiology, 14*, 1320312. https://doi.org/10.3389/fmicb.2023.1320312

World Bank. (2017). *Drug-resistant infections: A threat to our economic future*. World Bank Group. https://documents.worldbank.org/en/publication/documents-reports/documentdetail/323311493396993758/drug-resistant-infections-a-threat-to-our-economic-future

World Health Organization. (2020). *Antimicrobial resistance*. https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance

CURRICULUM VITAE

Name Surname : **Aleyna Begüm Orman**

Place and Date of Birth : **Istanbul 03.06.2003**

E-Mail : **ormana21@itu.edu.tr**

EDUCATION :

- **B.Sc.** : 2026, Istanbul Technical University, Faculty of Business, Industrial Engineering

CURRICULUM VITAE

Name Surname **: Hasan Ali Özdemir**

Place and Date of Birth **: Balıkesir 21.08.2001**

E-Mail **: ozdemirha19@itu.edu.tr**

EDUCATION **:**

- **B.Sc.** **:** 2026, Istanbul Technical University, Faculty of Business, Industrial Engineering

CURRICULUM VITAE

Name Surname **: Ayça Kaya**

Place and Date of Birth **: Ankara 06.05.2002**

E-Mail **: kayaay20@itu.edu.tr**

EDUCATION **:**

- **B.Sc.** **:** 2026, Istanbul Technical University, Faculty of Business, Industrial Engineering