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Health-economic model for cost-effectiveness of diagnostics

A public health perspective

Deliverable 5.5

VALUE-Dx

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1. Introduction

1.1. Health technology assessment

As healthcare costs have been rising in the past decades[1], governments worldwide have come with measures to curb increasing costs. This led to the rise of the field of pharmaco-economics, a field that relates the costs of drugs to the clinical outcomes experienced by patients[2]. Although this field has its roots in the assessment of medication, this can be applied to all health technologies. These economic evaluations usually relate the costs associated with the implementation of a health technology to a generalizable patient outcome, such as quality-adjusted life years (QALYs). Increasingly, other factors have also received attention regarding the implementation of health technologies, such as patient preferences, organization of the healthcare system and ethics; all these factors that can either promote or restrain a new intervention from being implemented, are assessed in a Health Technology Assessment (HTA).

HTA has been defined as a multidisciplinary process that uses explicit methods to determine the value of a health technology at different points in its lifecycle, with the purpose to inform decision-making in order to promote an equitable, efficient and high-quality health system[3]. This is an interdisciplinary field which has increasingly become important in making decisions related to interventions in healthcare and ensuring a sustainable health system. Globally, there are many guidelines on how to perform an HTA; for Europe the HTA Core Model has been developed which covers nine domains[4].

Table 1 shows how these domains are relevant for the assessment of diagnostics. Through HTA, the use and reimbursement of tests in clinical practice can be evaluated. However, the HTA process for diagnostics has been lagging behind compared to, for example, the process for pharmaceuticals[5]. Diagnostics are more complex to assess as the clinical outcomes will depend on the treatment options following the test results.

Table 1 health technology assessment domains in relation to diagnostics (general domains adapted from Kristensen et al. [4])

Domain[4]	Test characteristics
Health problem and current use of technology	Explanation of disease related to the biomarker that should be detected
Description and technical characteristics	Use of the test (by a lab technician, clinician, or patient) and characteristics such as sensitivity and specificity
Safety	Safety of performing the test
Clinical effectiveness	The effects on patient outcomes
Costs and economic evaluation	The cost-effectiveness of the test
Ethical analysis	Ethical considerations can vary, depending on the disease area and group that should be tested
Organizational aspects	The full pathway from taking a test sample to communicating and acting on the test result
Patient and social aspects	Patient preferences related to the performed diagnostics, also in relation to their social environment
Legal aspects	Laws and regulations, such as the IVDR

IVDR: in-vitro diagnostics regulation

1.1.1. Generalizable outcomes

In most economic evaluations in healthcare, the costs of a new medical technology are compared to the clinical effects, usually expressed as QALYs. QALYs combine the length of life, i.e., life years gained, and the quality of life. The quality of life usually is between 1 and 0, ranging from perfect health to death. The most-used outcome in cost-effectiveness analyses (CEAs) is the incremental cost-effectiveness ratio (ICER), the costs divided by the clinical effects. The ICER can then be related to a willingness to pay (WTP), which varies between countries. A strength of these analyses is that the effects of the intervention can be extrapolated beyond the time horizon usually captured within a clinical trial. Short-term clinical outcomes, such as the disease duration and effectiveness of treatment, usually can be captured in clinical trials, while long-term outcomes, such as life years gained, can be captured in post-market surveillance, or extrapolated using health-economic methods. For this purpose, health-economic models, in which individual patients or patient cohorts are followed for a certain period, are used. The modelled follow-up period varies between countries; e.g., the Dutch guidelines recommend a lifetime horizon, where patients are simulated for the remainder of their life[6]. Various costs should be considered, of course the costs directly related to the intervention, but in some countries also productivity losses or costs accrued elsewhere in the healthcare system.

1.1.2. A new regulatory framework

To improve patient safety, two European regulations have been launched in recent years: the medical device regulation (MDR) and in-vitro diagnostics regulation (IVDR). Especially for products that are qualified as high-risk products, including diagnostic tests for severe diseases, stricter safety requirements for gaining market entry are implemented and post-market surveillance is required. Also, more elaborate evidence on the clinical effectiveness of these health technologies will be required[7]. Under the previous legislation, there was a focus on technical standards, for diagnostics this may concern the sensitivity and specificity of a test[8]. Under the new regulations, clinical data needs to be collected, meaning that the relevance to the patient of the test result needs to be assessed. Especially for high-risk devices, more data will be available on the effectiveness of new medical devices and in-vitro diagnostics. This all brings these devices more in line with regulations introduced for pharmaceutical products in the 1960s.

1.2. Health-economic considerations related to antimicrobial resistance

Governments worldwide have made it a priority to counter AMR, covered in the global action plan on AMR from the World Health Organization, covering five objectives[9]:

1| Improving the awareness and understanding of AMR, by educating the public from a young age, but also improving AMR-related education for professionals in healthcare and the veterinary sector.
2| Strengthening surveillance and research, including more epidemiological data on AMR, but also more economic research on the costs of AMR and cost-effectiveness of AMR-reducing interventions.
3| Reducing the number of infections, both in healthcare, in the community and in the veterinary sector, through infection prevention, education and vaccines.
4| Optimizing the use of antimicrobial medicines, by collecting more data on antibiotic use, introducing effective diagnostics and improving the rational use of antibiotics.
5| Developing an economic case for sustainable investment in new medicines, affordable diagnostics and vaccines, including analysing the costs of the burden of AMR.

Collaboration across disciplines is important to reach these goals: medicine, microbiology, economics, sociology and agriculture, but also, collaboration across governments, both locally and globally; and across the public and the private sector. Within the health sector, this translates to various stewardship models[10]. Antimicrobial stewardship entails a collaboration between physicians, pharmacists and microbiologists on appropriate and timely diagnostics, empirical therapy based on up-to-date local epidemiology and streamlined personalized therapy. In addition, infection prevention stewardship considers hygienic measures to prevent

the spread of resistant bacteria and surveillance. In healthcare settings, patients carrying a resistant bug should be identified in an early stage and isolated to protect other patients. Finally, diagnostic stewardship makes sure the right diagnostic is performed at the right time. Rapid diagnostics can enable a theragnostic approach for antibiotic prescriptions, where targeted antibiotics are prescribed to patients within hours. Containing the spread of resistant organisms, preventing the use of unnecessary antibiotics and more targeted antibiotic treatment are required to combat AMR, and in all these processes, microbiological tests play a vital role.

In economic terms, AMR can be regarded a negative externality associated with the consumption of antimicrobials[11,12]. When taking an antibiotic, patients (understandably) prioritize their own health as opposed to the long-term effects on society. For a clinician, it usually is more important to treat the currently-consulting patient than to prevent potential (and highly uncertain) health losses caused by AMR in the future. AMR is an interpersonal issue, as it affects not only the individual taking antibiotics, but also surrounding people[11]. In many ways, there is a similarity to the issue of climate change, where individuals responsible for carbon emissions do not bear the cost of climate change in the future[13]. Both AMR and climate change are global issues, where nations responsible for antibiotic consumption or carbon emissions may not be hit hardest by the outcomes. Both issues are also inter-generational in nature, as the potential effects of AMR and climate change are long-term problems[11].

1.2.1. Previous incorporation of antimicrobial resistance in health-economic analyses

In deliverable 5.1 of VALUE-Dx, we reviewed previously published literature related to health-economic diagnostics of infectious diseases and their inclusion of AMR. Of the 159 included articles, 29 included in the model the appearance of antimicrobial resistance, among them eight articles related to respiratory tract infection disease[14–21], another nine to tuberculosis specifically[22–30], and another two to influenza specifically[21,31].

In respiratory tract infections disease articles AMR was included into the model mainly modifying the cost per antibiotic prescription (applied to 5 of the 6 papers). Oppong *et al.*[32] Zang *et al.*[33] and Holmes *et al.*[15] added a fixed cost for every antibiotic prescribed. This cost was based on annual cost of resistance in USA ($55 billion), EU (€1.5 billion) and total global resistance over a 35-year period ($2.8 trillion annually). Thus, the calculations were simple as authors divided the previous costs by the annual number of prescriptions in each region. Schuetz *et al.*[18] and Stojanovic *et al.*[19] also followed this method but they calculated the daily costs of antibiotic resistance by dividing the cost per prescription by the average duration (number of days) of a typical antibiotic treatment. Similarly, Michaelidis *et al.*[16] assumed that the intrinsic value of an antibiotic prescription safely avoided would equal the

health care system cost of antibiotic resistant infections attributable to that antibiotic prescription. In pneumonia one article also paid attention to costs. In Ost *et al.*[34] authors consider antibiotic use and survival rate simultaneously. They use the number of antibiotic days per survivor to report ICER so antibiotic use was viewed as a cost (in terms of promoting antibiotic resistance). A drawback of these methods is that they imply to consider that the antibiotic prescription in ambulatory care is the main cause of resistance dissemination while in real practice it depends on several aspects. For instance, the World Health Assembly global action plan as described above outlines five objectives[35], only one of them is to optimize the use of antimicrobial medicines in animal health[36].

Another approach to introduce AMR into the model was decreasing the efficacy of the treatment as the rate of resistance increases. Balk *et al.*[14] decreased the efficacy of the antibiotic compared to placebo to simulate an increasing AMR to amoxicillin in a paper of respiratory tract infection. Recently, studies aimed at determining the incidence of infections with resistant bacteria are arising. In this sense, we have found a study that used prevalence data from European Centre for Disease Prevention and Control (ECDC) to determine the annual burden of infection with antibiotic-resistant bacteria[37].

Some tests can detect if the pathogen is resistant to any antibiotic so the treatment could be adjusted in advance. In Dinh *et al.*[38] tests can yield not only positive or negative results in terms of diagnosing community-acquired pneumonia but also it can perform a microbiological identification. If *S. pneumoniae* was found, the treatment prescribed had a narrowed spectrum, which can reduce the probability of AMR. Also, in two sepsis articles test can differentiate among *Staphylococcus.* Brown *et al.*[39] test can detect and differentiate between methicillin-susceptible and methicillin-*resistant S. aureus* and in Harrison *et al.* the model included an extra empiric therapy (vancomycin) for possible methicillin-resistant Staphylococcus aureus. Similarly, in Steuten *et al.*[40] the duration of the antibiotic treatment was calculated based on the level of concentration of a procalcitonin test.

Another approach to introduce AMR into the model is the need of prescribing a second treatment in case of failing first treatment. This was not found for papers looking into respiratory tract infections, but Rothberg *et al.*[41], analysed urinary tract infection diagnostics. In their analysis a patient may fail empiric antibiotic therapy either because of misdiagnosis or antibiotic resistance. In the latter case, an initial culture result confirms the diagnosis, allowing immediate treatment with another antibiotic. When resistance is low, few patients fail therapy. When resistance increased the percentage of patients failing empiric therapy increased, and more benefited from urine culture. They found that for patients with pyuria who failed therapy, it was best to immediately retreat with a quinolone, without waiting for a culture result. For strategies that did not include immediate retreatment, initial urine cultures for pyuria were much more cost-effective.

In an influenza related article, authors assumed a given rate of resistance in circulating influenza virus. Lavelle *et al.*[31] create a primary scenario in which prevalence of oseltamivir resistance was 29%. In the absence of any drug resistance, treatment would shorten the duration of uncomplicated influenza symptoms by 36 hours. For the proportion of children infected with a resistant virus, no clinical benefit from treatment will be received. Results found that testing maintains a more favourable cost-effective profile for a higher prevalence of oseltamivir-resistant viruses compared with the empiric treatment strategy. However, this approach can only consider one type of resistance (caused by the H275Y mutation).

All of the previous authors included AMR into the model based on different hypotheses, such as that AMR was only caused by human antibiotic prescription. In practice, national and international programs against the emergence of antibiotic resistance fight this phenomenon from the fields of human and veterinary health[35]. However, as indicated in the methodology of the deliverable 5.1, articles on animals were excluded. Also, it was considered that a reduction in antibiotic prescription had an equal-direct effect (i.e. one-on-one) to reduction of AMR. In reality, this consumption-resistance elasticity may not be linear (for example, it seems plausible that if the consumption of antibiotics is reduced by a certain amount thanks to the introduction of a RDT, the resistance will be reduced by a smaller proportion)[42].

1.3. Aims

In this deliverable, we describe a health-economic model that can be used to investigate the long-term effects of the implementation of diagnostics for community-acquired acute respiratory tract infections (CA-ARTI), from a public health and economic perspective. The aim is to go beyond the trial setting as described in Deliverable 5.4 and to consider the country-wide impact, with a focus on AMR.

ICERs and QALYs are important indicators adopted by payers to assess the value of novel health innovations. In our health-economic framework, we describe considerations that are specific for diagnostics to derive these indicators. We also aim to perform a detailed analysis on health state utilities and QALYs in the PRUDENCE trial that can inform future research in the field of CA-ARTI.

Finally, we aim to estimate the budget impact of the implementation of novel diagnostics that reduce antibiotic prescriptions, which may be relevant in the context of affordability of these diagnostics.

2. Health-economic framework for diagnostics

Over the past decades, policy makers in the healthcare sector have tried to control the rising costs of pharmaceuticals in different ways[43,44]. As one approach, value-based pricing of new drugs aims to maximize the health-related and economic outcomes given a pre-specified WTP: this has become a widespread method in many countries to assess the pricing and reimbursement of new pharmaceuticals entering the market[45,46]. In recent years, attention has expanded towards companion diagnostics for innovative treatments as well: highly specialized diagnostic tests paired to a specific drug in the context of what is labelled personalized medicine[47,48]. Personalized medicine entails that drugs are targeted more to specific patient subgroups, with the aim of reducing the uncertainty of whether the drug will be effective before administration and correspondingly improve cost effectiveness of the drug considered.

Diagnostic tests are used more widely in modern medicine than just as companion diagnostics, and often in less well-defined populations. Examples include C-reactive protein (CRP) tests to check whether a patient with cough has a viral or bacterial infection, an International Normalized Ratio (INR) test to diagnose bleeding disorders or an HbA1c test for diabetes. Many national pharmacoeconomic guidelines nowadays also consider the assessment of non-pharmaceuticals, such as diagnostics, although in practice, these analyses are not as common[49]. There is limited evidence on pricing and reimbursement policies of diagnostics[50,51]. Deliverable 5.2, on pricing and reimbursement policies related to diagnostics in various European countries, concluded that health technology assessment is rarely used for diagnostics[50]. We believe the role of cost-effectiveness of diagnostic methods will increase in the coming years, but with that, certain challenges will arise.

Compared to pharmaceuticals, for which the market entry regulations are well established for various jurisdictions[44], the evidence for diagnostics, and medical devices in general, is very limited[50]. With the introduction of the IVDR (see also section 1.1.2) IVD companies will need to collect more data on the technical and clinical performance of new devices before market entry and also increase post-market surveillance[52]. Consistent and high-quality data will provide healthcare professionals and policy makers with more tools to assess the safety and effectiveness of new IVDs in clinical practice. We expect this will also lead to an increase in cost-effectiveness analyses (CEA) of these devices. Diagnostics are not limited to IVDs; software or devices used for the diagnosis of a disease fall under the EU regulation on medical devices (MDR)[53] which is very similar[52]. An example for this would be a smartphone app used by clinicians to determine the most likely disease and optimal treatment, based on a patient's symptoms.

Compared to pharmaceuticals there are major differences when assessing the clinical value of a diagnostic strategy. The accuracy (i.e. sensitivity and specificity) of a diagnostic needs to be adequate, but more important for its cost-effectiveness is the clinical utility[54]. The added value of the diagnostic in clinical practice will depend on the background incidence in the population that is tested, affecting metrics such as false positives and negatives. Additionally, it is important to consider how the diagnostic can be combined with other tests in diagnostic algorithms, either sequentially or simultaneously[55]. Finally, while pharmaceuticals directly influence patient outcomes, most diagnostics do not[55,56]; hence, the cost-effectiveness of a diagnostic is highly dependent on the cost-effectiveness of the treatment that follows and any lifestyle changes a patient may make. For example, a relatively expensive test to inform the prescribing of inexpensive treatment, as is often the case with antibiotics, has a negative effect on the cost-effectiveness. Additionally, screening for resistant bacteria may seem even worse considering the cost-effectiveness: many patients carrying a resistant bacterium do not experience any negative effect, but if a resistant bug is found in a hospitalized patient, this patient needs to be placed in costly patient isolation[57].

For an overview of some important determinants of the cost-effectiveness of diagnostics, see Figure 1.

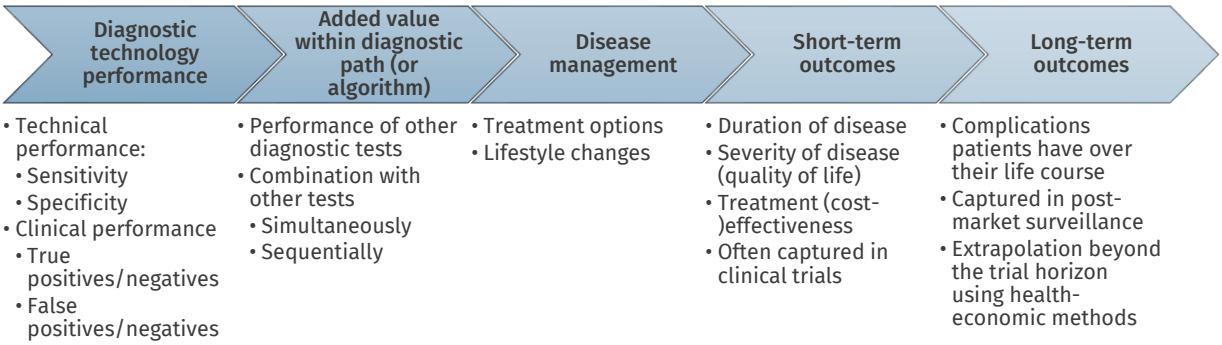


Figure 1 determinants of cost-effectiveness of diagnostics

2.1. Testing patients: a definition of diagnostics

The word “diagnostics” is often used interchangeably with the word “tests”. For health-economic analyses, it is important to make the distinction between various types of tests used for individual patients: screening, diagnosing and monitoring. Although similar or identical tests may be used for each of the strategies, the

decision problem related to the various strategies are quite different, hence each strategy presents unique challenges when designing a CEA.

2.1.1. Screening

Screening tests are applied to a broad population, for example screening all school-going children for growth defects, breast cancer screening for all women from the age of 50 or screening all patients for vancomycin-resistant *Enterococcus* on the gastroenterology ward. The aim is to find disease in a defined population, in people without, or unaware of, symptoms[58]. Especially for diseases with better outcomes if treatment is started at an early stage, screening can be beneficial. A common example is cardiovascular risk management, which aims to place patients in a risk category based on a combination characteristics, such as sex, age and smoking behaviour, and simple diagnostic tests: blood pressure and cholesterol tests[59]. Lifestyle advice and treatment to lower cholesterol levels and blood pressure are aimed to prevent, among others, future cardiovascular disease, diabetes and chronic obstructive pulmonary disease (COPD).

2.1.2. Diagnosing

With diagnostics the aim is to identify the most likely cause of, and optionally optimal treatment for, a previously undetected disease in a clinically-suspect patients who is seeking care[60,61]. This concerns patients that experience complaints and consult a clinician who can hopefully prescribe a cure. This could be a person with a persistent cough, or a patient with shortness of breath after exercise. In the Netherlands and other countries where the general practitioner (GP) acts as a gatekeeper to the health system, the GP has an important role in determining whether a patient requires immediate treatment, should be referred to specialist care, or can wait for the complaints to fade without treatment. Next to clinical experience, GPs can use clinical rules and diagnostic tests to aid in this decision process. An example of a test commonly used to diagnose patients is a C-reactive protein (CRP) test, which can be used in the GP office for patients consulting for respiratory complaints. The CRP test can be used to discriminate between a viral and a bacterial infection and can inform the GP and patient on the decision to prescribe an antibiotic. An example of a clinical score, is a scoring system for deep-vein thrombosis (DVT) developed by Wells *et al.*, during clinical assessment, patients can be stratified in three risk categories during clinical assessment: low, moderate and high[62]. Patients in the high-risk group have an 85% risk of DVT, compared to 5% for the low-risk group. In the case of personalized medicine, having diagnosed a disease may not be sufficient to initiate treatment; especially if the treatment can cause severe adverse reactions or is very expensive, as is often the case in oncology for example. Companion diagnostics are used to predict whether a specific treatment option will be beneficial for an individual patient[47]. For example, a test to check whether a mutation is present in a tumour so that this can be targeted by antibody treatment.

2.1.3. Monitoring

Finally, there is monitoring, where a patient is tested periodically to assess a certain biomarker. A classic example is the monitoring of blood glucose levels for diabetes patients or international normalized ratios (INR) for patients on anticoagulation therapy. An extreme example would be a patient admitted to the intensive care unit, who is monitored for countless vital signs. As many diseases are chronic in nature, monitoring systems are important in treatment optimization and disease management[63].

2.2. Recommendations for the design and reporting of diagnostics

Our work within and outside the VALUE-Dx consortium has allowed us to identify specific gaps in the design and reporting of health-economic analyses of diagnostics[64]. This has led us to draft recommendations linked to best practices in the field. Already, excellent recommendations are available to aid in the design and reporting of economic evaluations. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement is a collection of 24 recommendations aiding in the reporting on methods and results of economic analyses for interventions in healthcare[65]. CHEERS is not tailored to any specific intervention and can be used for preventive measures, diagnostics and treatment[65]. The International Decision Support Initiative's reference case for economic evaluation provides eleven principles to guide the conduct and reporting of economic evaluations to improve their methodological quality and transferability[66]. The methodological specifications relate to the health outcomes used, the estimation of costs and transparency, among others.

However, due to their broad scope, these recommendations do not provide specific guidance for diagnostic strategies. We link this diagnostic-specific guidance to the related items of the more general CHEERS statement and the reference case[65,66], to enable other researchers to use this guidance in addition to the already available recommendations.

2.2.1. Overview of recommendations

An overview of our recommendations is displayed in Table 1, including related CHEERS recommendations[65] and specifications from the reference case for economic evaluations[66]. The recommendations are explained in more detail below.

Table 2 recommendations for CEAs of diagnostics, including direct quotations of relevant CHEERS recommendations[65] and reference case specifications[66]

Topic	CHEERS recommendation[65]	Reference case specification[66]	Diagnostic-specific recommendation	Relates to
Target population	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	The decision problem must be fully and accurately described.	Specify the target population of the test, including the symptoms patients experience and other relevant determinants which may influence the clinician when diagnosing patients. Clearly state whether the aim of the intervention is to screen, diagnose or monitor patients.	Reporting
Setting and location	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	The decision problem must be fully and accurately described.	Specify the clinical setting in which the clinician operates, and where the diagnostic test is performed. Factors impacting the decision for patients to seek care and factors influencing the disease prevalence are important aspects that may influence the cost-effectiveness of a diagnostic. The location where the diagnostic is performed may impact the costs and time to obtain a test result and subsequently its value within the diagnostic pathway.	Reporting
Comparators	Describe the interventions or strategies being	Current practice in context of decision problem to serve as comparator in the analysis.	Specify the diagnostic algorithm, including clinicians' decision processes (decision to perform the	Reporting

Topic	CHEERS recommendation[65]	Reference case specification[66]	Diagnostic-specific recommendation	Relates to
	compared and state why they were chosen.	Best supportive, noninterventional care in context of decision problem should be explored as comparator as additional analysis.	test), the diagnostic tests (including brand, type and frequency), and the relevant treatment options (the outcome of the diagnostic algorithm).	
Time horizon	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Lifetime time horizon should be used in first instance. A shorter time horizon may be used when shown that all relevant costs and effects are captured.	The assessed time horizon should be similar to the time horizon over which costs and consequences of treatment following the diagnostic process are typically evaluated.	Design
Choice of health outcomes	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Methodological choices include either DALYs averted or QALYs gained.	Include either QALYs or DALYs when assessing the cost-effectiveness of diagnostics. However, depending on the diagnostic technique and disease, other outcomes may be relevant to assess the value of the assessed diagnostic algorithm (e.g., adherence-improving factors, insurance value or real options value).	Design
Estimating resources and costs	Describe approaches and data sources used to estimate resource use associated with model health states.	Estimates should reflect the resource use and unit costs/prices that may be expected if the intervention is rolled out to the population	Consider the economy (or diseconomy) of scale related to collecting, transporting and performing more (or fewer) tests on the same equipment, as opposed to a fixed price per test.	Design

Topic	CHEERS recommendation[65]	Reference case specification[66]	Diagnostic-specific recommendation	Relates to
	Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.*	defined in the decision problem. Analysis should include estimation of changes in cost estimates due to economies (or diseconomies) of scale.		
Incremental costs and outcomes	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	No specification	Use an efficiency frontier to visualize the incremental costs and outcomes of the different strategies, if several diagnostic algorithms are assessed simultaneously.	Reporting
Affordability and reimbursement	No recommendation	Costs of all resource implications relevant to the decision problem, including donated inputs and out-of-pocket inputs from individuals.	Define the perspective of the economic evaluation and identify which payers are included in the budget impact analysis. Calculate the budget impact of implementing the assessed diagnostic algorithm within the overall clinical care pathway and	Design

Topic	CHEERS recommendation[65]	Reference case specification[66]	Diagnostic-specific recommendation	Relates to
		Budget impact analysis should estimate the implications of implementing the intervention on various budgets. Equity implications should be considered at all stages of the evaluation, including design, analysis, and reporting.	consider setting-specific reimbursement regulations	

**: for model-based economic evaluations, Husereau et al. also provide a separate recommendation for single study-based economic evaluations*

CEA: Cost-Effectiveness Analysis; CHEERS: The Consolidated Health Economic Evaluation Reporting Standards; DALY: Disability-Adjusted Life Year; QALY: Quality-Adjusted Life Year

2.2.2. Target population

A common way to specify a certain population in the medical field is to identify patients having a specific disease: for example, heart failure patients or patients with neuroendocrine tumours. Especially in clinical trials, these specifications often are extended with patient characteristics such as age and comorbidities or with ranges of disease-specific biomarkers. When diagnosing a patient, a specific disease often is not yet known, however, the symptoms are. These specific symptoms will influence the clinician's decision to request additional diagnostic tests or use point-of-care (POC) diagnostics. Other determinants a clinician may use in deciding to use certain diagnostics include age, comorbidities and, if available, vaccination status.

Therefore, when specifying the target population of a diagnostic intervention, it is highly important to specify the symptoms patients have and other relevant determinants which may influence the clinician's decision to continue diagnosing a patient. Additionally, it should be clear whether the patient population is screened, diagnosed, or monitored. However, this may be more difficult in the case of genomic tests, with potential spillover effects to relatives, where the population of interest is broader than just the patient tested[67]: the diagnosis of one patient may lead to the screening of family members or inform reproductive planning.

2.2.3. Setting and location

Linked to the target population are the setting and location. Populations presenting in primary care are different from patients who are referred to hospital care, who are different from patients admitted to the intensive care unit. In a healthcare system where the general practitioner (GP) has a gate-keeping role, a decision based on clinical experience to refer a patient to a hospital, without performing any test, already should be regarded as a diagnostic intervention. The probability of having a disease will be higher in the hospital setting, considering the GP does not refer everyone and does not refer at random. Not all health systems rely on the gate-keeping role of the GP[68] and also factors for patients seeking care differ culturally[69]. These factors will have an influence on the prevalence and severity of diseases at different settings within the healthcare sector. Hence, this context is important to include when describing the setting in which diagnostic tests are performed.

Currently, the majority of clinical tests are performed in hospitals and diagnostic laboratories, although the exact setting varies between countries[70]. In some countries, centralized, external laboratories have focussed on scale: by improving efficiency, the costs per test can be reduced. Although the large-scale laboratories place the tests further away from patients, there is also an opposite trend: point-of-care (POC) tests and self-tests bring the tests closer. These tests can provide information on the cause of disease or the effectiveness of medication within

minutes and immediately inform the shared decision-making process of the clinician and patient. This knowledge can lead to improved treatment decisions and also to better adherence[63]. Although these POC tests are more expensive than the equivalent tests performed in large-scale laboratories, these patient-level improvements may make them a worthwhile investment: to make this decision, health technology assessment (HTA) can play an important role. Clearly specifying the location of sample collection and analysis is important, especially when a CEA compares different tests at different locations. This may be especially relevant for low- and middle-income countries, where logistics can be more challenging. Although POC tests may be relatively expensive compared to tests analysed in large-scale laboratories[63], having a test result available during a consult can more directly influence a clinician's decision on prescribing treatment and enables the clinician to use the information when communicating with the patient[54].

2.2.4. Comparators

The strategies being compared in the CEA should be clearly described[65]. While it may be convenient to think about comparing different, individual tests in the context of CEAs of diagnostics, it may be more fitting to compare different diagnostic algorithms. A diagnostic cannot be regarded in isolation. If we consider a single diagnostic test, the diagnostic algorithm already contains three steps. First the clinician decides to perform the test, which is influenced by guidelines and the clinician's experience; then there is the diagnostic itself, which may present a binary result, i.e. positive or negative, but also a quantitative result, an image or a recommendation; the final step is the interpretation of this result by the clinician and/or the patient, which may result in a decision to make lifestyle changes, to start treatment or continue with other diagnostics. Different diagnostics can be added, either simultaneously or sequentially, based on the results of prior tests. There may also be differences in the implementation of the algorithm in clinical practice, e.g., the implementation in clinical decision support software. Eventually, a diagnostic algorithm should lead to determining the most-likely cause of a patient's symptoms and aid in identifying the most suitable treatment. These types of algorithms are already very common in economic analyses, where they translate into decision tree models[61,71,72]. For diagnostic algorithms that include many different outcomes, i.e., a decision tree branching out to hundreds of outcomes, simplifications may be warranted or more flexible modelling approaches can be considered [73].

We highly recommend specifying these algorithms very clearly in any economic analysis of a diagnostic strategy. Even when comparing a switch from one diagnostic test to another, the algorithm in which the test operates may have a major impact. The decisions made and information gathered before performing the test influences the prior probabilities of obtaining a positive or negative test result. For diagnostic algorithms that are more expensive than the comparator, the eventual cost-effectiveness is determined by to what extent the information gathered can improve patient outcomes, i.e., whether the information leads to more tailored treatment.

2.2.5. Time horizon

Many economic evaluations of diagnostics primarily use the algorithm or decision tree to model the health-economic outcomes, as specified above. However, this may lead to challenges in assessing the long-term clinical outcomes for patients as these cannot be modelled explicitly. Generally, a lifetime horizon should be used[66], however, there could be reasons to have a shorter time horizon, but they should cover all relevant costs and outcomes. Economic analyses only assessing a time horizon as long as the diagnostic process, as seen rather frequently in literature[61], will in most cases not cover all relevant costs and outcomes. The time horizon should be similar to the time horizon over which costs and consequences of treatment following the diagnostic process are typically evaluated.

An additional factor to consider for economic evaluations of diagnostics, is the time to correct diagnosis. A faster diagnostic algorithm may result in time reductions for patients, clinicians or laboratory technicians, leading to a more efficient decision-making process[54]. In case of infectious disease, faster diagnosis may reduce the transmission of a disease, a factor generally considered to be an important aspect of value in health care (fear and risk of contagion)[74].

Combining very short-term (time to correct diagnosis) and long-term modelling (a lifetime time horizon) may lead to rather complex models for economic assessments of diagnostics , such as a combination of a discrete-event simulation and a transmission model to model tuberculosis diagnostics in Tanzania[75]. Depending on clinical perspectives, but also on data availability, it may be feasible to focus on only short- or long-term modelling. This decision process should be reported in a transparent manner.

2.2.6. Choice of health outcomes

Quality- or disability adjusted life years (QALYs and DALYs) generally are the preferred outcomes for economic analyses [66]. Possibly due to the relatively many studies in the field of diagnostics with a short time horizon, authors commonly focus on rather short-term outcomes other than QALYs and DALYs[61,76,77]. Examples are outcomes based on the technical performance of the test (e.g. proportion of correct diagnoses) or the treatment decision (e.g. antibiotics prescribed)[61]. As stated in the introduction, IVD companies will be required to gather more information on the clinically relevant outcomes of novel diagnostics[78], which presents an opportunity to include utility-based outcomes as well. This is not to say that other outcome measures are not relevant; we believe they are.

Other elements of value of particular interest to diagnostics are reduction of uncertainty due to a new diagnostic, adherence-improving factors, fear of contagion (already described above), insurance value and real options value[74]. The reduction of uncertainty is relevant for both payers, as it reduces the uncertainty of the effectiveness of reimbursed care, and for patients and providers, as it may lead to more informed treatment decisions. This may also lead to increased

adherence to treatment. There are several elements of value for diagnostics that may not only benefit the individual patient and have broader societal advantages. The fear of contagion is already described above, closely related to this is the insurance value, which may relate to the risk of an individual to become sick[74]. For hereditary diseases, the results of diagnosing one patient may affect family members[67] and for infectious diseases the data gathered by diagnosing one group of patients may inform empiric treatment for another group of patients[79]. Finally, real options value is relevant for infectious disease where resistance may occur. Prescribing treatment provides a risk that the treatment will be less effective in the future; simultaneously, it is uncertain that novel treatment options will be developed in the future. A diagnostic, which increases the adequacy of prescriptions, can decrease the probability of untreatable, resistant infections in the future[80]. Discussions on how to include these other, still novel, elements of value are ongoing and will depend on factors such as the disease area covered and health system assessed[67,74]. Continuing this discussion with all stakeholders, including policy makers, clinicians and patients, is important, as well as experimentation with novel methods in the field of CEAs. For some diseases with limited data on the effectiveness of treatment, such as genomic tests used for rare genetic disorders, it may be challenging to perform a CEA[67]. In these cases multi-criteria decision analysis may be a feasible alternative[81].

2.2.7. Estimating resources and costs

For CEAs in general, the included costs depend on the perspective used and the decision problem analysed. Depending on the perspective used, diagnostic and subsequent treatment costs may be included differently or even not be considered at all. For diagnostics, the costs are of particular interest as there may be more flexibility as compared to most drugs. The whole chain from collecting the patient sample to the reporting of the result will impact the eventual cost of the diagnostic. While large volumes of tests performed in laboratories will be relatively inexpensive, a POC test performed by the GP may yield more diagnostic value, i.e., the test can immediately influence the clinical decision. The following costs will be relevant for a CEA assessing a novel diagnostic:

- Diagnostic sample collection costs (including personnel, reagent and material cost);
- Transport costs (if the test is not performed at POC);
- Costs of performing the test (including personnel, reagent, materials and depreciation costs);
- Costs associated with reporting the test result to the clinician and/or the patient and, if applicable, changing the clinical decision.

How precise test-related costs should be estimated depends on the perspective and decision problem, micro-costing will not always be useful or feasible[72]. However, using a fixed price per diagnostic test may underestimate the scale benefits associated with performing more tests using the same equipment [82]. Sensitivity analyses to assess the impact of various assumptions to the economies

(and diseconomies) of scale related to performing more (or fewer) tests should be considered and should be consistent with the evaluated setting and populations, including any health system factors that may limit scale-up. For tests that can be used to diagnose various diseases (i.e., are part of several diagnostic algorithms, with patients experiencing different symptoms), these scale advantages should also be considered.

2.2.8. Incremental costs and outcomes

It is common to compare various diagnostic algorithms simultaneously within a CEA[61], as explained above. The different algorithms may contain different diagnostic techniques but may also be performed in different sequences or at different locations (e.g., at POC or in a laboratory). Clearly presenting the differences in incremental costs and outcomes is important. A common graphical method to present the incremental costs and outcomes of a various algorithms is an efficiency or cost-effectiveness frontier[75,83,84]. This may be more easily interpretable than only providing a table of the results. An added benefit is that the efficiency frontier can be used to draw conclusions about the cost-effectiveness in the absence of a WTP threshold, as described elsewhere[85].

2.2.9. Affordability and reimbursement

Factors outside of the direct scope of a CEA, but very relevant for its context, are the affordability and reimbursement of diagnostic interventions. The budget impact was seldom included in CEAs of diagnostics[61]; however, we believe this may provide important information regarding the affordability[86]. Especially if the current standard-of-care is based on clinical expertise, a new diagnostic test may greatly increase the total costs and may have a major budget impact. This is particularly relevant for low- and middle-income countries (LMICs), where resource constraints are more prevalent than in high-income countries. An additional constraint in LMICs may be the availability of skilled personnel to perform and operate new diagnostic tests[66].

In general, the perspective of the budget impact analysis is important, also in relation to the reimbursement of the various diagnostics considered and the payers involved: can health-care providers claim the diagnostic costs, should they pay for it themselves or should a patient pay a fee? Additionally, it is relevant whether the diagnostic test is funded out of the same budget as subsequent treatment. This does not directly influence the cost-effectiveness, but it will probably affect the implementation and uptake of a novel diagnostic test: e.g., a very cost-effective test for which the patient has to pay, may have a lower uptake than a test which is provided free of charge (i.e., paid for by the health system). These factors can be explored in the discussion of an economic analysis of a novel diagnostic.

2.2.10. Concluding remarks

These diagnostic-specific recommendations are not meant to supplant the CHEERS recommendations or reference case for economic evaluations but may provide useful additions when designing and reporting CEAs of diagnostics. Although we based these recommendations on an extensive review of the literature as described in deliverable 5.1, they were not developed or validated through a formal process, such as a Delphi process. Although we expect the issues raised in the paper to be generalizable to diagnostics for all disease areas, some issues relevant for specific disease areas may not have been included. However, this research could be used as a starting point for a follow-up project to further develop diagnostic-specific guidelines or a reference case for diagnostic CEAs.

3. Proposed health-economic model for VALUE-Dx trials

3.1. Overview model

MERIAM (Modelling the Economics of Respiratory tract Infections and AMr) is a model built to assess the long-term health-economic effects of improved diagnostics for community-acquired acute respiratory tract infections at the first point of care. MERIAM, see overview in Figure 2, has three modules:

- the demographic module, used to model the population over a long time horizon
- the consultation module, used to model patients going to care with an acute respiratory tract infection
- the AMR forecasting module, used to forecast AMR levels.

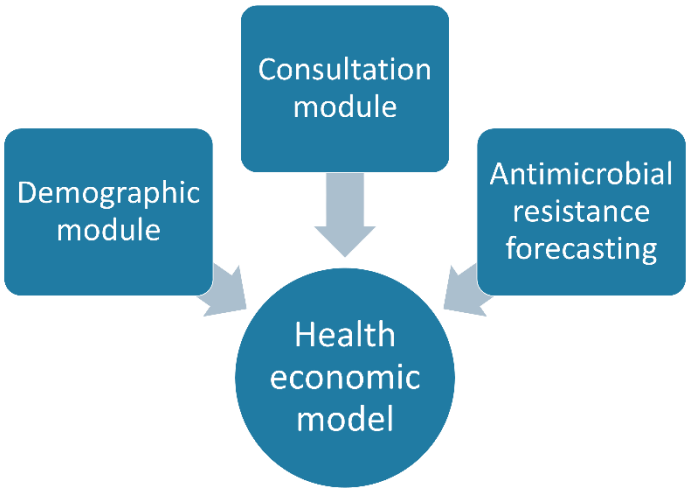


Figure 2 overview of MERIAM

The demographic module contains a representative sample of the modelled country. The consultation model uses incidence data to simulate the care-seeking behaviour for community-acquired respiratory tract infections of a subset of individuals from the demographic model and their outcomes, including diagnostics, costs and antibiotic consumption. The AMR module uses antibiotic consumption data to forecast AMR levels.

3.2. Demographic module

Within the model, individuals are simulated, i.e., the model can be considered agent-based. Populations are based on demographic data from Eurostat mainly incorporating age and sex and can be made as large as needed for the analysis.

3.2.1. Annual demographic changes

Every year the population is updated to reflect the Eurostat projections, here we use model cycles of one year. The following is included:

- Mortality
- Ageing
- Fertility
- Migration

The assumption is made that the population changes are made on January 1, improving the efficiency of the modelling approach.

Mortality
Mortality is based on the Eurostat mortality probability projections. The mortality probability is sampled for all individuals alive. A major assumption in the model is that all individuals aged over 99 are excluded: we do not include centennials in the model.

Ageing
Ageing is straightforward in that it increases the age with 1 every year.

Fertility
Data on births are used from the Eurostat population projections. The number of babies born is related to the population aged 15-45.

Migration
The model accounts for migration by using the Eurostat projections. The Eurostat projections provide total numbers of immigration (positive number) and emigration (negative number). In MERIAM this is related to the total population and converted to a rate. This rate is then used to calculate the total number of immigrants and emigrants. This basically assumes that both immigration and emigration increase when the population size increases.

Data sources
For countries within the European Union, the Eurostat[87] data sources used are displayed in Table 3. For the United Kingdom, the population projection data from the Office for National Statistics are used.

Table 3 main data sources demographic module for Eurostat

Data	Used for	ID
Population projections	Population, sex, age, fertility	proj_23np
Migration rates	Migration	proj_23nanmig
Mortality rates	Mortality	proj_23naasmr

3.3. Consultation module

Each week, a subset of nodes will seek care. These nodes are selected based on real-world incidence data.

3.3.1. Incidence

To estimate the number of individuals entering the consultation module, a country-specific number of new cases with cough or sore throat is needed. Incidence data from the European Surveillance System (TESSy) of the European Centre for Disease Control (ECDC) was found to be the best available source. Data was requested for the period 2010 to 2023 and contained incidence of acute respiratory infections (ARI) and Influenza-like-Illness (ILI) from countries within the European Economic Area (EEA)(n=27). Data was aggregated by week.

Data cleansing and analysis of incidence were performed using R. Data from two countries were excluded from the original dataset: Cyprus, Finland, Luxembourg, and Malta. The denominator values of Cyprus and Finland fluctuated unreasonably high. The data of Luxembourg and Malta were deemed not representative to the rest of countries within the EU/EEA, due to very low denominator values. Weekly incidence of ARI and ILI were calculated per 100,000 population to enable comparison across countries. This resulted in prepared datasets with ARI and ILI incidence grouped by country, season (splitting at ISO week 35), and age group (ages 0-4, 5-14, 15-64, 65 and older). Only countries with data available for the full season were included. Seasons during the COVID-19 pandemic (2019-2020, 2020-2021, and 2021-2022) were excluded. Incidence was converted into an incidence object and modelled using the Incidence package [88]. To be able to identify the influenza season, two exponential models will be created for each season: one where the number of cases increases over time and one where the number of cases decreases. In this way an annual peak is created and the influenza season can be determined using a consensual threshold value.

Index consultation

During the index consultation, a clinician will perform tests, prescribe antibiotics etc. on the individuals seeking care. For all nodes seeking care (as described above), tests and antibiotic prescriptions are sampled.

As far as the tests are not part of the intervention (in the CRP testing scenario, everyone received a CRP test), they are sampled using the PPAS data[89].

Antibiotics are also sampled using the PPAS data: the proportion of antibiotic prescriptions is stratified by age (two categories: younger than 60 and 60 and older).

3.3.2. Consultation decision tree

Model structure

A decision tree was developed to model the patient journey as per the clinical algorithm of PRUDENCE. Figure 3 provides a schematic overview of the decision tree. All patients present with CA-ARTI and are classified as having a positive COVID-test or a negative COVID-test. In case of a positive COVID-test, patients will follow Standard-of-Care or will be tested with an Afinion CRP test. Subsequently, the decision on the treatment with or without antibiotics will be made by the GP. In case the patient had a negative COVID test, a distinction was made between in and out flu season. Subsequently, patients' main symptom results in a further segregation between cough and sore throat. For each of the resulting branches, different point-of-care diagnostic tests were applied. In all cases, patients could receive standard-of-care which could include tests performed as part of standard clinical procedures. In case of cough during the flu season, patients were tested with the Afinion CRP test or the Veritor influenza A/B test. In case of sore throat, patients were tested with Veritor Total which includes an influenza A/B test and/or a Group A streptococcus (GAS) test (decided by the GP). Outside the influenza season, patients with cough were tested with the Afinion CRP test. Patients with a sore throat were tested with a Veritor GAS test. Each branch ended with the decision to prescribe antibiotics or not. Subsequently, patients continued to the post consultation Markov model (refer to section 4.4.3 for more details).

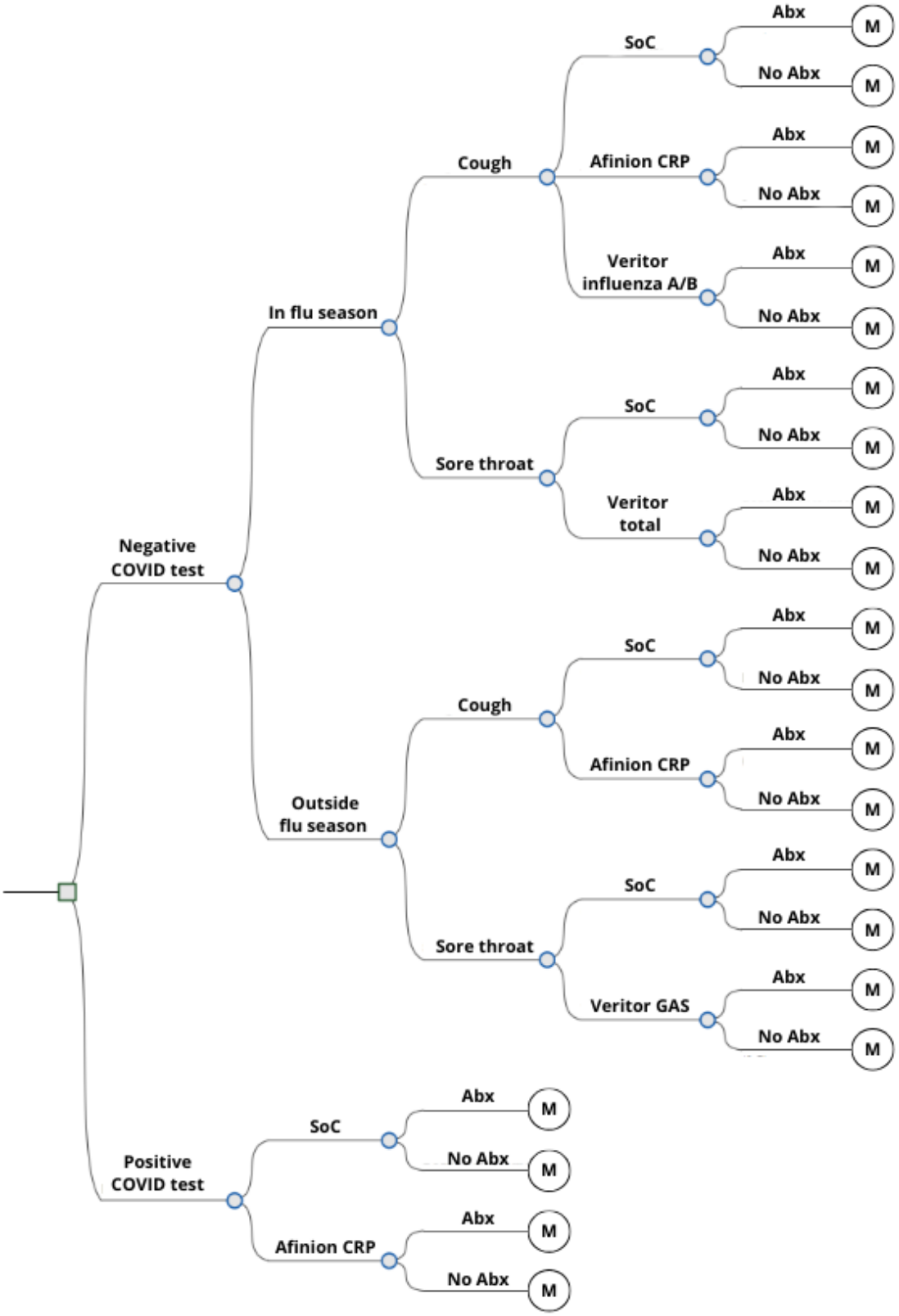


Figure 3 Decision-tree model

3.3.3. Input parameters

Costs

The costs that were considered within the decision tree include the cost of the point-of-care diagnostics, any additional diagnostics performed at the same encounter, costs of antibiotics and costs of other drugs prescribed by the GP. The frequency of additional diagnostic performed, type of antibiotic prescribed and frequency of other medication prescribed were based on the PRUDENCE trial and were multiplied by the costs as per Table 4. The cost values in Table 4 were sourced from publicly available sources in Spain and the United-Kingdom and translated to International Dollars using the Purchasing Power Parities (PPP).

Table 4 Model cost parameters

Cost parameter	United-Kingdom (£)	Spain (€)
Test cost		
CRP test	5.5	8
Influenza test	9	9
Group A streptococcus test	5	5
COVID test	10	10
Drug cost (per regimen)		
Tetracycline	6.22	5.11
Narrow spectrum	2.39	6.61
Broad spectrum	2.05	3.93
Coamoxiclav	2.98	8.03
Macrolide	7.79	6.69
Quinolone	9.38	10.48
Cephalosporin	12.07	12.59
Other antibiotics	8.15	10
Inhalation medication	12.56	17.48
Antiviral drug	10	10.4
Antihistamines	2.29	3.51
Paracetamol	0.45	1.6
Cough suppressor	3.91	1.8
Other medication	9.03	10

Probability

For each sub-branch, a direct comparison was made, which means that patients in the same branch were compared. As such, patients with a negative Covid test, within the influenza season with cough were compared when receiving Standard of Care vs Afinion CRP or Standard of Care vs. Veritor influenza A/B. A similar approach was taken for the other branches.

As a result, the only probability that impacted the result was the probability of prescribing antibiotics. The probability of a positive covid test, the probability of being in the influenza season and the probability of having cough as a main

symptom were only used to inform the total impact of applying diagnostics vs. following standard of care. In table 5, an overview is provided of the branch specific probabilities.

Table 5 Branch specific probabilities for prescribing antibiotics.

COVID status	Main symptom	Influenza season?	Arm	Probability of prescribing antibiotics
FALSE	Sore throat	No	SoC	0.565
			Group A streptococcus test	0.552
		Yes	SoC	0.456
			Group A streptococcus test + Influenza test	0.402
	Cough	No	SoC	0.482
			CRP test	0.466
		Yes	SoC	0.436
			CRP test	0.478
			Influenza test	0.437
TRUE			SoC	0.237
			CRP test	0.238

Abbreviations: CRP = C-reactive protein; SoC = Standard-of-Care

Outcome parameters

The primary model outcome measures include:

- Total cost
- Percentage point reduction in antibiotic prescriptions
- The cost per percentage point reduction in antibiotic prescription.

3.3.4. Post-consultation follow-up

Model overview

For the post-consultation follow-up, a Markov model was developed consisting of the health states “sick” and “healthy”. Patients could transition from the “sick” to the “healthy” health state on a daily basis (one day cycle length) over a maximum of 28 days (28 day time horizon). The “Healthy” health state was considered an absorbing health state, patients could not get sick again within the 28 day time horizon after they became healthy.

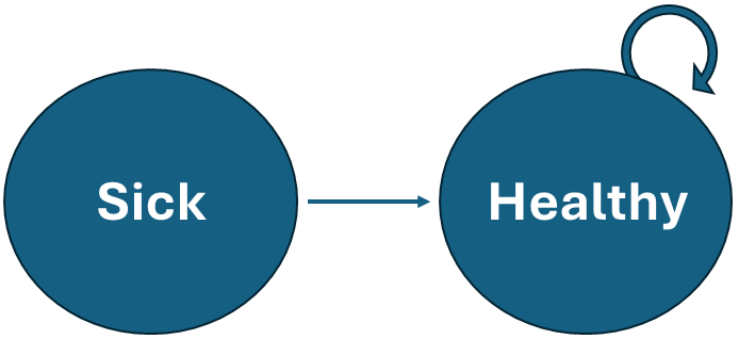


Figure 4 Post-consultation Markov model.

Due to the short time horizon, discounting of costs and effects were not applicable.

Cost and effects

The input parameters for the post-consultation model included resource costs (visit of GP, pharmacy, paediatrician, A&E, specialist or out of hours service, hospital day, ICU day), societal costs (work hours missed, hours spend on caregiving, over the counter drug costs, out-of-pocket costs for childcare) travel costs and quality of life expressed in QALY. An overview of the cost parameters is provided in Table 6. The ratio of the cost parameter per health state are sourced from the PRUDENCE trial and calculated as an overall average for all participating countries together.

Table 6 Overview of cost parameters used in the Markov model.

Cost parameter	**United-Kingdom (£)**	**Spain (€)**
GP visit	33	47
Pharmacy visit	6	6
Paediatrician visit	33	47
Accident and emergency visit	200	139
Specialist visit	155	137
Out-of-hours service	86	94
Hospital day	827.12	681
ICU episode	6834.54	5013
Hourly wage, general population	24.5	16.8
Hourly wage, caregiver	24.5	16.8
x-ray	31	23
Other diagnostic tests	18	26.05
Wbc point of care test	10	10
Wbc lab test	9	9
COVID lab test	20	20
COVID point-of-care test	10	10
Travel cost regional hospital	5	5
Travel cost to local care center	1	1

Transition probability

The transition probability from "sick" to "healthy" was based on the day patients returned to their daily activities as captured within the PRUDENCE trial. A survival model was established based on key characteristics (geography, age, study arm, influenza season, symptom severity, treated with antibiotics) and the day the patient returned to their daily activities. The following parametric distributions were applied:

- Generalized gamma
- Generalized F
- Weibull
- Gamma
- Exponential
- Log-logistic
- Log-normal
- Gompertz

Table 7 AIC and BIC values per distribution.

Distribution	**AIC**	**BIC**
Gengamma	13200	13351
Generalized F	13202	13358
Log normal	13210	13355
Log-logistic	13283	13429
Gamma	13460	13606
Weibull	13540	13686
Gompertz	13649	13794
Exponential	13655	13794

Out of the eight distributions, the distribution with the most optimal AIC and BIC value (lowest value for both AIC and BIC) was selected which was the Log-normal distribution.

Based on the resulting survival curve, the probability of transitioning from "sick" to "Healthy" was estimated for day 1 until day 28.

Quality of life

The Health Related Quality of Life (HRQoL) was measured using the EQ-5D-5L questionnaire. The EQ-5D-5L questionnaire is a validated, generic (non-disease-specific) instrument for valuing health-related quality of life[90]. The EQ-5D contains five dimensions, each with five levels of severity. The five dimensions are: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The patient had to select the most appropriate level for each of the five dimensions, resulting in a 1-digit number for each of the five dimensions. The resulting 5-digit number describes the patient's health state[91]. Applying a specific algorithm to the 5 responses to the EQ-5D will result in a single score expressing quality of life, the so-called utility. The algorithm, or tariff, is country-specific. When it is not available for a certain country, the tariff of a neighbouring country (or country similar in culture) may be applied.

For the base-case, the UK crosswalk tariff was applied. Since the current analysis is based on a heterogenous patient population across different age groups and countries, the disutility due to a CA-ARTI was estimated which is the decrement in utility between the initial utility and the utility when the patient resumed to their daily activities (represented by the results from day 14 or day 28). In an effort to reduce the heterogeneity, the analysis of disutilities was focused on the primary care facilities, patients in the long-term care facilities were excluded from the analysis. The resulting disutility is reported as negative value and could be considered as the CA-ARTI specific impact on the quality of life of the patient.

An additional analysis was performed in which the EQ-5D-5L data was split by the disease severity as assessed by the GP at day 1. Additionally, the disutility value was calculated for countries that had an EQ-5D-5L tariff or a crosswalk set available, which were the following countries:

- Germany
- United-Kingdom
- Italy
- France
- Spain
- Poland
- Romania
- Netherlands
- Belgium
- Sweden
- Portugal
- Hungary
- Denmark
- Ireland
- Slovenia
- Russia

3.4. Antimicrobial resistance forecasting

The AMR model uses a two-step approach. First, the baseline AMR projections are generated, using an ensemble model. This is a data-driven approach where current trends are used to forecast future AMR rates. These baseline projections are then used for the current-care scenario, where we assume current patterns in AMR will continue in the future. The second step is to incorporate the impact on antibiotic consumption from the diagnostic strategies, in the baseline AMR projections. This uses a more mechanistically driven approach. The steps are described in more detail below.

The first step in this process is to forecast AMR rates when the status quo is preserved, i.e. current AMR policies remain, but no additional measures are taken. Predicting antimicrobial resistance (AMR) is a challenging task, as the development and subsequent spread of resistance genes is highly uncertain. Two methods of modelling AMR in the population over time have been identified[92]:

- Mechanistic dynamic transmission models, which models the transmission of resistant pathogens through populations, requiring information on the mechanisms of spread of resistant pathogens.
- Statistical forecasting methods, which is a data-driven approach where the underlying mechanisms of resistance is not considered: past trends are used to forecast future AMR rates.

Additionally, expert elicitation is a viable method to forecast AMR, which can be combined with these modelling approaches[93]. The mechanisms to attain and retain resistance may differ between various pathogens. As we aim to assess the impact of diagnostics for all community-acquired respiratory-tract infections in the population, which can be caused by various pathogens[94], we considered a mechanistic dynamic transmission model not to be a viable strategy. A statistical forecasting method, comparable to the methods used by Hashiguchi et al. was used instead[95].

Several methods are available for time series forecasting[96,97], but selecting a single 'best' model is challenging. Ensemble methods are an often-used technique to improve forecasts: instead of picking one model, several models are used simultaneously and then combined to provide an average. We developed an ensemble model, averaging three models:

- An exponential smoothing (ETS) model, which forecasts future data using weighted averages of past observations[96].
- A random forest, which aggregates many regression trees to estimate the outcome of interest (AMR rates in our case)[98]. Bagging (bootstrapping and aggregating) is used, where each decision tree is informed by a random

sample, with only a subset of the available regressors, of the original data set. The different trees are grown in parallel, i.e. new trees are not informed by previous trees.

- An XGBoost model, which also combines many regression trees to estimate the outcome of interest, however, as opposed to random forests, a sequential tree growing algorithm (boosting) is used, where each new tree informs the creation of the next tree[99].

3.4.1. Missing data

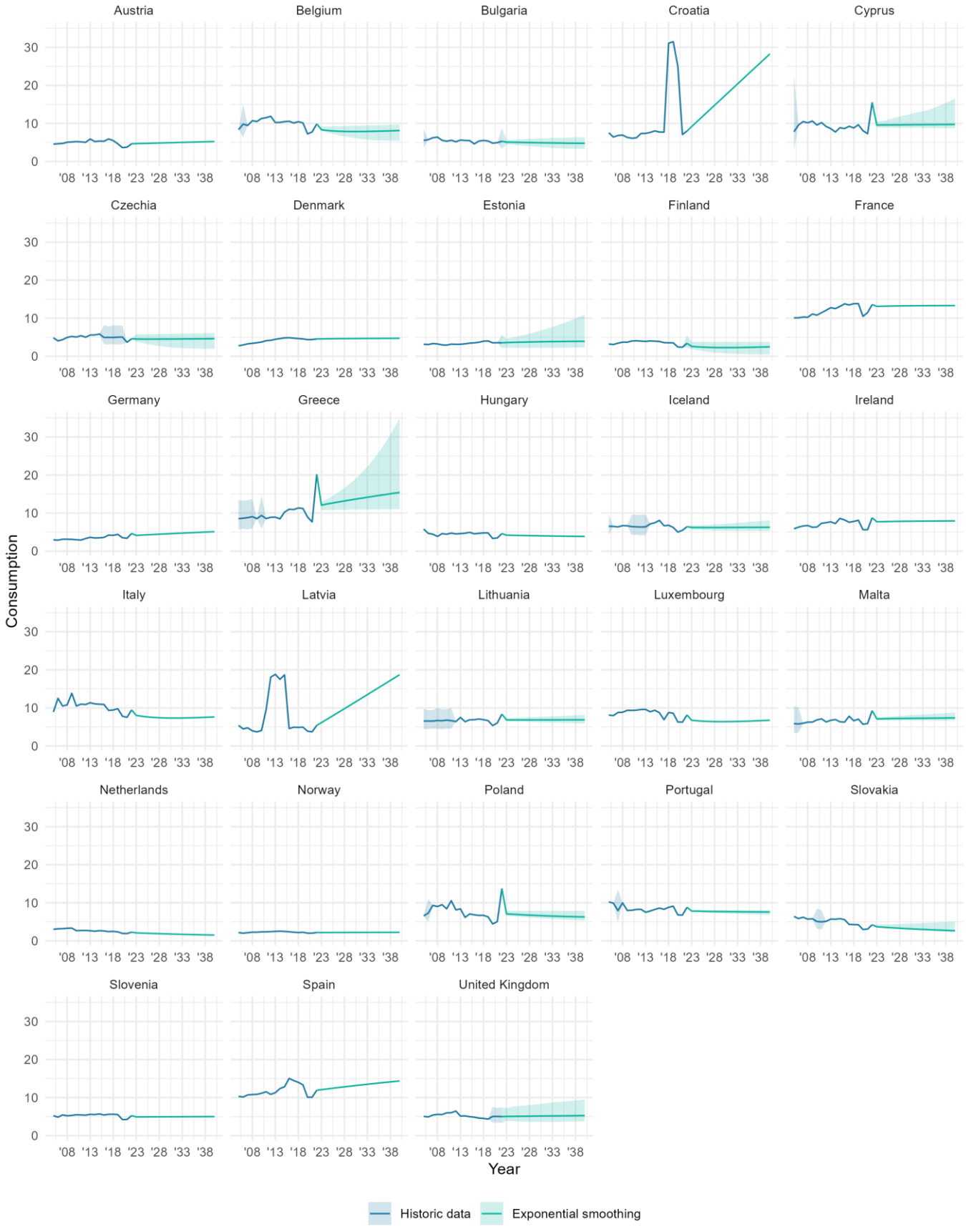
The European consumption and AMR data had some missing data. These were imputed using the Amelia algorithm[100] which allows for time-series-cross-sectional data to be imputed. To incorporate uncertainty in the various forecasts, the imputation algorithm was run 2000 times to incorporate uncertainty.

3.4.2. Forecasts of antibiotic consumption

Antibiotic consumption of broad-spectrum penicillins was forecast using an ETS model.

There are different ETS methods. As we considered annual data, we did not consider seasonal components. The trend can be either none, additive, additive damped or multiplicative. Multiplicative trends tend to produce poor forecasts and additive trends can overestimate the trend on the long term[96], hence we considered an additive damped trend. The consumption data were box-cox transformed so that the data resembled a normal distribution.

The results of this analysis are displayed in Figure 5. The raw results and accuracy metrics are included in appendix I.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Spain
United Kingdom
Consumption
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'08 '13 '18 '23 '28 '33 '38
Year
Historic data
Exponential smoothing

Figure 5 forecasts of antibiotic consumption in defined daily doses per 1,000 inhabitants per day of broad-spectrum penicillins. Historic data based on data collected in the TESSy database[101].

3.4.3. AMR forecasts

For the antimicrobial resistance forecasts the dataset was split into a training and a testing set (training: 2005-2017, testing: 2018-2022), to be able to measure the performance of the forecasts. After fitting the different models to the training set, the prediction of the testing set was assessed. Then the models were refit to the full dataset to forecast the AMR rates up to 2050.

Although we focussed on *Streptococcus pneumoniae* to broad-spectrum penicillins in the Netherlands in this paper, we incorporated data from other bug-drug combinations and European countries as regressors in the random forest and XGBoost models.

Exponential smoothing model

The exponential smoothing model uses a similar approach as described for the consumption forecasts, hence an additive, damped, trend.

Random forest model

The random forest model uses the following regressors to predict the AMR rate:

- Antibiotic consumption
- GDP forecasts (corrected for purchasing power parities)
- Forecasts proportion population aged < 15 years
- Forecasts proportion population aged > 64 years
- Forecasts healthcare expenditure (% of GDP)
- Forecasts out-of-pocket spending on health (% of total spending on health)

XGBoost model

The XGBoost[99] model uses the same dependent variables as the random forest model.

Ensemble

The ensemble model is created by averaging (with equal weights) the predicted values across the best performing models, one variant of each of the model types (see below).

Accuracy of predictions

The accuracy of the different models is calculated on the testing set, using the models trained only on the training set. Figure 6 shows an example of the calibration of one model iteration.

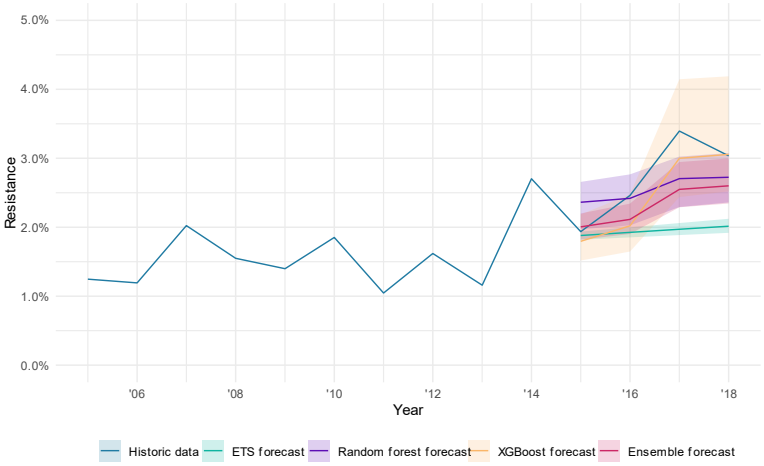

Figure 6 example of model accuracy, based on the three individual models and model ensemble.

The performance of time-series forecasts are often represented using the root mean squared error (RMSE), which is calculated using the following formula[96]:

$$RMSE = \sqrt{mean(e_t^2)}$$

Where e_t is the forecast error of values from the testing set.

The values differ within the probabilistic analysis, table 6 gives an overview.

Hyperparameter tuning of machine learning models

The Random Forest and XGBoost models were tuned using a Bayesian grid search, to select three optimal model candidates. Optimal models were based on minimizing the RMSE.

For each of the countries, the optimal random forest and XGBoost model was selected out of three fitted models, again minimizing the RMSE.

Incorporating uncertainty

The previously described forecasting methods generate point forecasts, that is, a mean is forecast, but no statistical distribution. To incorporate uncertainty in the AMR forecasting model, the following input parameters are varied and the models are fitted for 2000 iterations:

- A different imputed data set is used for both the historical AMR data and antibiotic consumption
- Forecasts healthcare expenditure (% of GDP) are varied for the model replications
- Forecasts out-of-pocket spending on health (% of total spending on health) are varied for the model replications

Consequently, all model replications use slightly different AMR projections. However, we have not quantified all uncertainty associated with the projections, i.e. not all possible future AMR rates are included in the modelling.

Predictions of antimicrobial resistance

The results of this analysis are displayed in Figure 7. The raw results and accuracy metrics are included in appendix II.

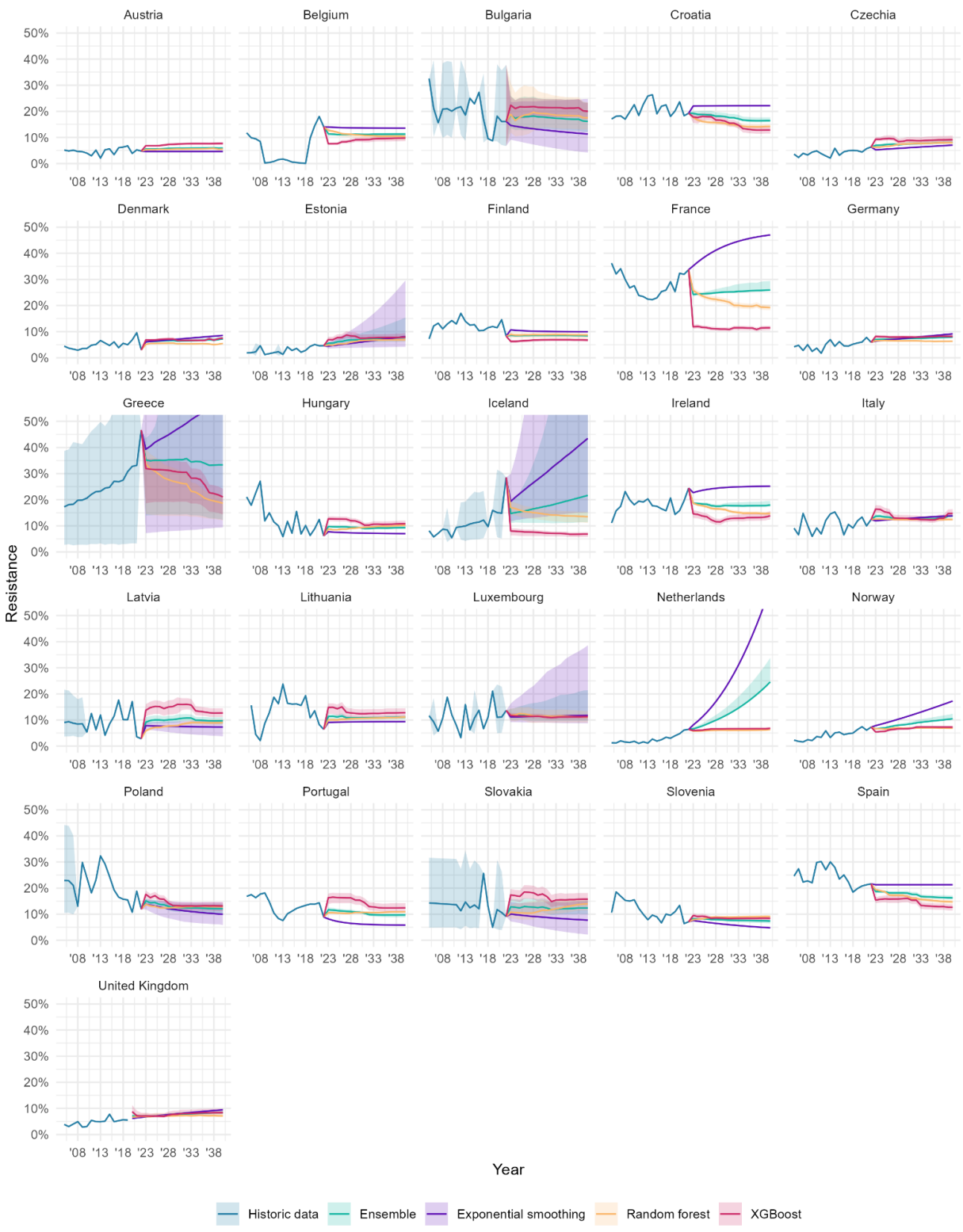

Figure 7 forecasts of antibiotic resistance of Streptococuus pneumoniae against broad-spectrum penicillins. Historic data based on data collected in the TESSy database[101].

3.4.4. Incremental effects of diagnostic strategies

As has been described elsewhere, there is a clear relationship between antibiotic consumption and national AMR rates[102,103]. We use this relationship to relate the change in antibiotic consumption, as estimated in MERIAM, to future AMR levels (projected as described above). The following formula is used:

$$p_{Test,t}^{Ab,B} = p_{Base,t}^{Ab,B}\left(1 + \frac{C_{Test,t-1}^{Ab} - C_{Base,t-1}^{Ab}}{C_{Base,t-1}^{Ab}} \times \epsilon^{Ab,B}\right)$$

Where $p_{Test,t}^{Ab,B}$ is the proportion of resistance of bacterium B to antibiotic Ab under the testing scenario in the year t; $p_{Base,t}^{Ab,B}$ the proportion of resistance of bacterium B to antibiotic Ab under the base case scenario in the year t; $C_{Test,t-1}^{Ab}$ the antibiotic consumption of antibiotic Ab in the year t–1 in the testing scenario; $C_{Base,t-1}^{Ab}$ the antibiotic consumption of antibiotic Ab in the year t–1 in the base case scenario and ϵ the elasticity between antibiotic consumption of antibiotic Ab and the development of resistance in bacterium B.

Estimating elasticity

The elasticity ϵ is given by the following formula:

$$\epsilon = \frac{\%\ change\ in\ resistance}{\%\ change\ in\ consumption}$$

The correlation as published by Goossens *et al.* was used as the elasticity, i.e., 0.84 (CI: 0.62 – 0.94) for *S. pneumoniae* against penicillins[102].

3.4.5. Mortality due to antimicrobial resistance

An exploratory analysis was performed to estimate the impact of AMR on quality of life (QoL). A decision tree was created to calculate excess mortality and subsequent QALYs lost due to resistance for a particular pathogen-drug combination.

As streptococcus pneumoniae was the most frequently implicated bacterial infection for community-acquired pneumoniae (CAP) in Europe, and penicillin was the most frequently prescribed antibiotic for ARI and ILI cases in PRUDENCE, the QALY loss of patients with the pathogen-drug combination 'penicillin *S. pneumoniae*' was estimated[104]. The scope of the decision tree was therefore narrowed down to patients diagnosed with pneumoniae. The probability of S. pneumoniae was 26.6%, based on findings from a recent study on serotype distribution among adults with CAP[105]. The proportion of penicillin-resistant S. pneumoniae patients between 2010 and 2022 followed from data published by the Surveillance Atlas for Infectious Disease of the ECDC[101].

Data on mortality and QoL was scarcely available in literature and was derived from a variety of sources. A key source among these was the study on the global burden of bacterial antimicrobial resistance in 2019, which provided a comprehensive

overview of relative risk estimates on mortality for various pathogen-drug combinations [106]. Here, a relative risk of death of 1.27 (1.18-1.36) was reported for penicillin-resistant *S. pneumoniae* compared to penicillin-sensitive S. pneumoniae. Risk of mortality for the resistant group was derived from the modelling analysis performed by Cassini *et al.*[37]. With a median mortality of 0.03 deaths over a median incidence of 0.55 per 100,000 of penicillin-resistant *S. pneumoniae* (excluding those resistant to macrolides), a mortality probability of 0.053 was calculated. The probability of mortality in the sensitive group was calculated by dividing the probability of the resistant group by the relative risk of mortality derived from Murray *et al*. This resulted in a mortality probability of 0.042 for the sensitive group.

Mortality risk of pneumonia other than *S. pneumoniae* was not explicitly reported in literature. Consequently, the mortality of three aetiologies other than *S. pneumoniae* (i.e. respiratory syncytial virus, *haemophilus influenzae* type b, and influenza) as part of lower respiratory tract infections reported by the Global Burden of Disease Study 2016 was taken as a proxy for non-*S. pneumoniae* mortality[107]. Incidence and mortality per 100,000 were 960 and 2.4, respectively, resulting in a mortality probability of 0.002.

QoL estimates in terms of QALYs were estimated from a cost-effectiveness analysis performed in the Netherlands[108]. Relevant input parameters of the model used in the analysis we the QALY loss due to inpatient CAP (0.0709±0.020, using a PERT distribution).

An overview of probabilities and payoffs is presented in Table 8. The decision tree is visualised in Figure 8.

Table 8 parameters for in the decision tree to calculate the excess mortality of streptococcus pneumoniae patients due to penicillin resistance.

Type of parameter	Description	Value
probability	The probability of Streptococcus pneumoniae among patients diagnosed with pneumoniae	0.266
probability	The probability of penicillin-resistance among streptococcus pneumoniae patients	0.126
probability	The probability of dying from penicillin-resistant streptococcus pneumoniae	0.053
probability	The probability of dying from penicillin-sensitive streptococcus pneumoniae	0.042
probability	The probability of dying from pneumoniae other than streptococcus pneumoniae	0.002
payoff	QALYs lost due to penicillin-resistant streptococcus pneumoniae	0.071

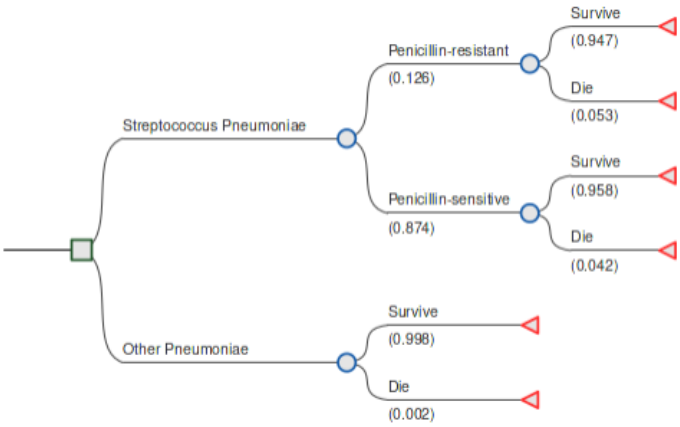

Figure 8 Decision tree showing the relevant pathways and associated probabilities to calculate the excess mortality of streptococcus pneumoniae patients due to penicillin resistance.

3.4.6. Overview data sources

The input data were used based on literature[95] and export opinion, see Table 9 for an overview.

Table 9 Overview data sources AMR model

Data	Database	Notes	Reference
Antimicrobial resistance	Surveillance Atlas for Infectious Disease		109
Antibiotic consumption	ECAC-Net		110
Population projections	Eurostat		111
Historical demographic data	Eurostat		112
GDP projections	OECD	Used for OECD countries	113
GDP per capita	World Bank	Used for non-OECD countries	114

Health expenditure projections	Literature		1
Out-of-pocket healthcare payments projections	Literature		1

4. Results of the health-economic model

4.1. Quality of life estimates

For the base-case, the disutility values were calculated per treatment arm. Based on the results in Table 10, it can be concluded that no between arm differences in utility values were present except. The average disutility was -0.219 (median = -0.205; SE = -0.0042) for a duration of 5.34 days (SE = 0.118).

Table 10 Overview of disutility values per treatment arm

COVID status	Main symptom	Influenza season?	Arm	Disutility value			Number of patients
				Mean	Lower limit	Upper limit	
FALSE	Sore throat	No	SoC	-0.2386	-0.2083	-0.2690	176
			Group A streptococcus test	-0.2296	-0.2005	-0.2587	173
		Yes	SoC	-0.2582	-0.2222	-0.2942	135
			Group A streptococcus test + Influenza test	-0.2219	-0.1915	-0.2522	141
	Cough	No	SoC	-0.1967	-0.1753	-0.2182	264
			CRP test	-0.1909	-0.1710	-0.2107	286
		Yes	SoC	-0.2284	-0.2039	-0.2530	192
			CRP test	-0.2020	-0.1796	-0.2244	195
			Influenza test	-0.2098	-0.1861	-0.2334	192
TRUE			SoC	-0.1464	-0.1061	-0.1867	62
			CRP test	-0.1586	-0.1208	-0.1965	64

COVID positive patients experienced a lower disutility as a result of the disease. It appeared that these patients had a higher average utility value at day 1 compared to the patients testing negative for COVID, with an average of 0.784 and 0.721, respectively.

4.2. Additional analysis

Disutility by disease severity

The average disutility value by disease severity (as assessed by the GP at day 1) was -0.188 (median = -0.178; SE: 0.005), -0.250 (median = -0.220; SE: 0.007) and -0.341 (median = -0,308; SE: 0.036) for a mild, moderate and severe disease, respectively. When combined with the disease duration, the average disutility expressed in QALY is -0.0025 (disease duration: 4.91 days; SE: 0.14 days), -0.0041 (disease duration: 6.04 days; SE: 0.20 days) and -0.0054 (disease duration: 5.74 days; SE: 1.10 days) for a

mild, moderate and severe disease episode, respectively. Figure 9 illustrates that the mean and median disutility value is increasing with disease severity.

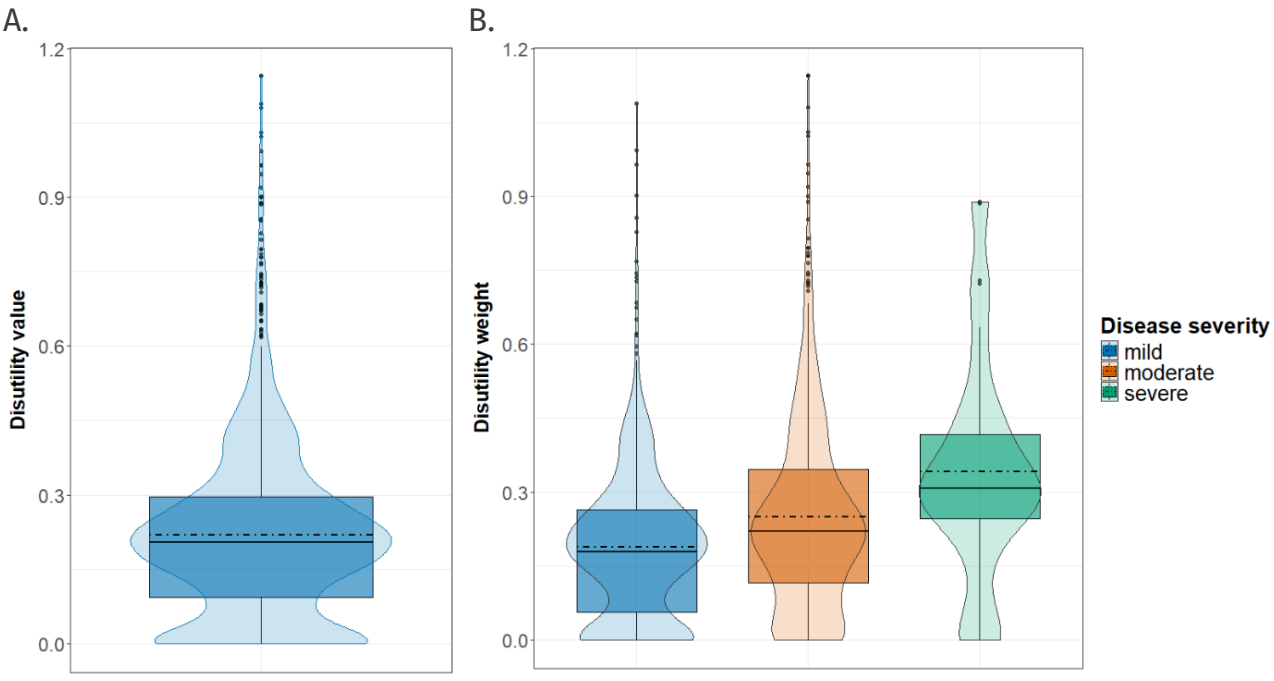

Figure 9 Utility values based on UK value set. A) Overall disutility value, B) Disutility value per disease severity at day 1 (assessed by GP). *Dashed line = mean, solid line = median.

Disutility per country

In Table 11, the overall disutility value per country is provided which illustrates the differences in disutility estimates between the countries. For each entry in the table, all available EQ-5D-5L data were used (i.e. from all countries in the clinical study), the differences can be explained solely by the differences in the country specific tariffs (value sets) that were applied.

The value sets that accompany EQ-5D instruments provide a means of summarising, via a single number, a patient's health status as described by the EQ-5D. These numbers lie on a scale anchored at 1 (full health) and 0 (dead). The values are built up from a set of sub-weights which represent the relative importance of each level of problem in each dimensiozzzzzz

Table 11 Average disutility value per country.

	Aggregated results		By disease severity					
Country	**Average (SE)**	**Average disease duration (days)**	**Mild disease (SE)**	**Mild disease duration (days)**	**Moderate disease (SE)**	**Moderate disease duration (days)**	**Severe disease (SE)**	**Severe disease duration (days)**
Poland	0.096 (0.003)	5.44	0.069 (0.003)	4.91	0.125 (0.006)	6.04	0.174 (0.03)	5.74
Sweden	0.107 (0.004)		0.071 (0.004)		0.143 (0.006)		0.206 (0.034)	
France	0.108 (0.004)		0.075 (0.003)		0.141 (0.006)		0.200 (0.033)	
Romania	0.118 (0.003)		0.096 (0.003)		0.140 (0.004)		0.197 (0.022)	
Russia	0.127 (0.003)		0.104 (0.003)		0.150 (0.005)		0.210 (0.024)	
Portugal	0.146 (0.004)		0.11 (0.004)		0.182 (0.006)		0.254 (0.033)	
Hungary	0.150 (0.004)		0.109 (0.004)		0.194 (0.008)		0.267 (0.039)	
Germany	0.151 (0.004)		0.113 (0.004)		0.190 (0.007)		0.262 (0.038)	
Denmark	0.160 (0.005)		0.120 (0.005)		0.201 (0.008)		0.288 (0.039)	
Italy	0.162 (0.004)		0.120 (0.005)		0.205 (0.008)		0.287 (0.04)	
Spain	0.167 (0.004)		0.137 (0.004)		0.197 (0.006)		0.274 (0.03)	
Slovenia	0.179 (0.005)		0.131 (0.005)		0.229 (0.009)		0.315 (0.043)	
Belgium	0.180 (0.004)		0.144 (0.005)		0.217 (0.007)		0.297 (0.037)	
Ireland	0.192 (0.005)		0.148 (0.005)		0.236 (0.009)		0.336 (0.043)	
Netherlands	0.195 (0.004)		0.157 (0.005)		0.234 (0.007)		0.323 (0.037)	
United-Kingdom	0.219 (0.004)		0.188 (0.005)		0.250 (0.007)		0.341 (0.036)	

Abbreviations: SE = standard error.

The between country differences from Table 11 can be explained by the breakdown in dimensions in Figure 10. For each of the 5 dimensions, the day 1 average score (including the interquartile ranges) and the score when returning back to the usual activities is reflected. As can be concluded from Figure 10, the major pre- post differences were found on the dimensions of pain and usual activities. Depending on the country specific value sets, the relatively higher scores on the dimensions of pain and usual activities translate into a reduction of the overall single value that represents the health state of the patient.

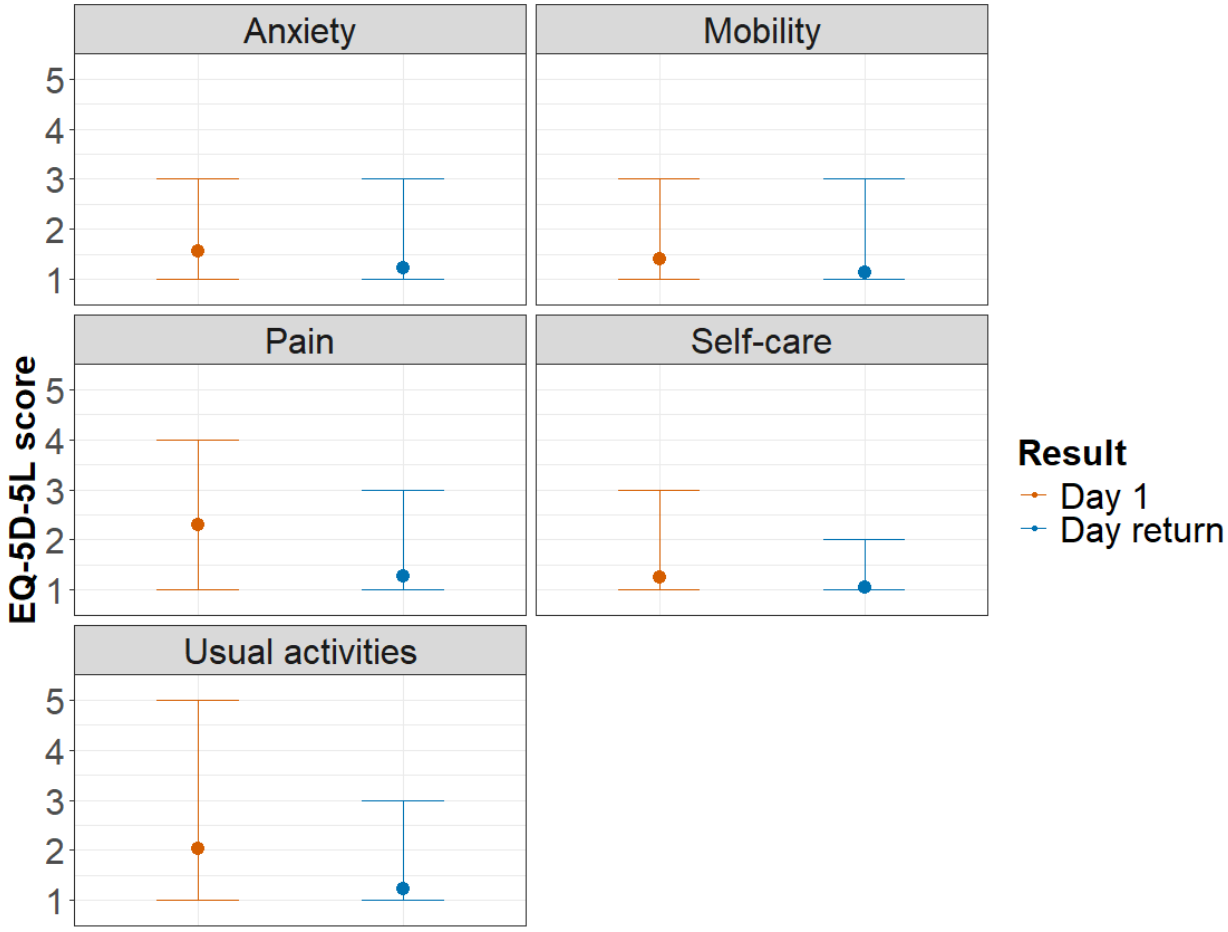

Figure 10 EQ-5D-5L dimension relative differences

In Figure 11 the impact of the score on each of the five dimensions is reflected against the impact on the utility score, with the Netherlands and Poland taken as an example. As can be concluded from Figure 11, the utility score is reduced more steeply at the lower scores (1-3) for the Netherlands compared to Poland. Since most of the EQ-5D-5L scores in the PRUDENCE trial were in the 1 to 3 level range, countries such as the Netherlands have higher disutility scores for a CA-ARTI compared to countries such as Poland.

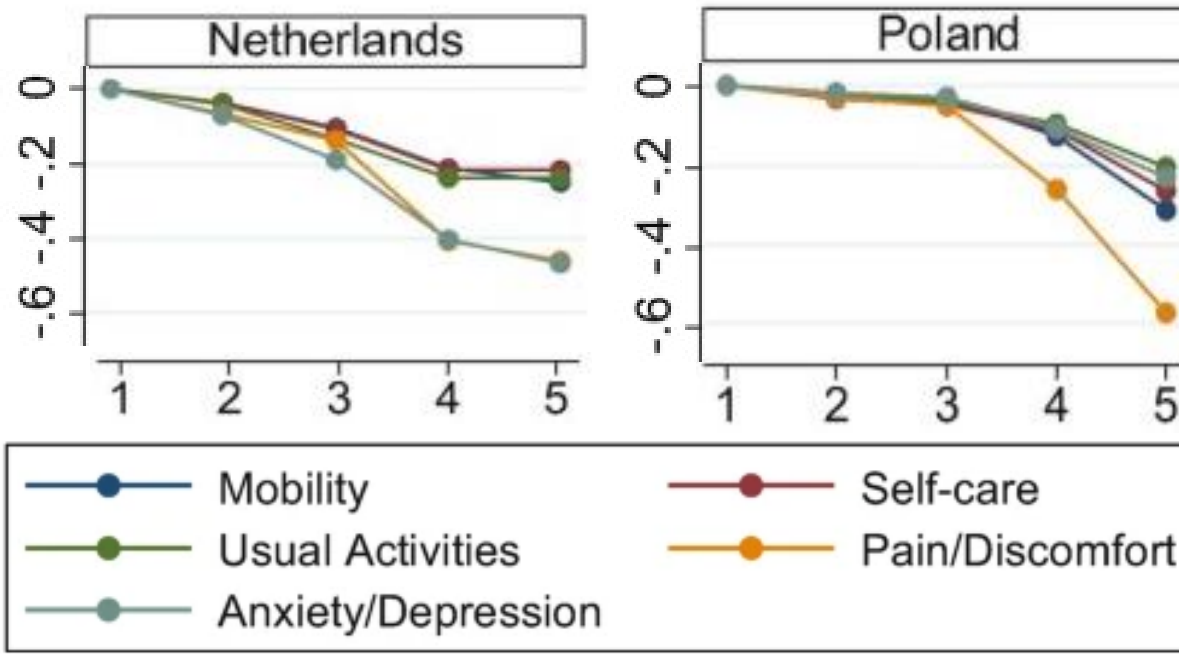

Figure 11 Overview of score vs. impact on utility value.[115]

4.3. PRUDENCE analysis

The results of the main PRUDENCE analysis can be found in Deliverable 5.3. The current section covers a sub-analysis in which the incremental costs, incremental effects in QALYs and the incremental effect on antibiotic prescription rate was calculated for each of the branches of the decision tree (see Figure 3).

The results of the deterministic analysis are summarized in Table 12. Three out of the six comparisons resulted in a decrease in the antibiotic prescription rate, including the Group A streptococcus test vs. SoC, the CRP-test vs. SoC (outside the flu season) and the Group A streptococcus test + Influenza test vs. SoC. Unfortunately, in line with the results of the main analysis, the incremental differences in the antibiotic prescription rate were very small. Interestingly, the comparison of the Group A streptococcus test vs. SoC resulted in both a decrease in the antibiotic prescription rate and in cost-savings. As a result, the Group A streptococcus test was considered dominant compared to SoC.

Table 12 Overview of health economic outcomes PRUDENCE (deterministic analysis)

Comparison	Incremental cost (societal perspective)	Incremental cost (healthcare perspective)	Incremental Effect (QALY)	Percentage point difference in antibiotic prescriptions	Cost per percentage point reduction in antibiotic prescription (societal)	Cost per percentage point reduction in antibiotic prescription (Payer)
Veritor gas vs. SoC	Cost-saving	Cost-saving	0.0003	1.32	Dominant	Dominant
CRP vs. SoC (no flu season)	€ 25.12	€ 9.17	0.0000	1.65	€ 15.22	€ 5.56
Veritor gas/inf vs. SoC	€ 201.11	€ 10.53	0.0005	5.44	€ 36.93	€ 1.93
CRP vs. SoC (flu season)	Cost-saving	Cost-saving	0.0001	-4.19	Dominated	Dominated
Veritor infl vs. SoC	€ 19.63	Cost-saving	0.0001	-0.12	Dominated	Dominated
CRP vs. SoC (pos. Covid)	Cost-saving	174.64	-0.0002	-0.07	Dominated	Dominated

To assess the uncertainty of the deterministic results (as reflected in Table 12), a probabilistic sensitivity analysis (PSA) was performed. Beta (for probabilities) and Gamma (for costs) distributions were applied to the variables and the model was run for 1,000 simulations. The results of the PSA are presented Figure 12. The results of the PSA highlight the great uncertainty of the results in terms of the incremental costs and effect on the antibiotic prescription rate. Based on the deterministic results, the Group A streptococcus test was considered dominant. However, the results of the PSA highlight that the cost-effectiveness profile of the Group A streptococcus test is very similar to that of the other tests and therefore deterministic results should be interpreted with caution given the uncertainty of the results.

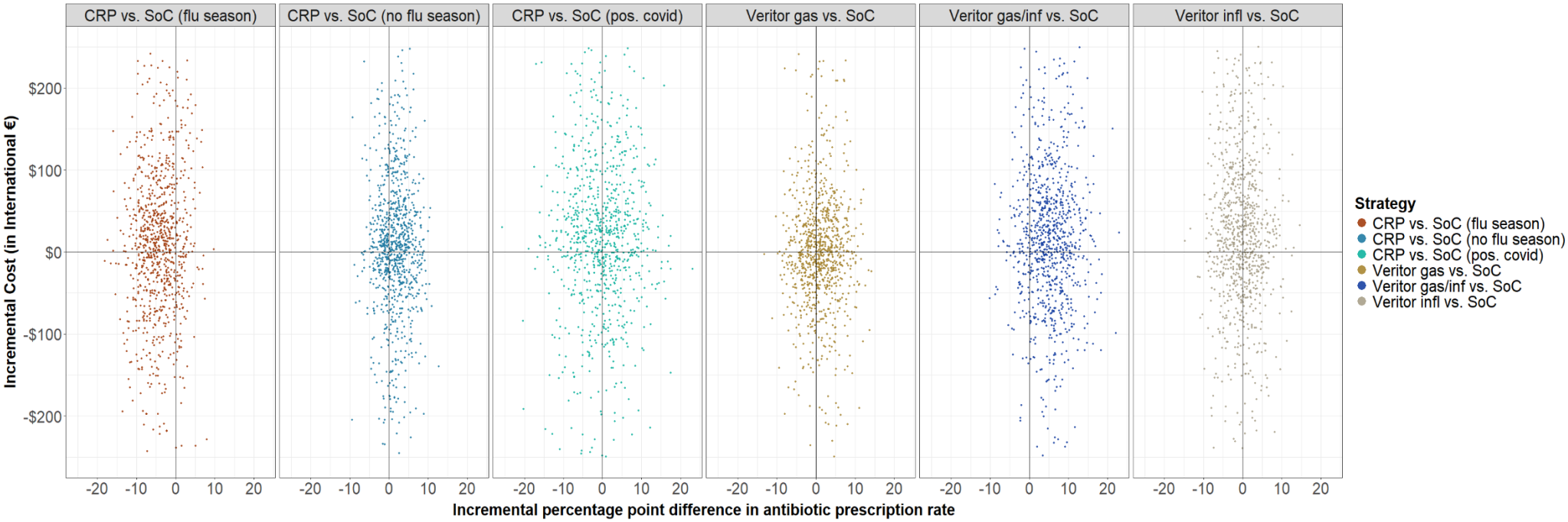

Figure 12 Cost-effectiveness plane

4.4. ADEQUATE main analysis

For the results of the health-economic analysis and scenario analyses for ADEQUATE, please refer to Deliverable 5.3. The scope of the ADEQUATE study was limited to costs, antibiotic prescriptions, and a small patient population. Hence, an alongside clinical trial analysis was considered to be the most appropriate way to assess its cost-effectiveness.

The adult trial has been terminated at an early stage and the trial continued for children. This had a major impact on the effect diagnostics could have on long-term antimicrobial resistance due to the limited scope. The proportion of antibiotics prescribed at the emergency department is only a small number of the total number of antibiotics prescribed. Furthermore, the antibiotics prescribed to children is a small proportion of the total number of antibiotics prescribed at the emergency department. Hence, the reduction in antibiotic prescriptions realized in the ADEQUATE trial, within the trial population, would not demonstrate any effect on the development of long-term antimicrobial resistance.

By integrating the data collected in the halted adult trial with the paediatric trial data using Bayesian analysis, a long-term model would be feasible, as the patient population and coverage of total antibiotic prescriptions would increase. However, the impact still would be limited: in a previous analysis[116], it was estimated that around 80% of Broad Spectrum Penicillin (BSP) for CA-ARTI in the Netherlands are prescribed in primary care. At most, 20% of total BSP prescriptions could be influenced by the interventions included in ADEQUATE. Assuming an 28% reduction in antibiotic prescriptions as measured in the ADEQUATE paediatric trial, the highest estimate of antibiotic prescriptions reduced would be 5.7% if both adults and children would be considered. Given this as the best case scenario, it seems unlikely that the interventions currently included in the ADEQUATE trial would have a measurable impact on AMR in the population as a whole.

4.5. Budget impact of novel diagnostics

As the PRUDENCE trial showed no reductions in antibiotic prescribing and incidence-estimates related to the ED consultations as relevant for ADEQUATE were too limited, it was not deemed relevant to calculate budget impact estimates based on the trial results. Using MERIAM, we can calculate the budget impact per 100,000 population in a straightforward manner. We present a hypothetical example for the Netherlands in Figure 13 and

Table 13. This analysis assumed a 21% reduction in antibiotic prescriptions as a result of the hypothetical diagnostic algorithm based on the meta-analysis by Martínez-González *et al*[117]. On average, the diagnostic strategy increases the total costs with 9% at the €5 price point (price per test) and with 19% at the €10 price point over 10 years for a population of 100,000 individuals, with the only significant difference being the costs of the diagnostics. In the hypothetical diagnostic scenario fewer antibiotics were prescribed, but the cost savings are not sufficient to offset all costs of the additional POC tests. The hypothetical diagnostic strategy did not produce overall cost savings in any of the model replications. This analysis is described in full detail in a paper published by Van der Pol *et al*. as part of the VALUE-Dx project[116].

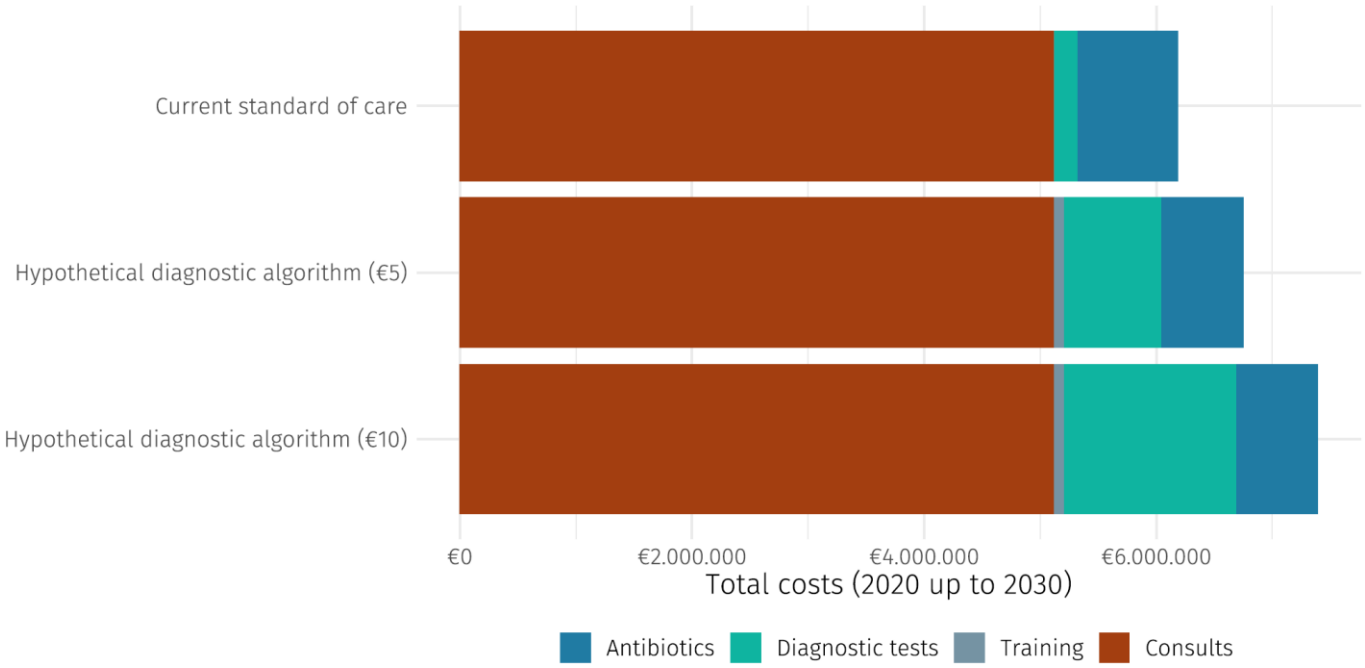

Figure 13 budget impact related to consultations for community-acquired respiratory tract infections in the period 2020-2030, per 100,000 individuals[116]

Table 13 10-year costs of the base-case and hypothetical diagnostic strategy scenarios at two price points (median, including 95% credible interval in brackets)

	Current standard-of-care	**Incremental costs hypothetical diagnostic strategy**	
		€10	**€5**
Antibiotics	€868,100 (€718,100 - €1,036,000)	-€162,200 (-€324,400 - €8,300)	-€162,800 (-€321,800 - €11,800)
Consultations	€5,119,500 (€4,599,600 - €5,721,900)	€0 (-€200 - €200)	€0 (-€200 - €200)
Diagnostics	€199,300 (€165,000 - €240,500)	€1,282,300 (€1,146,900 - €1,437,500)	€640,900 (€565,400 - €728,400)
Training	€0 (€0 - €0)	€82,200 (€82,100 - €82,200)	€82,200 (€82,100 - €82,200)
Total	€6,189,000 (€5,554,900 - €6,907,700)	€1,202,000 (€999,100 - €1,425,400)	€559,100 (€391,600 - €757,800)

4.6. Hypothetical example AMR forecasting

As mentioned, a 28% reduction in BSP prescriptions was measured in the ADEQUATE paediatric trial. In Figure 14, we present a purely theoretical scenario where these results could be extrapolated to the full scope of national BSP prescriptions, and we apply the AMR forecast method as described in Chapter 3 for the countries included within the PRUDENCE and ADEQUATE trials. In line with our assumptions, a reduction in AMR is then simulated in all countries.

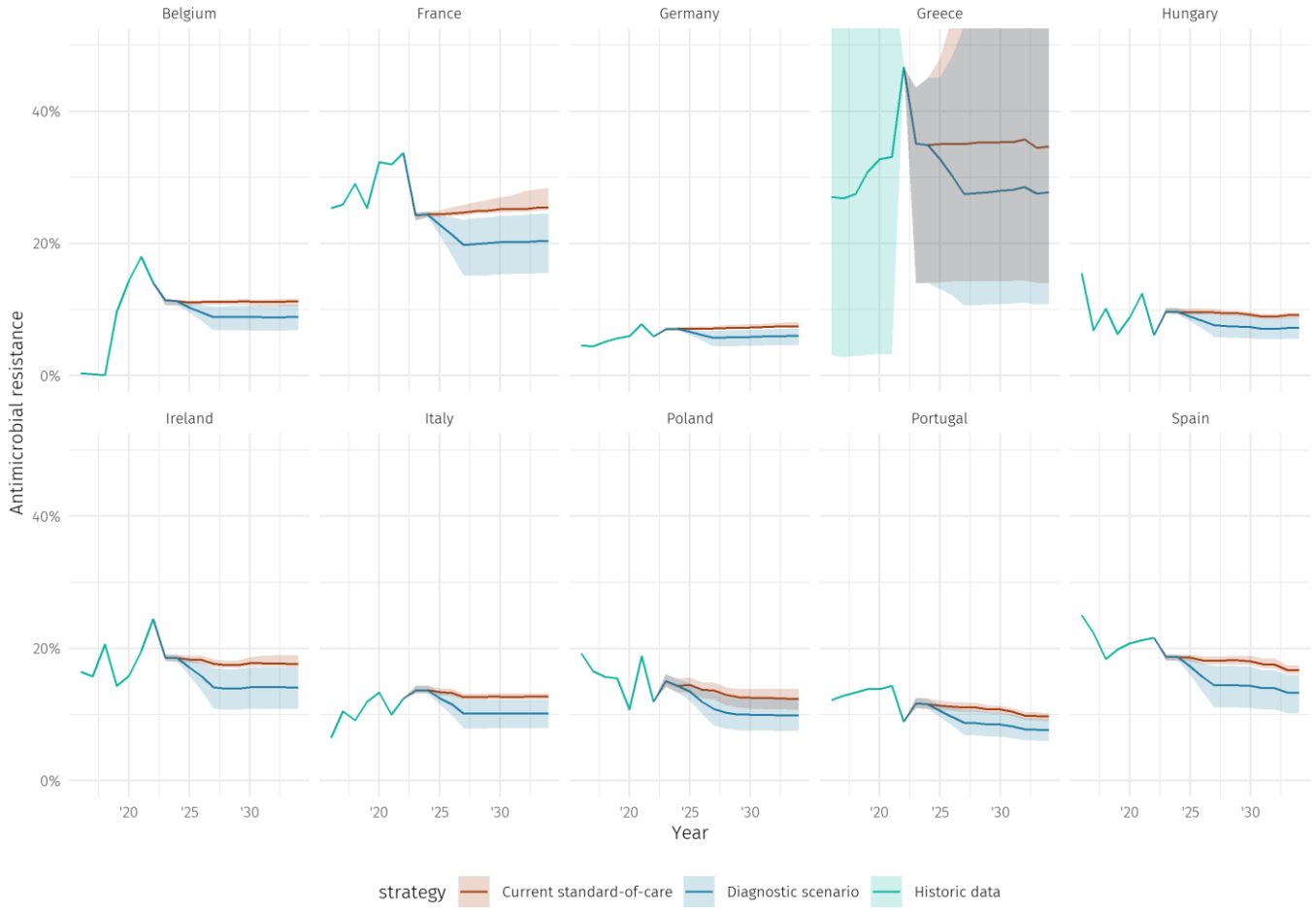

Figure 14 forecasts of antibiotic resistance of Streptococuus pneumoniae against broad-spectrum penicillins (BSP). Historic data based on data collected in the TESSy database[1], diagnostic scenario based on a purely theoretical scenario assuming a 28% reduction in all BSP prescriptions.

5. Lessons related to the value of diagnostics

5.1. Optimizing Diagnostic Value: New EU Regulations and the Future of Health Data Utilization

In the next few years, we may see the effects of the new regulations from the European Union (EU) for market entry of non-pharmaceutical medical innovations: the MDR and IVDR. They aim to improve patient safety by requiring more robust clinical evidence before a new product can be brought to market. The clinical data collected for market authorization can likely be used to inform HTAs that focus on the actual effects a new diagnostic has on patients, instead of theoretical effects that are mainly relevant for laboratory technicians. Clinical evidence should focus on how the tests are used in practise by clinicians and patients and how relevant changes to the medical decision-making process are made.

However, patient access is broader than gaining market access: they should also be implemented in clinical practice. As the clinical evidence supporting the introduction of novel tests will be more extensive under the new regulations, this may be used to inform the implementation. Currently, the long-term clinical evidence supporting economic evaluations of diagnostics is lacking. Using standard health-economic methods, the clinical effects can subsequently be extrapolated to longer time horizons[118].

Diagnostics do not provide direct improvements for patient health in most cases, different ways to assess their value may be required. In the case of infectious disease, the cost-effectiveness of a diagnostic strategy is highly dependent on the disease incidence. In the case of all diagnostics, the cost-effectiveness ultimately depends on the treatment options that follow. To construct cost-effective testing algorithms, it may be vital to look towards improved predictive models that aid in testing tailored populations that benefit from the test result. Little *et al*, compared care-as-usual, a clinical score and an antigen test combined with a clinical score for patients consulting a GP for acute sore throat in England. They found that the clinical score reduced antibiotic prescribing with 29%, but did not find an additional benefit related to the use of the antigen test[119]. Deciding whom to test may be very important for the testing strategy to remain cost-effective. In essence, testing is all about probabilities: test results change the probability of a patient having a specific condition, which in turn guides treatment decisions. Combining epidemiological data and patient characteristics may enable testing algorithms more tailored to the individual, and, as less tests need to be performed, improved cost effectiveness. As more health data become available and accessible, for example through the

European Health Data Space[120], data scientists gain the tools to build better models to predict diseases. These models can be used to quantify the added value of specific tests for individual patients; using tests to fill in missing data points will change the probability of having the disease and be informative to estimate the effectiveness of specific treatment options.

5.2. From a patient to a health system perspective

In HTAs, the effectiveness and cost-effectiveness of new interventions usually is mainly considered from the perspective of individual patients. However, in the case of diagnostics for infectious disease we expect that the value is broader than that. The testing infrastructure and organisation is an essential part of European healthcare systems. To prioritize decisions and further improve this area, it is critical to have a better overview of these organisational aspects, regardless of where the tests are performed.

As has become clear from the PRUDENCE trial, but also various studies that have been conducted before[119,121], the implementation of POCTs is critical in achieving the potential impact of the tests. This requires a thorough overview of the existing diagnostic algorithms, the patient pathway, regulatory requirements, and the needs and expectations from clinicians. If the required change goes beyond the replacement of a current test with a new test, simply making available or reimbursing a new test will not be sufficient. Clinical guidelines will need to be updated and clinicians need to receive training on how to perform and act on the tests.

Improving diagnosis may not always need the implementation of new tests. As mentioned in the previous subchapter, incidence data of different infections in the population can be incorporated in predictive models and combined with patient symptoms and characteristics to estimate the disease aetiology before any tests. These data are highly valuable and would usually be collected in public health surveillance systems. An integrated surveillance infrastructure would use data from advanced diagnostics to estimate in real-time the incidence of certain pathogens in the population. Such an approach was researched for febrile illness in South-East Asia, where regional surveillance data for diseases like dengue, scrub typhus, influenza and leptospirosis were collected using a relatively expensive multiplex PCR in the hospital setting to inform empirical treatment in rural areas[79]. Although the use of surveillance data only was not deemed to be cost-effective, combining surveillance data obtained with PCR tests with CRP testing at the individual patient level was considered to be highly cost-effective and was estimated to prevent hundreds of deaths while reducing antibiotic prescribing[79].

Further research could focus on the development and implementation of flexible diagnostic algorithms for infectious disease that recommend tests and treatment

in clinical practice based on the real-time aetiology of infections, while considering the overall cost effectiveness. This approach could also allow for more flexible antibiotic treatment options, as local resistance rates could feed into the system, preventing the use of antibiotics a patient is likely to be or become resistant to. Privacy of patients remains an important issue to consider in the context of large-scale data collection but should not be a major barrier as aggregated test results should not be traceable to individuals.

6. Lessons related to the value of AMR-reducing interventions

6.1. Challenges and opportunities related to the quality of data

Experts warn of a post-antibiotic era[13,122]: a future which is difficult to predict, but would be detrimental to healthcare as we know it today. As can be seen from our forecasts of resistance, this is not something that seems likely if only current trends are extrapolated to the future. Globally however, in some countries resistance rates for specific bacterium-antibiotic pairs exceed 90%[123]. Considering the low number of new antibiotics in development[124,125], the development and spread of these resistant bacteria needs to be prevented. In many cases, AMR develops by chance, as random mutations introduce a benefit to survival to resistant organisms[126]. This is the case for tuberculosis, caused by *Mycobacterium tuberculosis*, for which already variants exist that are resistant to all known antibiotics[126,127]. Surveillance of AMR is an important aspect to be able to act on changes in the population, e.g., by changing treatment guidelines.

Looking at national resistance rates, the data used to support decision making currently is highly limited[128]: they are derived from a limited number of samples and primarily from the hospital setting. More standardized data from more different isolates would be key to have a better overview of AMR in EU countries and make estimates that are less prone to random variation which is caused by the limited number of included samples. The EU is investing heavily in cross-border health and pandemic preparedness through the Health Emergency preparedness and Response Authority (HERA)[129,130]. One of the included aspects is an intensive collaboration with the European Centre for Disease Prevention and Control (ECDC) to improve surveillance of potential pandemic pathogens[129]. During the COVID-19 pandemic, the ECDC already played an important role in drafting guidelines[131] and sharing relevant data[132]. One of the ECDC's strategic goals for the coming years is to enhance surveillance and emergency preparedness by streamlining epidemiological information from existing systems[133]. If innovative, widely applied microbiological tests would feed into these surveillance systems, this can be used to identify potential threats faster, enabling authorities to hit hard and early to potentially prevent the next pandemic and related economic and health damage.

Implementing diagnostics capable of detecting resistant organisms in a way where the collected data do not only benefit the individual patient but can also be used for AMR surveillance on the population level, can be highly beneficial. These data can be used to develop the personalized testing algorithms described earlier, to inform empirical treatment decisions, to develop improved AMR prediction models and to draft AMR-related policy. While having a good diagnostic infrastructure is

valuable during “inter-pandemic” times, it has become very evident during the COVID-19 pandemic that it is key to have an adequate testing infrastructure during pandemics and other outbreaks of infectious disease.

6.2. Towards a generalizable framework to value AMR

Improved diagnostics may play an important in preventing AMR. Still, the true value of this is difficult to predict and express in an ICER. Who knows whether the post-antibiotic world will become a reality and what this will mean for modern healthcare? Considerable uncertainty stems from the fact that estimating the costs related to changes in resistance levels is complex[13]. Additionally, the costs per QALY paradigm works well when thinking of a specific disease but is more complicated when thinking about broad public health investments, where it is impossible to *a priori* identify the benefits associated with the intervention. Within the framework of CEAs the goal is to maximize the total health gains, without regarding the distribution of these gains; for example globally or inter-generationally[11]. Investments made from this public health perspective may need to be assessed differently from the investments we make in the health of individual patients. The health-economic toolset to determine which investments to make, may need to be adapted.

There is inherent value in reducing AMR, as this contributes to preventing the worst-case scenario, a post-antibiotic era. Dorgali *et al*. previously estimated that the WTP for containing AMR in the United Kingdom was around £8.35 billion annually[134]. Like a WTP for a QALY, a WTP to safeguard the availability of antibiotics may make investment decisions in new antibiotics, effective diagnostics, or AMR stewardship interventions more straightforward to substantiate. This could be assessed within a discrete choice experiment[134]. An often-seen outcome in health-economic analyses is the reduction in DDDs or antibiotic prescriptions, as this is relatively easy to capture within trials and within modelling exercises, see also Deliverable 5.1. Ideally, such a WTP would directly relate to reductions in antibiotic consumption. Alternatively, valuing AMR reductions within the context of Societal Cost Benefit Analyses may be a feasible approach that is transparent and interpretable for decision makers.

In the Paris climate agreement, the international community agreed to limit global warming to 1.5 °C above pre-industrial levels[135]. Specific goals to curb the spread of AMR could also be set. Within such a mission-oriented approach, budgets should be structured in a way so that the long-term AMR goals can be reached[12]. Any innovative intervention that aids in reaching these goals should be assessed based

on its relative contribution and investment, i.e., the AMR reduction in relation to the additional costs.

Like the advanced models for climate change, that incorporate among others CO_2 emissions, and enable the calculation of increasing temperature and sea levels on the long term, we need a scientific consensus on the linkage of antibiotic consumption to antimicrobial resistance on the long term. Notably, it is important to find a method that does not oversimplify the matter, e.g., assuming perfect elasticity between the two may be problematic, but remains straightforward to implement in a range of scenarios. Such a model may not need to incorporate all the intricacies of AMR spread, such as transferring genes from one species of bacteria to another. However, it probably should consider differences in resistance development between species of bacteria, as well as multi-resistant bacteria. The model should be developed by a large team of experts in the fields of (clinical) microbiology, epidemiology, and health economics. Although we used a national scope for the current project, improved surveillance data would ideally allow such a model to incorporate a regional perspective, as regions within countries can have very different AMR rates[136].

Appropriate forecasts on how AMR will develop in the decades to come is a requirement for this model and for decision makers to estimate the impact of this issue. We used a machine learning approach in this project, which works quite well in extrapolating current trends, but may not be the most appropriate method for something as unpredictable as AMR. A reservoir of resistant organisms may build up in regions like former Soviet countries, North America, Sub-Saharan Africa and South-East Asia that may find their way into European countries[123], which is not covered by the methods included in this project. Expert elicitation may be a more appropriate way to come to these estimates[93], but is quite time consuming, especially if AMR rates for many countries and bacteria-antibiotic combinations have to be assessed simultaneously. A combination of expert elicitation and inclusion of statistical forecasting may be an optimal approach to come to appropriate forecasts of AMR on the long term. We expect that capturing these dynamics in a transmission model simply is not a feasible approach, with the exception of very specific pathogens such as *Mycobacterium tuberculosis*[137].

7. Conclusions

Within the VALUE-Dx project, we developed an innovative health-economic framework that allows for the assessment of novel POC diagnostics from a public health and economic perspective. This model, called MERIAM, was ready to be utilized to assess the value of the diagnostics included in the PRUDENCE trial. Due to the change in scope of the ADEQUATE trial, with a focus on children only, while MERIAM was already far in development, we were unable to include this trial in the analysis in the absence of results for the adult population.

The PRUDENCE trial showed no effect of any of the included tests on antibiotic prescriptions or health outcomes. The health-economic conclusion can be rather straightforward: there is no reason to implement these diagnostics, as they were dominated by the standard of care. The standard of care was as effective and less costly.

Lessons drawn from the PRUDENCE trial likely will inform future research on diagnostics in primary care and MERIAM can be used to assess these diagnostics from a health-economic and public health perspective. The model is adaptable in that it can accommodate various types of diagnostics and compare their impact from various perspectives. Additionally, other public health interventions could also make use of the framework developed within this task to advance their analyses. For example, vaccination programmes are a likely target to influence antibiotic prescriptions: citizens who do not have respiratory complaints, will not consider consulting a clinician and will not be prescribed an antibiotic.

The work in task 5.4 has yielded other relevant information for future research in the field of diagnostics and ca-arti. We have provided guidance for the design and reporting of health-economic modelling of diagnostic interventions[64]. We have also provided disutility estimates related to ca-arti that can be applied to a wealth of HTAs of respiratory infections.

In conclusion, although the scope of ADEQUATE and results of PRUDENCE did not warrant the application of MERIAM on the trial results at this time, we have developed a useful framework that has many applications within the field of health economics. It certainly will be a useful tool for future research on the cost-effectiveness of diagnostics of ca-arti.

8. Bibliography

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Appendices

I. Results antibiotic consumption forecasts

Raw results: Antimicrobial consumption forecasts

Broad-spectrum penicillins, displayed in defined daily doses per 1,000 inhabitants

	Exponential smoothing
Austria	
2023	4.7
2024	4.7
2025	4.7
2026	4.8
2027	4.8
2028	4.8
2029	4.9
2030	4.9
2031	4.9
2032	5
2033	5
2034	5
2035	5.1
2036	5.1
2037	5.1
2038	5.2
2039	5.2
2040	5.2
Belgium	

2023	8.3 (8 - 9.1)
2024	8.2 (7.7 - 9.2)
2025	8.1 (7.4 - 9.2)
2026	8 (7.1 - 9.2)
2027	7.9 (6.8 - 9.3)
2028	7.9 (6.6 - 9.3)
2029	7.9 (6.4 - 9.3)
2030	7.9 (6.2 - 9.4)
2031	7.9 (6 - 9.4)
2032	7.9 (5.9 - 9.4)
2033	7.9 (5.7 - 9.5)
2034	7.9 (5.6 - 9.5)
2035	7.9 (5.6 - 9.5)
2036	8 (5.5 - 9.5)
2037	8 (5.5 - 9.6)
2038	8 (5.4 - 9.6)
2039	8.1 (5.4 - 9.6)
2040	8.1 (5.4 - 9.6)
Bulgaria	
2023	5.1 (4.5 - 5.6)
2024	5 (4.4 - 5.7)
2025	5 (4.3 - 5.8)
2026	5 (4.2 - 5.8)
2027	5 (4.1 - 5.8)
2028	5 (4 - 5.9)

2029	4.9 (3.9 - 6)
2030	4.9 (3.8 - 6.1)
2031	4.9 (3.7 - 6.1)
2032	4.9 (3.6 - 6.1)
2033	4.9 (3.6 - 6.2)
2034	4.8 (3.5 - 6.2)
2035	4.8 (3.4 - 6.2)
2036	4.8 (3.4 - 6.3)
2037	4.8 (3.4 - 6.3)
2038	4.8 (3.3 - 6.3)
2039	4.8 (3.3 - 6.3)
2040	4.8 (3.3 - 6.4)
Cyprus	
2023	9.6 (8.9 - 10.4)
2024	9.6 (8.9 - 10.6)
2025	9.6 (8.9 - 10.8)
2026	9.6 (8.9 - 11.2)
2027	9.6 (8.9 - 11.5)
2028	9.6 (8.9 - 11.8)
2029	9.6 (8.8 - 12.1)
2030	9.6 (8.8 - 12.3)
2031	9.7 (8.8 - 12.7)
2032	9.7 (8.8 - 12.9)
2033	9.7 (8.8 - 13.2)
2034	9.7 (8.8 - 13.4)

2035	9.7 (8.8 - 13.8)
2036	9.7 (8.8 - 14.3)
2037	9.7 (8.8 - 14.8)
2038	9.7 (8.7 - 15.4)
2039	9.7 (8.7 - 15.9)
2040	9.7 (8.7 - 16.5)
Czechia	
2023	4.5 (3.8 - 5.8)
2024	4.5 (3.6 - 5.8)
2025	4.5 (3.3 - 5.8)
2026	4.5 (3.1 - 5.8)
2027	4.5 (2.9 - 5.8)
2028	4.5 (2.7 - 5.8)
2029	4.5 (2.6 - 5.8)
2030	4.5 (2.4 - 5.9)
2031	4.5 (2.3 - 5.9)
2032	4.5 (2.2 - 5.9)
2033	4.6 (2.1 - 5.9)
2034	4.6 (2.1 - 6)
2035	4.6 (2 - 6)
2036	4.6 (2 - 6)
2037	4.6 (2 - 6)
2038	4.6 (2 - 6)
2039	4.6 (2 - 6.1)
2040	4.6 (2 - 6.1)

Germany	
2023	4.1
2024	4.2
2025	4.3
2026	4.3
2027	4.4
2028	4.4
2029	4.5
2030	4.6
2031	4.6
2032	4.7
2033	4.7
2034	4.8
2035	4.8
2036	4.9
2037	4.9
2038	5
2039	5.1
2040	5.1
Denmark	
2023	4.6
2024	4.6
2025	4.6
2026	4.6
2027	4.6

2028	4.6
2029	4.6
2030	4.7
2031	4.7
2032	4.7
2033	4.7
2034	4.7
2035	4.7
2036	4.7
2037	4.7
2038	4.7
2039	4.7
2040	4.7
Estonia	
2023	3.6 (2.3 - 4.6)
2024	3.7 (2.3 - 4.8)
2025	3.7 (2.2 - 5.1)
2026	3.7 (2.2 - 5.4)
2027	3.7 (2.2 - 5.7)
2028	3.8 (2.2 - 6)
2029	3.8 (2.2 - 6.3)
2030	3.8 (2.2 - 6.6)
2031	3.8 (2.3 - 6.9)
2032	3.8 (2.3 - 7.3)
2033	3.9 (2.3 - 7.7)

2034	3.9 (2.3 - 8.1)
2035	3.9 (2.3 - 8.5)
2036	3.9 (2.3 - 9)
2037	3.9 (2.3 - 9.4)
2038	3.9 (2.3 - 9.9)
2039	3.9 (2.3 - 10.5)
2040	3.9 (2.3 - 11)
Spain	
2023	12.1
2024	12.2
2025	12.4
2026	12.5
2027	12.7
2028	12.8
2029	13
2030	13.1
2031	13.2
2032	13.4
2033	13.5
2034	13.6
2035	13.8
2036	13.9
2037	14
2038	14.1
2039	14.3

2040	14.4
Finland	
2023	2.6 (1.9 - 3.8)
2024	2.5 (1.6 - 3.8)
2025	2.4 (1.4 - 3.8)
2026	2.4 (1.3 - 3.8)
2027	2.3 (1.1 - 3.8)
2028	2.3 (1 - 3.8)
2029	2.3 (0.9 - 3.8)
2030	2.3 (0.8 - 3.8)
2031	2.3 (0.7 - 3.8)
2032	2.3 (0.7 - 3.8)
2033	2.3 (0.6 - 3.8)
2034	2.3 (0.6 - 3.8)
2035	2.3 (0.6 - 3.8)
2036	2.4 (0.5 - 3.8)
2037	2.4 (0.5 - 3.8)
2038	2.4 (0.5 - 3.8)
2039	2.5 (0.5 - 3.8)
2040	2.5 (0.5 - 3.8)
France	
2023	13.1
2024	13.1
2025	13.2
2026	13.2

2027	13.2
2028	13.2
2029	13.2
2030	13.3
2031	13.3
2032	13.3
2033	13.3
2034	13.3
2035	13.3
2036	13.3
2037	13.3
2038	13.3
2039	13.3
2040	13.3
United Kingdom	
2023	5.1 (3.9 - 7.2)
2024	5.1 (3.9 - 7.5)
2025	5.1 (3.8 - 7.7)
2026	5.1 (3.7 - 7.8)
2027	5.1 (3.7 - 7.9)
2028	5.1 (3.6 - 8.1)
2029	5.1 (3.6 - 8.2)
2030	5.2 (3.6 - 8.3)
2031	5.2 (3.6 - 8.4)
2032	5.2 (3.6 - 8.6)

2033	5.2 (3.6 - 8.7)
2034	5.2 (3.6 - 8.8)
2035	5.2 (3.6 - 8.9)
2036	5.2 (3.7 - 9)
2037	5.2 (3.7 - 9.1)
2038	5.2 (3.7 - 9.3)
2039	5.3 (3.7 - 9.4)
2040	5.3 (3.8 - 9.5)
Greece	
2023	12.1 (10.8 - 12.9)
2024	12.3 (10.8 - 13.5)
2025	12.5 (10.8 - 14.2)
2026	12.8 (10.9 - 14.9)
2027	13 (10.9 - 15.7)
2028	13.2 (10.9 - 16.6)
2029	13.4 (10.9 - 17.5)
2030	13.6 (10.9 - 18.5)
2031	13.8 (10.9 - 19.6)
2032	14 (10.9 - 20.9)
2033	14.1 (11 - 22.2)
2034	14.3 (11 - 23.6)
2035	14.5 (11 - 25.2)
2036	14.7 (11 - 26.9)
2037	14.9 (11 - 28.7)
2038	15.1 (11 - 30.6)

2039	15.3 (11 - 32.7)
2040	15.4 (11.1 - 34.9)
Croatia	
2023	9.2
2024	10.3
2025	11.4
2026	12.5
2027	13.7
2028	14.8
2029	15.9
2030	17
2031	18.1
2032	19.3
2033	20.4
2034	21.5
2035	22.6
2036	23.8
2037	24.9
2038	26
2039	27.1
2040	28.3
Hungary	
2023	4.2
2024	4.2
2025	4.1

2026	4.1
2027	4.1
2028	4.1
2029	4
2030	4
2031	4
2032	4
2033	4
2034	4
2035	3.9
2036	3.9
2037	3.9
2038	3.9
2039	3.9
2040	3.9
Ireland	
2023	7.7
2024	7.7
2025	7.8
2026	7.8
2027	7.8
2028	7.8
2029	7.8
2030	7.9
2031	7.9

2032	7.9
2033	7.9
2034	7.9
2035	7.9
2036	7.9
2037	7.9
2038	7.9
2039	7.9
2040	7.9
Iceland	
2023	6.2 (5.7 - 6.7)
2024	6.2 (5.6 - 6.7)
2025	6.2 (5.6 - 6.8)
2026	6.2 (5.5 - 6.9)
2027	6.2 (5.4 - 6.9)
2028	6.2 (5.4 - 7)
2029	6.2 (5.4 - 7.1)
2030	6.2 (5.4 - 7.2)
2031	6.2 (5.3 - 7.3)
2032	6.2 (5.3 - 7.3)
2033	6.2 (5.3 - 7.4)
2034	6.2 (5.3 - 7.5)
2035	6.2 (5.3 - 7.6)
2036	6.2 (5.3 - 7.7)
2037	6.3 (5.3 - 7.8)

2038	6.3 (5.3 - 7.9)
2039	6.3 (5.3 - 8)
2040	6.3 (5.3 - 8.1)
Italy	
2023	8
2024	7.8
2025	7.7
2026	7.6
2027	7.5
2028	7.4
2029	7.4
2030	7.3
2031	7.3
2032	7.3
2033	7.4
2034	7.4
2035	7.4
2036	7.4
2037	7.5
2038	7.5
2039	7.6
2040	7.6
Lithuania	
2023	6.8 (6.5 - 7.3)
2024	6.8 (6.5 - 7.3)

2025	6.8 (6.4 - 7.4)
2026	6.8 (6.4 - 7.4)
2027	6.8 (6.4 - 7.5)
2028	6.8 (6.3 - 7.5)
2029	6.8 (6.3 - 7.6)
2030	6.8 (6.3 - 7.6)
2031	6.8 (6.2 - 7.7)
2032	6.8 (6.2 - 7.7)
2033	6.9 (6.1 - 7.8)
2034	6.9 (6.1 - 7.8)
2035	6.9 (6.1 - 7.9)
2036	6.9 (6 - 8)
2037	6.9 (6 - 8)
2038	6.9 (6 - 8.1)
2039	6.9 (6 - 8.1)
2040	6.9 (5.9 - 8.2)
Luxembourg	
2023	6.8
2024	6.6
2025	6.6
2026	6.5
2027	6.4
2028	6.4
2029	6.4
2030	6.4

2031	6.4
2032	6.4
2033	6.4
2034	6.5
2035	6.5
2036	6.6
2037	6.6
2038	6.7
2039	6.7
2040	6.8
Latvia	
2023	6.1
2024	6.9
2025	7.6
2026	8.3
2027	9.1
2028	9.8
2029	10.5
2030	11.3
2031	12
2032	12.8
2033	13.5
2034	14.2
2035	15
2036	15.7

2037	16.5
2038	17.2
2039	18
2040	18.7
Malta	
2023	7.1 (6.7 - 7.5)
2024	7.1 (6.7 - 7.6)
2025	7.2 (6.7 - 7.7)
2026	7.2 (6.7 - 7.7)
2027	7.2 (6.7 - 7.8)
2028	7.2 (6.7 - 7.9)
2029	7.2 (6.7 - 8)
2030	7.3 (6.7 - 8.1)
2031	7.3 (6.7 - 8.2)
2032	7.3 (6.7 - 8.2)
2033	7.3 (6.7 - 8.3)
2034	7.3 (6.7 - 8.3)
2035	7.3 (6.7 - 8.4)
2036	7.3 (6.7 - 8.5)
2037	7.3 (6.7 - 8.5)
2038	7.4 (6.7 - 8.6)
2039	7.4 (6.7 - 8.7)
2040	7.4 (6.7 - 8.8)
Netherlands	
2023	2.1

2024	2
2025	2
2026	2
2027	1.9
2028	1.9
2029	1.8
2030	1.8
2031	1.8
2032	1.7
2033	1.7
2034	1.7
2035	1.6
2036	1.6
2037	1.6
2038	1.6
2039	1.5
2040	1.5
Norway	
2023	2.2
2024	2.2
2025	2.2
2026	2.2
2027	2.2
2028	2.2
2029	2.2

2030	2.2
2031	2.2
2032	2.2
2033	2.2
2034	2.2
2035	2.2
2036	2.2
2037	2.2
2038	2.2
2039	2.2
2040	2.2
Poland	
2023	7.1 (6.6 - 7.9)
2024	7 (6.5 - 7.9)
2025	6.9 (6.4 - 7.9)
2026	6.9 (6.3 - 7.9)
2027	6.8 (6.2 - 7.9)
2028	6.7 (6.1 - 7.9)
2029	6.7 (6 - 7.9)
2030	6.6 (6 - 7.9)
2031	6.6 (5.9 - 7.9)
2032	6.5 (5.8 - 7.9)
2033	6.5 (5.7 - 7.9)
2034	6.5 (5.7 - 7.9)
2035	6.4 (5.6 - 7.9)

2036	6.4 (5.5 - 7.9)
2037	6.4 (5.5 - 7.9)
2038	6.3 (5.4 - 7.9)
2039	6.3 (5.4 - 7.9)
2040	6.3 (5.3 - 7.9)
Portugal	
2023	7.8 (7.6 - 8.1)
2024	7.8 (7.5 - 8.1)
2025	7.8 (7.5 - 8.1)
2026	7.7 (7.4 - 8.1)
2027	7.7 (7.4 - 8.1)
2028	7.7 (7.3 - 8.1)
2029	7.7 (7.3 - 8.1)
2030	7.7 (7.2 - 8)
2031	7.7 (7.2 - 8)
2032	7.7 (7.1 - 8)
2033	7.6 (7.1 - 8)
2034	7.6 (7 - 8)
2035	7.6 (7 - 8)
2036	7.6 (7 - 8)
2037	7.6 (6.9 - 8)
2038	7.6 (6.9 - 8)
2039	7.6 (6.8 - 8)
2040	7.6 (6.8 - 8)
Slovenia	

2023	4.9
2024	4.9
2025	4.9
2026	4.9
2027	4.9
2028	5
2029	5
2030	5
2031	5
2032	5
2033	5
2034	5
2035	5
2036	5
2037	5
2038	5
2039	5
2040	5
Slovakia	
2023	3.7 (3.6 - 4.2)
2024	3.6 (3.5 - 4.3)
2025	3.5 (3.4 - 4.3)
2026	3.4 (3.3 - 4.3)
2027	3.4 (3.2 - 4.4)
2028	3.3 (3.1 - 4.4)

2029	3.2 (3 - 4.5)
2030	3.2 (3 - 4.5)
2031	3.1 (2.9 - 4.6)
2032	3.1 (2.8 - 4.6)
2033	3 (2.7 - 4.7)
2034	2.9 (2.7 - 4.7)
2035	2.9 (2.6 - 4.8)
2036	2.8 (2.5 - 4.8)
2037	2.8 (2.5 - 4.9)
2038	2.8 (2.4 - 4.9)
2039	2.7 (2.4 - 5)
2040	2.7 (2.3 - 5.1)
95% credible intervals are displayed between brackets, where applicable	
Based on antimicrobial consumption rates collected with ECDC's TESSy database	

RMSE - broad-spectrum penicillins

	Exponential smoothing
Austria	1.629
Belgium	1.805 (1.466 - 2.619)
Bulgaria	0.489 (0.248 - 1.676)
Cyprus	3.168 (2.726 - 3.655)
Czechia	1.59 (0.61 - 3.006)
Germany	0.514
Denmark	0.788
Estonia	0.371 (0.232 - 0.874)
Spain	4.185
Finland	0.685 (0.653 - 1.135)
France	2.451
United Kingdom	0.814 (0.231 - 1.845)
Greece	4.447 (4.159 - 4.986)
Croatia	16.72

Hungary	0.703
Ireland	1.971
Iceland	1.535 (0.9 - 2.29)
Italy	2.156
Lithuania	1.084 (1.012 - 1.476)
Luxembourg	2.261
Latvia	3.326
Malta	1.299 (1.268 - 1.527)
Netherlands	0.246
Norway	0.186
Poland	3.329 (3.31 - 3.549)
Portugal	1.048 (1.02 - 1.166)
Slovenia	1.013
Slovakia	1.273 (1.13 - 1.569)
95% credible intervals are displayed between brackets, where applicable	
Based on antimicrobial consumption rates collected with ECDC's TESSy database	

II. Results antimicrobial resistance forecasts

Antimicrobial resistance forecasts

Streptococcus pneumonia against broad-spectrum penicillins

	Exponential smoothing	Random forest	XGBoost	Ensemble
United Kingdom				
2020	6.2%	6.6% (6.4 - 7.6)	8.8% (8.1 - 11.3)	7.2% (6.9 - 8.3)
2021	6.4%	6.8% (6.4 - 7.7)	7.2% (6.6 - 9.1)	6.8% (6.5 - 7.7)
2022	6.6%	6.9% (6.6 - 8)	7% (6.5 - 8.3)	6.8% (6.6 - 7.6)
2023	6.7%	6.9% (6.6 - 8)	7.1% (6.6 - 8.3)	6.9% (6.7 - 7.6)
2024	6.9%	6.8% (6.5 - 7.9)	7% (6.6 - 8.1)	6.9% (6.7 - 7.5)
2025	7.1%	7.1% (6.7 - 8.2)	7% (6.6 - 8.1)	7.1% (6.8 - 7.7)
2026	7.3%	7.1% (6.7 - 8.3)	7% (6.5 - 8.1)	7.1% (6.9 - 7.8)
2027	7.5%	7.1% (6.7 - 8.3)	6.9% (6.5 - 8)	7.2% (7 - 7.8)
2028	7.6%	7.1% (6.7 - 8.3)	7.4% (6.9 - 8.7)	7.4% (7.1 - 8.1)
2029	7.8%	7.1% (6.8 - 8.3)	7.7% (7.2 - 9.1)	7.6% (7.3 - 8.3)
2030	8%	7.2% (6.9 - 8.4)	7.8% (7.2 - 9.1)	7.7% (7.4 - 8.4)
2031	8.1%	7.2% (6.9 - 8.5)	8% (7.4 - 9.5)	7.8% (7.5 - 8.6)
2032	8.3%	7.3% (6.9 - 8.5)	8.1% (7.4 - 9.6)	7.9% (7.6 - 8.7)
2033	8.4%	7.2% (6.8 - 8.5)	8.1% (7.5 - 9.6)	7.9% (7.6 - 8.7)
2034	8.6%	7.3% (6.9 - 8.5)	8.2% (7.5 - 9.6)	8% (7.7 - 8.9)
2035	8.7%	7.4% (7 - 8.6)	8.2% (7.6 - 9.8)	8.1% (7.8 - 9)
2036	8.9%	7.3% (6.9 - 8.6)	8.3% (7.6 - 9.8)	8.2% (7.9 - 9)
2037	9%	7.2% (6.8 - 8.6)	8.3% (7.7 - 9.9)	8.2% (7.9 - 9.1)
2038	9.2%	7.3% (6.8 - 8.6)	8.4% (7.7 - 9.9)	8.3% (8 - 9.1)
2039	9.3%	7.2% (6.7 - 8.5)	8.4% (7.7 - 9.9)	8.3% (8 - 9.2)
2040	9.5%	7.2% (6.7 - 8.5)	8.4% (7.7 - 9.9)	8.4% (8.1 - 9.2)
Austria				
2023	4.6%	5.3% (5.2 - 5.4)	6.8% (6.5 - 7.2)	5.6% (5.5 - 5.8)
2024	4.6%	5.4% (5.3 - 5.5)	6.8% (6.5 - 7.2)	5.6% (5.5 - 5.8)
2025	4.6%	5.3% (5.2 - 5.5)	6.8% (6.5 - 7.2)	5.6% (5.5 - 5.8)
2026	4.6%	5.4% (5.3 - 5.6)	6.9% (6.5 - 7.3)	5.7% (5.5 - 5.8)
2027	4.6%	5.4% (5.3 - 5.6)	7.1% (6.7 - 7.5)	5.7% (5.6 - 5.9)
2028	4.6%	5.4% (5.3 - 5.6)	7.3% (6.8 - 7.8)	5.8% (5.6 - 6.1)
2029	4.6%	5.5% (5.3 - 5.6)	7.4% (6.9 - 7.9)	5.8% (5.6 - 6.1)
2030	4.6%	5.5% (5.4 - 5.7)	7.5% (7 - 8)	5.9% (5.7 - 6.2)
2031	4.6%	5.5% (5.3 - 5.7)	7.5% (7 - 8.1)	5.9% (5.7 - 6.2)
2032	4.6%	5.5% (5.3 - 5.7)	7.6% (7.1 - 8.1)	5.9% (5.7 - 6.2)

	Exponential smoothing	Random forest	XGBoost	Ensemble
2033	4.6%	5.6% (5.4 - 5.8)	7.6% (7.1 - 8.1)	5.9% (5.7 - 6.2)
2034	4.6%	5.6% (5.4 - 5.8)	7.6% (7.1 - 8.1)	6% (5.7 - 6.2)
2035	4.6%	5.6% (5.4 - 5.8)	7.6% (7.1 - 8.1)	6% (5.8 - 6.2)
2036	4.6%	5.6% (5.4 - 5.9)	7.6% (7.1 - 8.1)	6% (5.8 - 6.3)
2037	4.6%	5.7% (5.5 - 5.9)	7.6% (7.1 - 8.1)	6% (5.8 - 6.2)
2038	4.6%	5.8% (5.6 - 6)	7.6% (7.1 - 8.2)	6% (5.8 - 6.3)
2039	4.6%	5.5% (5.3 - 5.7)	7.7% (7.2 - 8.2)	5.9% (5.7 - 6.3)
2040	4.6%	5.5% (5.3 - 5.7)	7.7% (7.2 - 8.2)	6% (5.7 - 6.3)
Belgium				
2023	14%	12.7% (11.5 - 13.1)	7.6% (7.1 - 8.1)	11.4% (10.7 - 11.6)
2024	13.9%	12.4% (11.1 - 12.8)	7.6% (7.1 - 8.1)	11.3% (10.6 - 11.5)
2025	13.8%	12% (10.7 - 12.4)	7.6% (7.1 - 8.1)	11.1% (10.6 - 11.4)
2026	13.8%	11.4% (10.3 - 11.8)	8.3% (7.7 - 9.1)	11.1% (10.7 - 11.4)
2027	13.7%	11.3% (10.2 - 11.7)	8.4% (7.7 - 9.1)	11.1% (10.7 - 11.4)
2028	13.7%	11.2% (10.1 - 11.6)	8.7% (7.9 - 9.4)	11.2% (10.7 - 11.5)
2029	13.6%	11% (10 - 11.4)	9.1% (8.2 - 9.9)	11.2% (10.8 - 11.6)
2030	13.6%	10.9% (9.9 - 11.3)	9.1% (8.3 - 9.9)	11.2% (10.7 - 11.6)
2031	13.6%	10.8% (9.6 - 11.2)	9.1% (8.1 - 10)	11.2% (10.5 - 11.5)
2032	13.6%	10.7% (9.5 - 11.1)	9.2% (8.1 - 10)	11.2% (10.5 - 11.6)
2033	13.6%	10.7% (9.4 - 11.1)	9.5% (8.4 - 10.3)	11.2% (10.6 - 11.7)
2034	13.6%	10.5% (9.2 - 11.1)	9.6% (8.5 - 10.4)	11.2% (10.5 - 11.7)
2035	13.6%	10.5% (9.1 - 11)	9.6% (8.5 - 10.5)	11.2% (10.5 - 11.7)
2036	13.6%	10.5% (9.1 - 11)	9.6% (8.4 - 10.5)	11.2% (10.4 - 11.7)
2037	13.6%	10.5% (9.1 - 11)	9.6% (8.5 - 10.6)	11.2% (10.4 - 11.8)
2038	13.6%	10.5% (9.1 - 11)	9.7% (8.5 - 10.6)	11.3% (10.4 - 11.8)
2039	13.6%	10.5% (9.1 - 11)	9.7% (8.6 - 10.6)	11.3% (10.4 - 11.8)
2040	13.5%	10.4% (9 - 11)	9.8% (8.6 - 10.7)	11.3% (10.5 - 11.8)
Bulgaria				
2023	14.6% (9.2 - 23.5)	18.8% (11.9 - 30.8)	22.3% (18.5 - 25.7)	18.5% (13.7 - 25.9)
2024	14.3% (8.8 - 23.6)	16.5% (10.4 - 27.1)	21.1% (17.4 - 24.3)	17.3% (12.8 - 24.3)
2025	14% (8.4 - 23.7)	17.8% (10.6 - 28.9)	21.7% (17.3 - 25)	17.8% (12.9 - 25.2)
2026	13.7% (8 - 23.9)	18.5% (10.9 - 29.9)	21.6% (17.4 - 25.1)	18% (12.8 - 25.6)
2027	13.5% (7.7 - 23.8)	18.9% (11.4 - 29.6)	21.7% (17.7 - 25.1)	18% (12.9 - 25.4)
2028	13.3% (7.3 - 23.8)	19.6% (12.5 - 29.5)	21.8% (18 - 25.2)	18.2% (13.3 - 25.6)
2029	13.1% (7 - 23.9)	19.3% (13.5 - 27.7)	21.5% (17.9 - 24.8)	17.9% (13.4 - 25)
2030	12.9% (6.7 - 24)	19.2% (13.8 - 27.1)	21.5% (18 - 24.7)	17.8% (13.4 - 24.8)
2031	12.7% (6.4 - 24.1)	19.1% (13.8 - 26.9)	21.4% (17.9 - 24.6)	17.7% (13.2 - 24.8)

	Exponential smoothing	Random forest	XGBoost	Ensemble
2032	12.6% (6 - 24.1)	18.7% (13.6 - 26.2)	21.4% (17.9 - 24.6)	17.5% (13.2 - 24.7)
2033	12.4% (5.8 - 24.2)	18.5% (13.5 - 26)	21.4% (17.8 - 24.7)	17.4% (13 - 24.6)
2034	12.2% (5.5 - 24.2)	18.5% (13.4 - 25.7)	21.4% (17.9 - 24.6)	17.3% (12.9 - 24.6)
2035	12.1% (5.3 - 24.3)	18.4% (13.3 - 25.5)	21.2% (17.7 - 24.5)	17.1% (12.8 - 24.6)
2036	11.9% (5 - 24.3)	18.4% (13.3 - 25.5)	21.3% (17.8 - 24.6)	17% (12.7 - 24.6)
2037	11.7% (4.8 - 24.4)	18.3% (13.2 - 25.4)	21.3% (17.8 - 24.6)	17% (12.6 - 24.6)
2038	11.6% (4.6 - 24.5)	18.3% (13.1 - 25.4)	21.3% (17.9 - 24.7)	17% (12.6 - 24.6)
2039	11.5% (4.4 - 24.6)	17.6% (13 - 23.8)	20.2% (17.1 - 23.3)	16.3% (12.1 - 23.5)
2040	11.3% (4.2 - 24.8)	17.5% (13 - 23.4)	20% (17 - 23.3)	16.2% (12.1 - 23.3)
Czechia				
2023	5.3%	6.3% (6.1 - 6.5)	9.3% (8.6 - 10.2)	7% (6.7 - 7.4)
2024	5.4%	6.3% (6.1 - 6.6)	9.3% (8.6 - 10.2)	7% (6.8 - 7.5)
2025	5.5%	6.6% (6.3 - 7.1)	9.5% (8.7 - 10.7)	7.2% (6.9 - 7.8)
2026	5.6%	6.6% (6.4 - 7.3)	9.6% (8.8 - 10.8)	7.3% (7 - 7.9)
2027	5.7%	7% (6.6 - 7.7)	9.5% (8.6 - 10.7)	7.4% (7.1 - 8)
2028	5.8%	7.3% (7 - 8.3)	8.4% (7.7 - 9.5)	7.2% (6.9 - 7.7)
2029	5.9%	7.4% (7.1 - 8.6)	8.5% (7.8 - 9.7)	7.3% (7 - 7.9)
2030	6%	7.5% (7.1 - 8.8)	8.9% (8.1 - 10.2)	7.5% (7.2 - 8.2)
2031	6.1%	7.6% (7.2 - 9)	8.9% (8 - 10.2)	7.5% (7.2 - 8.3)
2032	6.2%	7.7% (7.3 - 9.1)	8.7% (7.9 - 10.1)	7.6% (7.2 - 8.3)
2033	6.4%	7.7% (7.3 - 9.1)	8.7% (7.9 - 10.1)	7.6% (7.2 - 8.4)
2034	6.5%	7.7% (7.3 - 9.1)	8.9% (8 - 10.3)	7.7% (7.3 - 8.5)
2035	6.6%	7.8% (7.4 - 9.2)	9% (8.1 - 10.4)	7.8% (7.4 - 8.6)
2036	6.7%	7.8% (7.5 - 9.3)	9% (8.2 - 10.5)	7.8% (7.5 - 8.6)
2037	6.8%	7.9% (7.5 - 9.4)	9.1% (8.2 - 10.5)	7.9% (7.6 - 8.7)
2038	6.9%	7.9% (7.5 - 9.3)	9.1% (8.2 - 10.5)	8% (7.6 - 8.8)
2039	7%	7.9% (7.6 - 9.3)	9.1% (8.3 - 10.6)	8% (7.7 - 8.8)
2040	7.1%	8% (7.6 - 9.3)	9.1% (8.3 - 10.6)	8.1% (7.7 - 8.9)
Germany				
2023	6.3%	6.5% (6.4 - 6.6)	8.2% (7.7 - 8.7)	7% (6.8 - 7.3)
2024	6.5%	6.6% (6.5 - 6.7)	8.1% (7.6 - 8.6)	7.1% (6.9 - 7.4)
2025	6.7%	6.6% (6.5 - 6.7)	8% (7.5 - 8.6)	7.1% (6.9 - 7.4)
2026	6.9%	6.5% (6.4 - 6.6)	7.9% (7.4 - 8.4)	7.1% (6.9 - 7.4)
2027	7%	6.5% (6.3 - 6.7)	7.9% (7.4 - 8.4)	7.2% (7 - 7.5)
2028	7.2%	6.5% (6.3 - 6.6)	7.9% (7.4 - 8.4)	7.2% (7 - 7.6)
2029	7.4%	6.5% (6.3 - 6.6)	7.9% (7.4 - 8.5)	7.3% (7.1 - 7.7)
2030	7.5%	6.5% (6.3 - 6.7)	7.9% (7.4 - 8.4)	7.3% (7.1 - 7.8)

	Exponential smoothing	Random forest	XGBoost	Ensemble
2031	7.7%	6.5% (6.3 - 6.7)	7.9% (7.4 - 8.4)	7.4% (7.2 - 7.9)
2032	7.9%	6.5% (6.3 - 6.7)	7.9% (7.4 - 8.4)	7.4% (7.2 - 8)
2033	8%	6.4% (6.2 - 6.6)	7.9% (7.4 - 8.4)	7.5% (7.3 - 8.1)
2034	8.2%	6.3% (6.2 - 6.5)	8% (7.5 - 8.5)	7.5% (7.3 - 8.2)
2035	8.4%	6.4% (6.2 - 6.6)	8% (7.5 - 8.5)	7.6% (7.4 - 8.3)
2036	8.5%	6.3% (6.1 - 6.5)	8.1% (7.6 - 8.6)	7.6% (7.4 - 8.4)
2037	8.7%	6.3% (6.1 - 6.5)	8.2% (7.7 - 8.7)	7.7% (7.5 - 8.5)
2038	8.8%	6.3% (6.1 - 6.5)	8.2% (7.6 - 8.7)	7.8% (7.6 - 8.6)
2039	9%	6.3% (6.1 - 6.5)	8.2% (7.7 - 8.7)	7.8% (7.6 - 8.7)
2040	9.1%	6.3% (6.1 - 6.6)	8.2% (7.7 - 8.7)	7.9% (7.7 - 8.7)
Denmark				
2023	6.1%	5.1% (5 - 5.3)	6.8% (6.4 - 7.2)	6% (5.9 - 6.5)
2024	6.2%	5.5% (5.3 - 5.6)	6.8% (6.4 - 7.2)	6.2% (6 - 6.6)
2025	6.4%	5.5% (5.3 - 5.6)	6.8% (6.4 - 7.2)	6.2% (6.1 - 6.7)
2026	6.5%	5.5% (5.4 - 5.7)	7% (6.6 - 7.4)	6.4% (6.2 - 6.9)
2027	6.7%	5.5% (5.4 - 5.7)	7.1% (6.7 - 7.6)	6.5% (6.3 - 7)
2028	6.8%	5.6% (5.4 - 5.7)	7.2% (6.7 - 7.7)	6.5% (6.3 - 7.1)
2029	7%	5.6% (5.4 - 5.7)	7.2% (6.7 - 7.7)	6.6% (6.4 - 7.2)
2030	7.1%	5.4% (5.2 - 5.5)	6.6% (6.2 - 7.1)	6.4% (6.2 - 7)
2031	7.3%	5.4% (5.2 - 5.5)	6.7% (6.2 - 7.1)	6.4% (6.3 - 7.1)
2032	7.4%	5.3% (5.2 - 5.5)	6.7% (6.2 - 7.1)	6.5% (6.3 - 7.2)
2033	7.6%	5.3% (5.2 - 5.5)	6.7% (6.2 - 7.1)	6.5% (6.3 - 7.2)
2034	7.7%	5.3% (5.2 - 5.5)	6.7% (6.2 - 7.1)	6.6% (6.4 - 7.3)
2035	7.8%	5.4% (5.2 - 5.6)	6.7% (6.2 - 7.1)	6.6% (6.5 - 7.4)
2036	8%	5.4% (5.2 - 5.5)	6.7% (6.2 - 7.1)	6.7% (6.5 - 7.4)
2037	8.1%	5.3% (5.1 - 5.5)	7.3% (6.8 - 7.8)	6.9% (6.7 - 7.8)
2038	8.3%	5% (4.8 - 5.2)	6.7% (6.3 - 7.3)	6.7% (6.5 - 7.6)
2039	8.4%	5.2% (5 - 5.4)	7.3% (6.7 - 7.8)	7% (6.8 - 8)
2040	8.5%	5.5% (5.3 - 5.7)	7.5% (7 - 8.1)	7.2% (7 - 8.1)
Estonia				
2023	4.5% (3.6 - 5.9)	4.9% (4.7 - 5.2)	6.9% (6.4 - 8)	5.5% (5.1 - 6.1)
2024	4.7% (3.6 - 6.7)	4.8% (4.7 - 5.1)	6.9% (6.3 - 8)	5.6% (5.1 - 6.3)
2025	4.9% (3.7 - 7.5)	5.2% (5 - 5.6)	7.7% (6.9 - 9)	6.1% (5.4 - 7.1)
2026	5.1% (3.7 - 8.4)	5.3% (5.1 - 5.7)	7.8% (7 - 9.1)	6.2% (5.5 - 7.4)
2027	5.3% (3.8 - 9.4)	5.5% (5.2 - 5.8)	8.7% (7.7 - 10.1)	6.7% (5.8 - 8.2)
2028	5.5% (3.8 - 10.5)	6% (5.7 - 6.4)	8.4% (7.4 - 9.8)	6.8% (5.9 - 8.6)
2029	5.7% (3.9 - 11.6)	6.2% (5.9 - 6.7)	8.2% (7.2 - 9.7)	6.9% (6 - 9)

	Exponential smoothing	Random forest	XGBoost	Ensemble
2030	5.9% (3.9 - 12.8)	6.6% (6.3 - 7.1)	7.5% (6.7 - 8.8)	6.8% (5.9 - 9.3)
2031	6.1% (3.9 - 14.1)	6.7% (6.3 - 7.3)	7.5% (6.7 - 8.9)	6.9% (5.9 - 9.8)
2032	6.4% (3.9 - 15.5)	6.7% (6.4 - 7.4)	7.6% (6.8 - 8.9)	7% (6 - 10.3)
2033	6.6% (4 - 16.9)	6.8% (6.4 - 7.5)	7.6% (6.7 - 8.9)	7.1% (6 - 10.8)
2034	6.8% (4 - 18.5)	6.8% (6.4 - 7.5)	7.7% (6.8 - 9)	7.2% (6 - 11.4)
2035	7% (4 - 20.1)	6.8% (6.4 - 7.6)	7.8% (6.8 - 9)	7.3% (6.1 - 12)
2036	7.2% (4.1 - 21.8)	6.8% (6.4 - 7.7)	7.8% (6.9 - 9.1)	7.4% (6.1 - 12.6)
2037	7.5% (4.1 - 23.7)	6.8% (6.4 - 7.8)	7.8% (6.9 - 9.1)	7.5% (6.1 - 13.3)
2038	7.7% (4.1 - 25.5)	6.8% (6.3 - 7.8)	7.8% (6.9 - 9.1)	7.6% (6.1 - 13.9)
2039	7.9% (4.2 - 27.5)	6.9% (6.2 - 7.9)	7.9% (6.9 - 9.3)	7.7% (6.2 - 14.6)
2040	8.1% (4.2 - 29.5)	6.9% (6.1 - 7.9)	7.9% (7 - 9.4)	7.8% (6.2 - 15.4)
Spain				
2023	21.3%	19.4% (19.1 - 19.9)	15.4% (14.3 - 16.5)	18.7% (18.2 - 19.1)
2024	21.3%	19% (18.6 - 19.5)	15.7% (14.4 - 16.9)	18.7% (18.1 - 19.1)
2025	21.3%	18.6% (18.1 - 19.1)	15.9% (14.5 - 17.2)	18.6% (18 - 19.1)
2026	21.3%	17.4% (16.8 - 17.9)	15.8% (14.3 - 17.2)	18.2% (17.6 - 18.8)
2027	21.3%	17.3% (16.7 - 17.9)	15.8% (14.4 - 17.2)	18.2% (17.6 - 18.8)
2028	21.3%	17.3% (16.7 - 17.9)	15.8% (14.3 - 17.2)	18.2% (17.6 - 18.8)
2029	21.3%	17.2% (16.6 - 17.9)	15.9% (14.5 - 17.3)	18.2% (17.6 - 18.8)
2030	21.3%	16.8% (16.1 - 17.5)	16.1% (14.6 - 17.5)	18.1% (17.5 - 18.9)
2031	21.3%	16.1% (15.4 - 16.8)	15.4% (14 - 16.7)	17.6% (17.1 - 18.5)
2032	21.3%	16% (15.3 - 16.7)	15.3% (13.9 - 16.6)	17.6% (17 - 18.5)
2033	21.3%	15.6% (14.9 - 16.4)	13.4% (12 - 14.6)	16.8% (16.2 - 17.5)
2034	21.3%	15.6% (14.8 - 16.3)	13.2% (11.9 - 14.4)	16.7% (16.2 - 17.4)
2035	21.3%	15.3% (14.6 - 16.1)	13.1% (11.8 - 14.4)	16.6% (16.1 - 17.4)
2036	21.3%	15.2% (14.4 - 15.9)	13% (11.7 - 14.1)	16.5% (16 - 17.3)
2037	21.3%	15% (14.2 - 15.7)	12.9% (11.7 - 14.1)	16.4% (15.9 - 17.3)
2038	21.3%	14.9% (14.2 - 15.6)	12.9% (11.7 - 14.1)	16.4% (15.9 - 17.3)
2039	21.3%	14.8% (14.1 - 15.5)	12.7% (11.5 - 13.8)	16.3% (15.8 - 17.2)
2040	21.3%	14.7% (14 - 15.4)	12.6% (11.4 - 13.8)	16.3% (15.7 - 17.2)
Finland				
2023	10.7%	8.9% (7.7 - 9.8)	6.3% (5.7 - 6.7)	8.6% (8.1 - 9)
2024	10.5%	8.7% (7.5 - 9.6)	6.3% (5.7 - 6.8)	8.5% (8 - 8.9)
2025	10.4%	8.6% (7.5 - 9.5)	6.4% (5.8 - 6.9)	8.5% (8 - 8.9)
2026	10.3%	8.8% (7.6 - 9.7)	6.5% (6 - 7)	8.5% (8.1 - 9)
2027	10.2%	8.8% (7.5 - 9.6)	6.6% (6 - 7.2)	8.5% (8.1 - 8.9)
2028	10.2%	8.8% (7.6 - 9.7)	6.8% (6.2 - 7.3)	8.6% (8.1 - 9)

	Exponential smoothing	Random forest	XGBoost	Ensemble
2029	10.1%	8.8% (7.6 - 9.7)	6.8% (6.2 - 7.3)	8.5% (8.1 - 9)
2030	10.1%	8.8% (7.6 - 9.7)	6.8% (6.3 - 7.4)	8.5% (8.1 - 9)
2031	10.1%	8.8% (7.6 - 9.7)	6.9% (6.3 - 7.5)	8.6% (8.1 - 9)
2032	10%	8.8% (7.5 - 9.7)	6.9% (6.3 - 7.5)	8.6% (8.1 - 9)
2033	10%	8.9% (7.5 - 9.8)	6.9% (6.3 - 7.5)	8.6% (8.1 - 9)
2034	10%	8.8% (7.5 - 9.8)	6.9% (6.3 - 7.5)	8.5% (8.1 - 9)
2035	10%	8.8% (7.5 - 9.8)	6.9% (6.3 - 7.5)	8.5% (8.1 - 9)
2036	10%	8.8% (7.4 - 9.7)	6.9% (6.3 - 7.5)	8.5% (8 - 9)
2037	10%	8.8% (7.4 - 9.7)	6.8% (6.3 - 7.4)	8.5% (8 - 8.9)
2038	10%	8.8% (7.4 - 9.6)	6.8% (6.3 - 7.4)	8.5% (8 - 8.9)
2039	10%	8.7% (7.3 - 9.6)	6.8% (6.2 - 7.4)	8.5% (8 - 8.9)
2040	10%	8.7% (7.3 - 9.6)	6.7% (6.2 - 7.3)	8.4% (7.9 - 8.9)
France				
2023	35.2%	25.8% (25 - 26.7)	11.8% (11.1 - 12.6)	24.2% (23.5 - 24.7)
2024	36.6%	24.6% (23.8 - 25.7)	12% (11.3 - 12.8)	24.4% (24 - 24.9)
2025	37.9%	23.7% (22.7 - 24.8)	11.7% (11 - 12.3)	24.4% (24 - 25)
2026	39.1%	23% (22.1 - 24.1)	11.5% (10.8 - 12.2)	24.6% (24.1 - 25.5)
2027	40.2%	22.6% (21.6 - 23.6)	11.2% (10.4 - 11.9)	24.7% (24.2 - 25.8)
2028	41.2%	22.4% (21.4 - 23.4)	11.1% (10.4 - 11.8)	24.9% (24.5 - 26.3)
2029	42%	22% (21 - 23.1)	11% (10.3 - 11.6)	25% (24.6 - 26.6)
2030	42.8%	21.7% (20.7 - 22.8)	11% (10.3 - 11.6)	25.2% (24.7 - 27)
2031	43.5%	21.2% (20.2 - 22.4)	10.9% (10.1 - 11.5)	25.2% (24.8 - 27.3)
2032	44.1%	20.1% (19.1 - 21.2)	11.5% (10.6 - 12.2)	25.2% (24.8 - 27.9)
2033	44.6%	20% (19 - 21.1)	11.5% (10.6 - 12.2)	25.4% (25 - 28.2)
2034	45.1%	19.8% (18.8 - 20.9)	11.5% (10.5 - 12.2)	25.5% (25 - 28.4)
2035	45.5%	19.7% (18.7 - 20.8)	11.4% (10.5 - 12.1)	25.6% (25.1 - 28.6)
2036	45.9%	19.7% (18.7 - 20.7)	11.4% (10.5 - 12.1)	25.7% (25.2 - 28.8)
2037	46.2%	20.1% (19.2 - 21.2)	10.8% (10.1 - 11.5)	25.8% (25.4 - 28.7)
2038	46.5%	19.4% (18.4 - 20.4)	11.4% (10.5 - 12.1)	25.8% (25.3 - 29.1)
2039	46.8%	19.3% (18.3 - 20.3)	11.5% (10.5 - 12.2)	25.9% (25.4 - 29.3)
2040	47%	19.2% (18.2 - 20.3)	11.5% (10.5 - 12.2)	25.9% (25.5 - 29.4)
Greece				
2023	39.3% (7.2 - 57.4)	33.6% (14.5 - 39.4)	31.9% (18.6 - 35.7)	35.1% (14 - 43.6)
2024	40.5% (7.4 - 65.2)	31.9% (14.2 - 37.5)	31.7% (18.9 - 35.7)	34.9% (14.1 - 45)
2025	42% (7.5 - 81)	30.9% (14.1 - 36.4)	31.5% (19.2 - 35.6)	35.1% (14.2 - 48)
2026	43% (7.7 - 116.4)	29.6% (13.9 - 34.9)	31.5% (19.1 - 35.6)	35.1% (14.3 - 54.4)
2027	43.9% (7.8 - 157.8)	28.3% (13.7 - 33.6)	31.4% (19.1 - 35.4)	35.1% (14.3 - 66.9)

	Exponential smoothing	Random forest	XGBoost	Ensemble
2028	44.9% (7.9 - 209.4)	27.7% (13.8 - 32.9)	31.3% (19.2 - 35.3)	35.3% (14.4 - 87.1)
2029	46% (8 - 263.6)	27.1% (13.8 - 32.2)	30.9% (19.1 - 35.1)	35.3% (14.3 - 107.4)
2030	47.1% (8.1 - 327.5)	26.7% (13.8 - 31.6)	30.6% (19.2 - 34.8)	35.4% (14.3 - 137.5)
2031	48.2% (8.2 - 427.2)	26.2% (13.8 - 30.9)	30.5% (19.3 - 34.4)	35.3% (14.3 - 174.2)
2032	49.3% (8.3 - 549.1)	26.1% (13.8 - 30.6)	30.5% (19.3 - 34.5)	35.7% (14.4 - 204.8)
2033	50.6% (8.4 - 636.3)	23.3% (13.5 - 26.7)	28.3% (18.6 - 32)	34.5% (14 - 245)
2034	51.8% (8.5 - 786.7)	22.9% (13.5 - 26.2)	28.3% (18.6 - 32)	34.7% (14 - 303.2)
2035	52.8% (8.7 - 957.7)	21.9% (13.3 - 25)	27.8% (18.3 - 31.5)	34.6% (13.9 - 334.5)
2036	54.2% (8.9 - 1124.2)	20.6% (13 - 23.4)	25.6% (17.1 - 29.3)	33.9% (13.6 - 404.3)
2037	55.5% (9 - 1335)	20% (12.7 - 22.6)	22.7% (15.4 - 25.8)	33.2% (13 - 483.5)
2038	56.6% (9.2 - 1569.9)	19.5% (12.6 - 22.3)	22.4% (15.3 - 25.5)	33.2% (12.9 - 544.1)
2039	57.4% (9.3 - 1749.2)	19.1% (12.4 - 21.7)	21.9% (15 - 25.1)	33.4% (12.6 - 593.6)
2040	58% (9.4 - 2038)	18.7% (12.1 - 21.2)	21.1% (14.4 - 24.2)	33.4% (12.4 - 689.7)
Croatia				
2023	22%	17.7% (17.1 - 18.4)	17.8% (15.6 - 19.1)	19.2% (18.3 - 20.1)
2024	22%	16.7% (16 - 17.4)	17.6% (15.3 - 19.1)	18.8% (18 - 20)
2025	22.1%	16.1% (15.4 - 16.9)	18% (16.5 - 19.4)	18.8% (18.1 - 20.2)
2026	22.1%	15.9% (15.2 - 16.6)	18% (16.6 - 19.3)	18.7% (18.2 - 20.2)
2027	22.1%	15.7% (15 - 16.5)	17.9% (16.5 - 19.2)	18.6% (18.1 - 20.2)
2028	22.1%	15.7% (14.9 - 16.4)	16.7% (15.3 - 18)	18.2% (17.7 - 19.6)
2029	22.1%	15.6% (14.8 - 16.5)	16.6% (15.2 - 17.9)	18.1% (17.6 - 19.6)
2030	22.1%	15.5% (14.6 - 16.5)	16.3% (15 - 17.6)	18% (17.5 - 19.4)
2031	22.1%	15% (14.2 - 16)	15.5% (14.1 - 16.8)	17.6% (17.1 - 19)
2032	22.2%	14.8% (14.1 - 15.8)	15.5% (14.1 - 16.7)	17.5% (17 - 19)
2033	22.2%	14.5% (13.7 - 15.5)	14.7% (13.4 - 15.9)	17.2% (16.6 - 18.6)
2034	22.2%	14.3% (13.5 - 15.3)	13.3% (11.9 - 14.5)	16.6% (16.1 - 18)
2035	22.2%	14.1% (13.3 - 15.1)	13.2% (11.7 - 14.3)	16.5% (15.9 - 17.8)
2036	22.2%	14.1% (13.3 - 15.1)	12.9% (11.5 - 14)	16.4% (15.8 - 17.7)
2037	22.2%	14.1% (13.3 - 15)	12.8% (11.4 - 14)	16.4% (15.8 - 17.7)
2038	22.2%	14.1% (13.3 - 15)	12.8% (11.4 - 14)	16.4% (15.8 - 17.7)
2039	22.2%	14.2% (13.4 - 15.1)	12.9% (11.5 - 14)	16.4% (15.9 - 17.7)
2040	22.2%	14.2% (13.4 - 15.1)	12.9% (11.5 - 14)	16.5% (15.9 - 17.7)
Hungary				
2023	7.7%	8.8% (8.5 - 9)	12.7% (11.8 - 13.6)	9.7% (9.4 - 10.3)
2024	7.6%	8.5% (8.2 - 8.8)	12.7% (11.8 - 13.6)	9.6% (9.3 - 10.3)
2025	7.5%	8.5% (8.2 - 8.8)	12.6% (11.7 - 13.6)	9.6% (9.2 - 10.2)
2026	7.4%	8.7% (8.4 - 9.1)	12.6% (11.7 - 13.6)	9.6% (9.2 - 10.2)

	Exponential smoothing	Random forest	XGBoost	Ensemble
2027	7.4%	8.8% (8.4 - 9.1)	12.5% (11.6 - 13.5)	9.6% (9.2 - 10.1)
2028	7.3%	9.1% (8.7 - 9.4)	12% (11.1 - 12.9)	9.5% (9.1 - 9.9)
2029	7.3%	9.1% (8.8 - 9.5)	11.9% (11 - 12.8)	9.4% (9.1 - 9.8)
2030	7.2%	9.3% (8.9 - 9.7)	11.3% (10.4 - 12.2)	9.3% (8.9 - 9.6)
2031	7.2%	9.4% (9 - 9.8)	10.3% (9.4 - 11.2)	8.9% (8.6 - 9.3)
2032	7.2%	9.5% (9.1 - 9.9)	10.3% (9.5 - 11.3)	9% (8.6 - 9.3)
2033	7.1%	9.6% (9.2 - 10)	10.6% (9.7 - 11.8)	9.1% (8.7 - 9.5)
2034	7.1%	9.8% (9.3 - 10.2)	10.6% (9.7 - 11.8)	9.2% (8.7 - 9.6)
2035	7.1%	9.8% (9.4 - 10.2)	10.6% (9.6 - 11.7)	9.1% (8.7 - 9.6)
2036	7.1%	9.8% (9.3 - 10.2)	10.6% (9.7 - 11.8)	9.1% (8.7 - 9.6)
2037	7.1%	9.9% (9.5 - 10.3)	10.6% (9.7 - 11.8)	9.2% (8.7 - 9.6)
2038	7%	10.1% (9.7 - 10.5)	10.7% (9.8 - 11.9)	9.3% (8.8 - 9.7)
2039	7%	10.1% (9.7 - 10.6)	10.8% (9.9 - 12)	9.3% (8.8 - 9.7)
2040	7%	10.2% (9.8 - 10.7)	10.8% (9.9 - 12)	9.3% (8.8 - 9.7)
Ireland				
2023	22.7%	18.7% (18.3 - 19.2)	14.6% (13 - 16)	18.7% (18.1 - 19.2)
2024	23.2%	18% (17.5 - 18.6)	14.4% (12.9 - 15.7)	18.5% (18 - 19.1)
2025	23.6%	17.7% (17.2 - 18.3)	13.8% (12.4 - 15.1)	18.4% (17.9 - 18.9)
2026	23.9%	17.3% (16.7 - 17.9)	13.5% (12.1 - 14.8)	18.3% (17.7 - 18.9)
2027	24.2%	16.7% (16.1 - 17.3)	12.3% (11 - 13.6)	17.7% (17.2 - 18.4)
2028	24.4%	16.5% (15.9 - 17.2)	11.6% (10.5 - 12.7)	17.5% (17.1 - 18.2)
2029	24.5%	16.4% (15.8 - 17.1)	11.5% (10.3 - 12.7)	17.5% (17 - 18.2)
2030	24.7%	16.2% (15.7 - 16.9)	12.4% (11.3 - 13.4)	17.8% (17.3 - 18.7)
2031	24.8%	15.6% (15 - 16.3)	12.8% (11.7 - 14)	17.7% (17.3 - 18.9)
2032	24.9%	15.3% (14.7 - 16)	12.9% (11.8 - 14.2)	17.7% (17.2 - 19)
2033	24.9%	15.1% (14.5 - 15.8)	12.9% (11.8 - 14.3)	17.7% (17.2 - 19)
2034	25%	14.8% (14.3 - 15.5)	12.9% (11.7 - 14.5)	17.6% (17.1 - 19.1)
2035	25%	14.9% (14.3 - 15.5)	13.1% (12 - 14.7)	17.7% (17.2 - 19.1)
2036	25.1%	14.9% (14.2 - 15.5)	13.1% (11.9 - 14.7)	17.7% (17.2 - 19.1)
2037	25.1%	14.9% (14.2 - 15.5)	13.2% (11.9 - 14.8)	17.8% (17.2 - 19.2)
2038	25.1%	14.8% (14.2 - 15.4)	13.2% (12 - 14.9)	17.8% (17.2 - 19.3)
2039	25.1%	14.7% (14.1 - 15.2)	13.4% (12.1 - 15)	17.8% (17.2 - 19.4)
2040	25.2%	14.7% (14.1 - 15.3)	13.8% (12.5 - 15.7)	17.9% (17.4 - 19.6)
Iceland				
2023	19.3% (11.6 - 29.9)	17% (14.5 - 19.3)	8% (6.3 - 9)	14.7% (11.1 - 18.7)
2024	20.9% (12.2 - 35.8)	16.6% (14 - 18.8)	7.9% (6.3 - 9)	15.1% (11.3 - 20.7)
2025	22.3% (12.4 - 43.5)	16% (13.5 - 18.2)	7.8% (6.1 - 8.8)	15.3% (11.2 - 22.8)

	Exponential smoothing	Random forest	XGBoost	Ensemble
2026	23.8% (12.7 - 53)	15.5% (13.1 - 17.6)	7.7% (6.1 - 8.6)	15.6% (11.2 - 26)
2027	25.2% (12.9 - 64.3)	15.3% (12.9 - 17.4)	7.6% (6.1 - 8.6)	16.1% (11.2 - 29.5)
2028	26.5% (13.1 - 77)	15.1% (12.7 - 17.1)	7.6% (6.1 - 8.5)	16.5% (11.2 - 33.9)
2029	27.9% (13.2 - 90.8)	14.9% (12.5 - 16.8)	7.5% (6.1 - 8.3)	16.8% (11.1 - 38.7)
2030	29.2% (13.4 - 108.3)	14.6% (12.3 - 16.5)	7.3% (6.1 - 8.2)	17.2% (11.1 - 44.1)
2031	30.6% (13.6 - 127.9)	14.4% (12.1 - 16.2)	7.2% (6 - 8)	17.6% (11.1 - 50.5)
2032	32.1% (13.9 - 148.9)	14.1% (11.8 - 16)	7.1% (6 - 7.9)	17.9% (11 - 57.5)
2033	33.6% (14.1 - 172.1)	14.1% (11.7 - 15.9)	7.1% (6 - 7.9)	18.4% (11 - 65.3)
2034	34.9% (14.4 - 197.8)	14% (11.6 - 15.8)	7.1% (6 - 7.9)	18.9% (11.1 - 73.6)
2035	36.4% (14.6 - 225.9)	13.9% (11.5 - 15.6)	7% (5.9 - 7.8)	19.4% (11.1 - 82.9)
2036	37.7% (14.7 - 256.6)	13.8% (11.4 - 15.5)	6.8% (5.7 - 7.5)	19.8% (11.1 - 92.9)
2037	39.1% (14.9 - 289.9)	13.8% (11.4 - 15.5)	6.8% (5.7 - 7.6)	20.3% (11.2 - 103.5)
2038	40.6% (15 - 324.7)	13.7% (11.3 - 15.4)	6.8% (5.7 - 7.6)	20.7% (11.3 - 115.1)
2039	42% (15.1 - 361.8)	13.6% (11.3 - 15.4)	6.8% (5.8 - 7.6)	21.2% (11.4 - 128.1)
2040	43.5% (15.1 - 401.4)	13.5% (11.1 - 15.2)	6.8% (5.8 - 7.6)	21.7% (11.5 - 142)
Italy				
2023	11.9%	12.6% (12.3 - 12.9)	16.4% (15.1 - 17.9)	13.7% (13.2 - 14.4)
2024	12.1%	12.6% (12.3 - 13)	16.3% (15 - 17.8)	13.7% (13.2 - 14.4)
2025	12.2%	12.5% (12.2 - 12.9)	15.3% (14.1 - 16.9)	13.4% (12.9 - 14)
2026	12.3%	12.5% (12.2 - 12.9)	15% (13.7 - 16.5)	13.3% (12.8 - 14)
2027	12.5%	12.4% (12.1 - 12.9)	13.1% (12 - 14.4)	12.7% (12.3 - 13.2)
2028	12.6%	12.4% (12.1 - 12.9)	12.9% (11.9 - 14.2)	12.7% (12.2 - 13.2)
2029	12.7%	12.4% (12 - 12.8)	12.9% (11.9 - 14.2)	12.7% (12.3 - 13.2)
2030	12.9%	12.4% (12 - 12.9)	12.8% (11.8 - 14.2)	12.7% (12.3 - 13.2)
2031	13%	12.4% (12 - 12.9)	12.6% (11.6 - 14)	12.7% (12.3 - 13.2)
2032	13.1%	12.5% (12 - 13)	12.6% (11.6 - 13.9)	12.7% (12.4 - 13.3)
2033	13.2%	12.4% (12 - 13.1)	12.4% (11.4 - 13.7)	12.7% (12.3 - 13.2)
2034	13.3%	12.4% (12 - 13.1)	12.4% (11.4 - 13.7)	12.7% (12.3 - 13.2)
2035	13.4%	12.4% (11.9 - 13)	12.2% (11.2 - 13.6)	12.7% (12.3 - 13.2)
2036	13.5%	12.4% (11.9 - 13)	12.3% (11.2 - 13.6)	12.7% (12.3 - 13.3)
2037	13.6%	12.4% (11.9 - 13)	12.8% (11.8 - 14.3)	13% (12.5 - 13.5)
2038	13.7%	12.4% (11.9 - 13)	12.9% (11.9 - 14.3)	13% (12.6 - 13.6)
2039	13.8%	12.4% (12 - 13.1)	14.7% (13.4 - 16.3)	13.7% (13.2 - 14.5)
2040	13.9%	12.4% (12 - 13.1)	14.8% (13.5 - 16.4)	13.7% (13.2 - 14.5)
Lithuania				
2023	9.1%	10.1% (9.6 - 10.5)	14.8% (12.3 - 16.3)	11.4% (10.4 - 12.1)
2024	9.1%	10.1% (9.6 - 10.6)	14.9% (12.3 - 16.4)	11.4% (10.4 - 12.2)

	Exponential smoothing	Random forest	XGBoost	Ensemble
2025	9.2%	10% (9.2 - 10.6)	14.3% (11.8 - 15.9)	11.2% (10.1 - 12)
2026	9.2%	10.2% (9.4 - 10.8)	15% (12.1 - 16.8)	11.5% (10.3 - 12.5)
2027	9.2%	10.4% (9.5 - 11)	12.9% (10.7 - 14.7)	10.9% (9.8 - 11.6)
2028	9.3%	10.5% (9.8 - 11.1)	12.7% (10.8 - 14.5)	10.9% (10 - 11.5)
2029	9.3%	10.6% (10.1 - 11.1)	12.5% (10.6 - 14.2)	10.8% (10.1 - 11.5)
2030	9.3%	10.7% (10.1 - 11.2)	12.4% (10.5 - 14.1)	10.8% (10.1 - 11.5)
2031	9.3%	10.7% (10.1 - 11.2)	12.4% (10.5 - 14.1)	10.8% (10.1 - 11.5)
2032	9.3%	10.7% (10.1 - 11.2)	12.5% (10.6 - 14.2)	10.8% (10.1 - 11.5)
2033	9.3%	10.7% (10.2 - 11.3)	12.5% (10.6 - 14.2)	10.9% (10.1 - 11.6)
2034	9.3%	10.8% (10.2 - 11.3)	12.5% (10.6 - 14.2)	10.9% (10.1 - 11.6)
2035	9.4%	10.8% (10.2 - 11.3)	12.6% (10.6 - 14.3)	10.9% (10.1 - 11.6)
2036	9.4%	10.9% (10.3 - 11.4)	12.7% (10.7 - 14.4)	11% (10.2 - 11.7)
2037	9.4%	10.9% (10.3 - 11.5)	12.7% (10.7 - 14.4)	11% (10.2 - 11.7)
2038	9.4%	11% (10.4 - 11.5)	12.7% (10.7 - 14.4)	11% (10.3 - 11.7)
2039	9.4%	11% (10.4 - 11.6)	12.8% (10.7 - 14.5)	11.1% (10.3 - 11.7)
2040	9.4%	11.1% (10.5 - 11.7)	12.8% (10.8 - 14.6)	11.1% (10.3 - 11.8)
Luxembourg				
2023	11.2% (9.2 - 16.3)	11.9% (9.7 - 14.5)	11.7% (10.8 - 12.7)	11.6% (10.1 - 14.2)
2024	11.2% (9.2 - 17.8)	12% (9.5 - 14.6)	11.6% (10.7 - 12.6)	11.6% (10 - 14.6)
2025	11.3% (9.1 - 19)	12.5% (10 - 15)	11.6% (10.7 - 12.6)	11.8% (10.1 - 15.3)
2026	11.3% (9.1 - 20.5)	12.3% (9.8 - 14.8)	11.5% (10.6 - 12.5)	11.7% (10 - 15.6)
2027	11.4% (9.1 - 21.9)	12.1% (9 - 14.9)	11.4% (10.6 - 12.4)	11.6% (9.8 - 16.2)
2028	11.4% (9 - 23)	11.6% (8.9 - 14.3)	11.4% (10.6 - 12.4)	11.5% (9.7 - 16.5)
2029	11.4% (9 - 24.8)	11.6% (8.9 - 14.1)	11.4% (10.6 - 12.4)	11.5% (9.8 - 16.7)
2030	11.5% (9 - 26.6)	11.5% (9 - 14)	11.3% (10.5 - 12.3)	11.5% (9.7 - 17)
2031	11.5% (9 - 28.5)	11.5% (9 - 13.9)	11.1% (10.3 - 11.9)	11.4% (9.7 - 17.6)
2032	11.5% (8.9 - 29.5)	11.5% (8.9 - 13.9)	11% (10.2 - 11.8)	11.4% (9.6 - 18.2)
2033	11.6% (8.9 - 30.5)	11.5% (9 - 13.9)	11% (10.2 - 11.9)	11.4% (9.7 - 18.8)
2034	11.6% (8.9 - 31.4)	11.5% (9 - 14.1)	11.2% (10.3 - 12.1)	11.5% (9.7 - 19.7)
2035	11.6% (8.8 - 33.3)	11.4% (9 - 14)	11.2% (10.2 - 12.1)	11.4% (9.7 - 19.7)
2036	11.6% (8.8 - 34.4)	11.4% (9 - 13.9)	11.2% (10.3 - 12.1)	11.4% (9.7 - 19.9)
2037	11.7% (8.8 - 35.4)	11.3% (9 - 13.7)	11.2% (10.3 - 12.1)	11.4% (9.7 - 20.2)
2038	11.7% (8.7 - 36.3)	11.2% (9 - 13.6)	11.2% (10.3 - 12.1)	11.4% (9.7 - 20.8)
2039	11.7% (8.7 - 37.4)	11.1% (9 - 13.4)	11.3% (10.3 - 12.1)	11.4% (9.7 - 21.3)
2040	11.7% (8.7 - 38.6)	11.1% (9.1 - 13.4)	11.3% (10.3 - 12.2)	11.4% (9.7 - 21.5)
Latvia				
2023	7.8% (6.4 - 9.1)	5.9% (5.4 - 6.4)	13.7% (11.4 - 16)	9.2% (8.2 - 11.1)

	Exponential smoothing	Random forest	XGBoost	Ensemble
2024	7.8% (6.2 - 9.1)	6.7% (6 - 7.2)	14.8% (12 - 17)	9.8% (8.6 - 11.5)
2025	7.7% (6 - 9.2)	7.2% (6.6 - 7.8)	15.2% (12.4 - 17.6)	10.1% (8.8 - 11.8)
2026	7.7% (5.8 - 9.3)	7.2% (6.6 - 7.8)	15.2% (12.3 - 17.4)	10.1% (8.8 - 11.7)
2027	7.6% (5.6 - 9.4)	7.5% (7 - 8.1)	14.4% (11.7 - 16.7)	9.8% (8.7 - 11.4)
2028	7.6% (5.4 - 9.5)	7.7% (7.2 - 8.3)	15% (12.2 - 17.5)	10.1% (8.9 - 11.7)
2029	7.6% (5.2 - 9.5)	7.8% (7.3 - 8.3)	15.2% (12.2 - 17.7)	10.2% (8.9 - 11.7)
2030	7.5% (5 - 9.5)	7.8% (7.3 - 8.4)	16% (12.5 - 18.7)	10.4% (9 - 12.2)
2031	7.5% (4.8 - 9.6)	8.4% (7.9 - 9.1)	15.9% (13.8 - 18.4)	10.7% (9.4 - 12.2)
2032	7.5% (4.6 - 9.6)	8.7% (8.1 - 9.4)	16% (14 - 18.3)	10.8% (9.6 - 12.2)
2033	7.5% (4.5 - 9.7)	9% (8.3 - 9.8)	15.8% (13.9 - 18.1)	10.8% (9.7 - 12.1)
2034	7.4% (4.4 - 9.8)	9% (8.3 - 9.9)	13.5% (11.9 - 15.3)	10% (8.8 - 11.3)
2035	7.4% (4.3 - 9.8)	9% (8.3 - 9.9)	13.3% (11.7 - 15.1)	9.9% (8.7 - 11.2)
2036	7.4% (4.2 - 9.9)	8.9% (8.3 - 10.1)	13.1% (11.6 - 14.9)	9.8% (8.6 - 11.1)
2037	7.4% (4.1 - 9.9)	8.9% (8.3 - 10.1)	12.8% (11.2 - 14.6)	9.7% (8.5 - 11)
2038	7.3% (4 - 10)	8.9% (8.3 - 10.2)	12.6% (11.1 - 14.5)	9.7% (8.4 - 11)
2039	7.3% (3.9 - 10)	8.9% (8.3 - 10.2)	12.7% (11.1 - 14.5)	9.7% (8.4 - 11)
2040	7.3% (3.8 - 10.1)	9% (8.4 - 10.3)	12.7% (11.1 - 14.5)	9.7% (8.4 - 11.1)
Netherlands				
2023	8.1%	5.8% (5.6 - 5.9)	6% (5.5 - 6.3)	6.6% (6.5 - 7.1)
2024	9.5%	5.7% (5.6 - 5.9)	6.1% (5.6 - 6.5)	7.1% (6.9 - 7.8)
2025	11.1%	5.9% (5.7 - 6)	6.1% (5.6 - 6.5)	7.7% (7.5 - 8.7)
2026	12.9%	5.9% (5.8 - 6.1)	6.4% (5.9 - 6.8)	8.4% (8.2 - 9.7)
2027	14.9%	6% (5.9 - 6.2)	6.6% (6 - 7.1)	9.2% (8.9 - 10.8)
2028	17%	6.1% (5.9 - 6.2)	6.6% (6 - 7.1)	9.9% (9.7 - 11.9)
2029	19.4%	6.1% (5.9 - 6.3)	6.6% (6 - 7.1)	10.7% (10.5 - 13.1)
2030	22%	6.1% (5.9 - 6.3)	6.6% (6 - 7.1)	11.6% (11.3 - 14.4)
2031	24.8%	6% (5.8 - 6.3)	6.6% (6 - 7.2)	12.5% (12.2 - 15.8)
2032	27.8%	6.1% (5.8 - 6.3)	6.6% (6 - 7.2)	13.5% (13.3 - 17.3)
2033	31.1%	6.1% (5.8 - 6.3)	6.6% (6 - 7.2)	14.6% (14.3 - 18.9)
2034	34.6%	6.1% (5.8 - 6.3)	6.6% (6 - 7.2)	15.8% (15.5 - 20.7)
2035	38.3%	6.1% (5.8 - 6.3)	6.6% (6 - 7.2)	17% (16.7 - 22.5)
2036	42.2%	6.1% (5.8 - 6.3)	6.6% (6 - 7.2)	18.3% (18.1 - 24.5)
2037	46.5%	6.1% (5.8 - 6.4)	6.7% (6 - 7.2)	19.8% (19.5 - 26.6)
2038	50.9%	6.2% (5.9 - 6.4)	6.7% (6 - 7.2)	21.3% (21 - 28.9)
2039	55.6%	6.2% (5.9 - 6.4)	6.7% (6 - 7.2)	22.8% (22.6 - 31.2)
2040	60.6%	6.3% (6 - 6.6)	6.8% (6.2 - 7.4)	24.6% (24.4 - 33.8)
Norway				

	Exponential smoothing	Random forest	XGBoost	Ensemble
2023	7.8%	6.6% (6.5 - 6.7)	5.4% (5 - 5.8)	6.6% (6.5 - 6.8)
2024	8.3%	6.6% (6.5 - 6.8)	5.6% (5.1 - 5.9)	6.9% (6.7 - 7)
2025	8.8%	6.5% (6.4 - 6.7)	5.7% (5.2 - 6)	7% (6.8 - 7.3)
2026	9.3%	6.7% (6.5 - 6.8)	6.2% (5.7 - 6.6)	7.4% (7.2 - 7.8)
2027	9.8%	6.9% (6.8 - 7.1)	6.4% (5.9 - 6.8)	7.7% (7.5 - 8.2)
2028	10.3%	7.1% (6.9 - 7.2)	6.6% (6.1 - 7)	8% (7.8 - 8.5)
2029	10.8%	6.9% (6.7 - 7.1)	6.7% (6.1 - 7)	8.1% (7.9 - 8.8)
2030	11.4%	6.9% (6.7 - 7.1)	6.7% (6.2 - 7.1)	8.3% (8.1 - 9.1)
2031	11.9%	6.9% (6.7 - 7.1)	6.9% (6.3 - 7.3)	8.6% (8.4 - 9.5)
2032	12.5%	6.9% (6.8 - 7.2)	7.3% (6.6 - 7.8)	8.9% (8.7 - 10)
2033	13%	7% (6.8 - 7.2)	7.3% (6.6 - 7.9)	9.1% (8.9 - 10.3)
2034	13.6%	7% (6.8 - 7.2)	7.3% (6.6 - 7.9)	9.3% (9.1 - 10.6)
2035	14.2%	7% (6.8 - 7.2)	7.3% (6.6 - 7.9)	9.5% (9.3 - 10.9)
2036	14.8%	7% (6.8 - 7.2)	7.3% (6.6 - 7.8)	9.7% (9.5 - 11.2)
2037	15.4%	6.9% (6.6 - 7.1)	7.3% (6.6 - 7.8)	9.9% (9.6 - 11.4)
2038	16%	6.9% (6.6 - 7.1)	7.3% (6.6 - 7.8)	10.1% (9.8 - 11.7)
2039	16.6%	6.9% (6.6 - 7.1)	7.3% (6.6 - 7.8)	10.3% (10 - 12.1)
2040	17.3%	6.8% (6.6 - 7.1)	7.3% (6.6 - 7.8)	10.5% (10.2 - 12.4)
Poland				
2023	13.8% (11.9 - 15.7)	13.8% (13.3 - 14.3)	17.6% (16.4 - 19)	15.1% (14.2 - 16.2)
2024	13.5% (10.9 - 15.5)	13.2% (12.6 - 13.8)	16.3% (15.2 - 17.8)	14.4% (13.3 - 15.5)
2025	13.1% (10.2 - 15.3)	13% (12.5 - 13.5)	17.1% (16 - 18.6)	14.5% (13.3 - 15.6)
2026	12.8% (9.5 - 15.1)	12.5% (12 - 13.1)	15.9% (14.7 - 17.3)	13.8% (12.5 - 15)
2027	12.5% (8.9 - 15)	12.4% (11.8 - 13.1)	15.8% (14.5 - 17.2)	13.6% (12.3 - 14.9)
2028	12.1% (8.5 - 14.9)	12.4% (11.8 - 13.1)	14.2% (12.7 - 15.4)	13% (11.4 - 14.2)
2029	11.9% (8.1 - 14.8)	12.5% (11.8 - 13.3)	13.3% (11.7 - 14.7)	12.6% (11.1 - 13.9)
2030	11.6% (7.7 - 14.7)	12.7% (11.9 - 13.5)	13.2% (11.5 - 14.6)	12.6% (11 - 13.9)
2031	11.4% (7.3 - 14.7)	12.7% (11.9 - 13.6)	13.2% (11.5 - 14.4)	12.5% (10.9 - 13.9)
2032	11.2% (7 - 14.6)	12.9% (12.2 - 13.7)	13.2% (11.4 - 14.5)	12.5% (10.8 - 13.9)
2033	11% (6.8 - 14.6)	12.9% (12.2 - 13.7)	13.2% (11.4 - 14.5)	12.4% (10.8 - 13.9)
2034	10.8% (6.7 - 14.6)	13% (12.3 - 13.7)	13.1% (11.3 - 14.5)	12.4% (10.7 - 13.9)
2035	10.7% (6.5 - 14.6)	13% (12.3 - 13.8)	13.2% (11.3 - 14.5)	12.3% (10.6 - 13.9)
2036	10.5% (6.4 - 14.6)	12.9% (12.2 - 13.8)	13.2% (11.4 - 14.6)	12.3% (10.5 - 13.9)
2037	10.4% (6.3 - 14.6)	12.9% (12.2 - 13.8)	13.2% (11.3 - 14.6)	12.2% (10.4 - 13.9)
2038	10.2% (6.2 - 14.6)	12.9% (12.2 - 13.7)	13.2% (11.2 - 14.6)	12.2% (10.3 - 13.9)
2039	10.1% (6.1 - 14.6)	12.9% (12.2 - 13.7)	13.2% (11.1 - 14.6)	12.1% (10.2 - 13.9)
2040	10% (5.9 - 14.6)	12.9% (12.2 - 13.7)	13.2% (11.1 - 14.6)	12.1% (10.2 - 13.9)

	Exponential smoothing	Random forest	XGBoost	Ensemble
Portugal				
2023	8.2%	10.5% (10.3 - 11)	16.3% (14 - 17.9)	11.7% (11 - 12.6)
2024	7.7%	10.5% (10.3 - 11)	16.5% (14.2 - 18.2)	11.6% (10.9 - 12.4)
2025	7.2%	10.4% (10.2 - 10.9)	16.4% (14.2 - 18.1)	11.4% (10.7 - 12.1)
2026	6.9%	10.4% (10.1 - 10.9)	16.3% (14.2 - 18.1)	11.2% (10.6 - 12)
2027	6.7%	10.3% (10 - 10.8)	16.3% (14.2 - 18.1)	11.1% (10.5 - 11.9)
2028	6.5%	10.3% (10 - 10.8)	16.2% (14.3 - 18)	11% (10.4 - 11.8)
2029	6.4%	10.7% (10.4 - 11.1)	15.4% (13.7 - 17.1)	10.8% (10.2 - 11.4)
2030	6.2%	10.6% (10.3 - 11.1)	15.3% (13.6 - 17)	10.8% (10.2 - 11.4)
2031	6.1%	10.7% (10.3 - 11.1)	14.4% (12.8 - 16.1)	10.4% (9.8 - 11)
2032	6.1%	10.6% (10.3 - 11.1)	12.9% (11.5 - 14.5)	9.9% (9.2 - 10.4)
2033	6%	10.6% (10.3 - 11.1)	12.8% (11.4 - 14.4)	9.8% (9.1 - 10.3)
2034	6%	10.6% (10.2 - 11.1)	12.5% (11.2 - 14.2)	9.7% (9 - 10.3)
2035	5.9%	10.7% (10.3 - 11.1)	12.4% (11 - 14.1)	9.7% (8.9 - 10.2)
2036	5.9%	10.8% (10.4 - 11.2)	12.4% (11 - 14.1)	9.7% (8.9 - 10.2)
2037	5.9%	10.9% (10.5 - 11.3)	12.4% (10.8 - 14.2)	9.7% (8.8 - 10.3)
2038	5.9%	10.9% (10.5 - 11.3)	12.4% (10.8 - 14.2)	9.7% (8.8 - 10.3)
2039	5.8%	10.9% (10.5 - 11.3)	12.4% (10.8 - 14.2)	9.7% (8.9 - 10.3)
2040	5.8%	10.9% (10.5 - 11.3)	12.4% (10.9 - 14.3)	9.7% (8.8 - 10.3)
Slovenia				
2023	7.6%	7.9% (7.7 - 8)	9.5% (8.7 - 10.3)	8.3% (8 - 8.7)
2024	7.3%	8.1% (7.9 - 8.3)	9.1% (8.4 - 10)	8.2% (7.9 - 8.5)
2025	7.1%	8.2% (8 - 8.5)	9.3% (8.5 - 10.1)	8.2% (7.9 - 8.5)
2026	6.9%	8.5% (8.2 - 8.8)	9% (8.2 - 9.8)	8.1% (7.8 - 8.4)
2027	6.7%	8.9% (8.5 - 9.2)	8.4% (7.7 - 9.2)	8% (7.5 - 8.3)
2028	6.5%	8.9% (8.6 - 9.3)	8.6% (7.8 - 9.4)	8% (7.4 - 8.3)
2029	6.3%	8.9% (8.5 - 9.2)	8.5% (7.8 - 9.3)	7.9% (7.3 - 8.2)
2030	6.1%	8.9% (8.5 - 9.2)	8.4% (7.7 - 9.3)	7.8% (7.2 - 8.1)
2031	6%	8.9% (8.5 - 9.2)	8.4% (7.6 - 9.2)	7.7% (7.1 - 8.1)
2032	5.8%	8.9% (8.5 - 9.3)	8.4% (7.7 - 9.2)	7.7% (7 - 8)
2033	5.7%	8.9% (8.6 - 9.3)	8.4% (7.7 - 9.2)	7.7% (6.9 - 8)
2034	5.5%	9% (8.6 - 9.4)	8.4% (7.7 - 9.2)	7.6% (6.9 - 8)
2035	5.4%	9% (8.6 - 9.4)	8.4% (7.7 - 9.2)	7.6% (6.8 - 7.9)
2036	5.3%	9% (8.6 - 9.5)	8.4% (7.7 - 9.2)	7.5% (6.7 - 7.9)
2037	5.1%	9.1% (8.6 - 9.5)	8.4% (7.7 - 9.2)	7.5% (6.7 - 7.9)
2038	5%	9.1% (8.7 - 9.5)	8.4% (7.7 - 9.3)	7.5% (6.6 - 7.9)
2039	4.9%	9.1% (8.7 - 9.6)	8.4% (7.7 - 9.3)	7.5% (6.6 - 7.8)

	Exponential smoothing	Random forest	XGBoost	Ensemble
2040	4.8%	9.1% (8.7 - 9.5)	8.4% (7.7 - 9.3)	7.4% (6.5 - 7.8)
Slovakia				
2023	10.1% (7.3 - 14.6)	10.8% (8.4 - 13.6)	17.4% (15.2 - 19.7)	12.9% (10.7 - 15.8)
2024	9.8% (6.9 - 14.5)	10.6% (8.3 - 14.2)	17.1% (15 - 19.3)	12.6% (10.5 - 15.7)
2025	9.7% (6.6 - 14.2)	10.5% (8 - 14.1)	16.8% (14.6 - 19.1)	12.4% (10.2 - 15.5)
2026	9.5% (6.2 - 14.4)	10.5% (8 - 14.4)	18.5% (15.9 - 21.1)	12.9% (10.6 - 16.2)
2027	9.3% (5.8 - 14.5)	10.4% (7.9 - 14.8)	18.4% (15.9 - 21.1)	12.8% (10.5 - 16)
2028	9.1% (5.3 - 14.5)	10.5% (8.1 - 14.9)	18.2% (15.7 - 20.9)	12.7% (10.5 - 16)
2029	9% (5 - 14.8)	11% (9 - 15.1)	17.3% (14.9 - 20.1)	12.5% (10.5 - 15.7)
2030	8.9% (4.7 - 14.7)	11.5% (9.6 - 15.4)	17.7% (15.2 - 20.6)	12.8% (10.7 - 16.1)
2031	8.7% (4.3 - 14.6)	11.5% (9.6 - 15)	16.7% (14.1 - 19.7)	12.4% (10.2 - 15.5)
2032	8.6% (4.1 - 14.8)	11.7% (10 - 14.9)	14.9% (12.8 - 17.4)	11.7% (9.7 - 14.7)
2033	8.5% (3.8 - 14.6)	12.1% (10.2 - 14.9)	15.4% (13.1 - 17.9)	12% (9.8 - 14.9)
2034	8.3% (3.5 - 14.5)	12.4% (10.3 - 15.1)	15.5% (13.4 - 18.1)	12.1% (9.9 - 15)
2035	8.2% (3.2 - 14.4)	12.8% (10.6 - 15.4)	15.5% (13.1 - 17.9)	12.1% (9.9 - 15)
2036	8.1% (3 - 14.6)	13.1% (10.8 - 15.7)	15.6% (13.3 - 18)	12.2% (10 - 15.1)
2037	8% (2.8 - 14.8)	13.4% (11.1 - 15.8)	15.6% (13.3 - 18)	12.2% (10 - 15.2)
2038	7.9% (2.6 - 14.8)	13.7% (11.4 - 16)	15.7% (13.5 - 18.1)	12.4% (10.1 - 15.2)
2039	7.8% (2.4 - 14.8)	13.9% (11.4 - 16)	15.8% (13.5 - 18.1)	12.4% (10.1 - 15.2)
2040	7.7% (2.2 - 15)	14% (11.5 - 16.1)	15.8% (13.5 - 18.1)	12.4% (10.1 - 15.4)

95% credible intervals are displayed between brackets, where applicable

Based on antimicrobial resistance rates collected with ECDC's TESSy database

Accuracy of antimicrobial resistance forecasts

RMSE - *Streptococcus pneumonia* against broad-spectrum penicillins

	Exponential smoothing	Random forest	XGBoost
Austria	0.192	0.139 (0.128 - 0.145)	0.145 (0.124 - 0.171)
Belgium	2.154	1.152 (1.047 - 1.187)	1.003 (0.997 - 1.009)
Bulgaria	0.445 (0.293 - 0.661)	0.473 (0.28 - 0.685)	0.444 (0.335 - 0.602)
Czechia	0.13	0.122 (0.087 - 0.176)	0.358 (0.306 - 0.412)
Germany	0.119	0.125 (0.116 - 0.133)	0.117 (0.091 - 0.148)
Denmark	0.241	0.25 (0.246 - 0.254)	0.236 (0.232 - 0.24)
Estonia	0.27 (0.18 - 0.384)	0.124 (0.116 - 0.135)	0.366 (0.318 - 0.418)
Spain	0.154	0.054 (0.043 - 0.101)	0.227 (0.186 - 0.346)
Finland	0.19	0.215 (0.201 - 0.23)	0.451 (0.407 - 0.497)

	Exponential smoothing	Random forest	XGBoost
France	0.068	0.406 (0.377 - 0.43)	0.845 (0.805 - 0.906)
United Kingdom	0.119	0.032 (0.018 - 0.046)	0.025 (0.008 - 0.052)
Greece	0.346 (0.11 - 0.871)	0.461 (0.228 - 0.741)	0.369 (0.183 - 0.912)
Croatia	0.196	0.138 (0.116 - 0.199)	0.202 (0.166 - 0.284)
Hungary	0.234	0.269 (0.251 - 0.283)	0.331 (0.274 - 0.371)
Ireland	0.237	0.276 (0.261 - 0.291)	0.338 (0.292 - 0.384)
Iceland	0.334 (0.218 - 0.629)	0.518 (0.388 - 0.691)	0.697 (0.534 - 0.897)
Italy	0.093	0.103 (0.094 - 0.115)	0.381 (0.285 - 0.43)
Lithuania	0.612	0.352 (0.3 - 0.367)	0.307 (0.26 - 0.35)
Luxembourg	0.374 (0.269 - 0.549)	0.374 (0.315 - 0.519)	0.326 (0.271 - 0.461)
Latvia	0.479 (0.431 - 0.756)	0.608 (0.577 - 0.638)	0.539 (0.487 - 0.586)
Netherlands	0.359	0.233 (0.219 - 0.247)	0.115 (0.102 - 0.126)
Norway	0.065	0.193 (0.182 - 0.203)	0.242 (0.212 - 0.267)
Poland	0.374 (0.237 - 0.476)	0.187 (0.174 - 0.205)	0.166 (0.15 - 0.181)
Portugal	0.121	0.121 (0.114 - 0.126)	0.24 (0.128 - 0.279)
Slovenia	0.2	0.181 (0.178 - 0.185)	0.183 (0.177 - 0.194)
Slovakia	0.557 (0.277 - 0.898)	0.534 (0.45 - 0.695)	0.35 (0.284 - 0.516)

95% credible intervals are displayed between brackets, where applicable

Based on antimicrobial resistance rates collected with ECDC's TESSy database

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