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Transferability of health economic analyses between countries

Deliverable 5.7

VALUE-Dx

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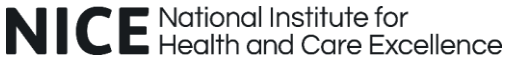
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1. Introduction

1.1. Background on health-economic analyses

Due to limited resources and ever-increasing healthcare costs globally, decision-makers in healthcare are challenged to balance societal affordability with patient access. An accurate overview of properties and impacts of a new healthcare intervention is therefore increasingly required in the planning, managing and evaluation of healthcare. Especially when health services are funded from public funds, health economic analyses are of particular interest. A health economic analysis generally aims to support decision-making on determining the relative value for money provided by the new intervention compared to one or more existing alternatives. Even in the phase of clinical research, an early assessment of the health technology in question can be applied to support the optimal allocation of the scarcely available resources in healthcare.

Although health economic analyses can be focused solely on the costs of different interventions, most types of analyses consider both costs and consequences. The ratio of incremental costs and effects expresses the cost-effectiveness of one intervention compared to the other(s). In these, the effect measure of a technology can be expressed in clinical outcomes as well as in quality-of-life (QoL) estimates. For the latter, the 'quality-adjusted life year' (QALY) is a common preference-based valuation of health outcome. This way, the incremental cost per QALY gained determines the cost-utility of the intervention. Regarding costs considered in a health economic analysis, the cost types included are dependent on the perspective chosen. A healthcare perspective would only include costs associated with resources used in healthcare (e.g. diagnostic tests, medication costs, medical staff), whereas a societal perspective would also include costs associated with resources used in healthcare and beyond. Travel costs to the healthcare facility, costs for family members to take care of the patient, and labour productivity losses as a consequence of the disease and intervention of interest are examples of cost types included in a health economic analysis using a societal perspective.

The economic evaluation of healthcare interventions is mostly drawn on the design and results of one or more clinical trials. In addition to economic evaluations based solely on trial results, modelling techniques are increasingly being applied. Decision-analytic modelling enables analysts to synthesise evidence from multiple sources and calculate long-term costs and consequences. A health economic model provides a framework in which treatment effectiveness, healthcare resource use, unit costs, and QoL data can be assembled.

1.2. Challenges in transferring health-economic results between countries

A key question for decision-makers is whether results of a health economic analysis are applicable to settings other than the setting where the intervention was originally studied. Applying evidence generated outside of a setting of interest may be questionable. This is not only true for economic measures, such as resource use and costs: treatment effectiveness may also vary across settings. Although multicentre and

multinational clinical trials are performed to increase among others the representativeness of participating patients and the generalisability of results, health economic results cannot always be directly applied to other settings. Apart from generalisability, where data can be applied to other settings without adjustment, transferability includes the option to adapt data to apply to other settings (1).

Several factors may play a role in the challenges of transferability of economic evidence, including disease risk and severity, mortality, availability of healthcare resources, and QoL and price weights. As such, population characteristics, clinical practice patterns and economic data may affect the transferability of evidence found through an health economic analysis. Transferability aspects are more extensively described in the next chapter.

1.3. Aims and contents

To maximize the potential of diagnostics in the prevention of antimicrobial resistance (AMR), it is essential to assess the transferability of the findings provided by the health economic analysis to other countries than the ones included in the clinical trials as part of the Value-Dx project. Similarly, transferring cost-effectiveness models that include various effects at the macro-economic level will require information on productivity and labour supply in the various countries considered. The current transferability task aims to explore the heterogeneity across countries in data that serve as input data for the health economic analysis. The exploratory measurements are preceded by two chapters shaping the context of the current task. Chapter 2 entails a description of determinants that plausibly influence the transferability of economic evidence across countries. Chapter 3 describes the decision-analytic model proposed for the health economic evaluation of the diagnostics studied in Value-Dx. The heterogeneity estimations in public data of Member States of the European Economic Area (EEA) are discussed in Chapter 4. The inter-country variation in PRUDENCE trial data needed for in the health economic model is described in Chapter 5. Parameter values with high heterogeneity across countries are identified and shortlisted for their relevance in transferring models. Notably, this procedure will result in minimal datasets that can be applied in countries with limited data availability as opposed to optimal datasets for countries with rich data availability. A transfer model based on a minimal dataset would increase the balance between complexity and applicability of the model, which can then be applied in various settings in both high- and middle-income countries. Chapter 6 includes an exploratory assessment of cost conversion, in which a cross comparison of actual costs in two countries is described. Moreover, the methods used for a country-specific cost calculation in the economic evaluation alongside the ALIC^{4}E trial are discussed. Finally, conclusions and recommendations are given in Chapter 7.

2. Transferability aspects in health-economic analyses

Aspects of transferability encompass both the characteristics related to the methodologies used in the analysis and beyond, as well as the contextual characteristics of the setting to which the health-economic analysis is applied. Both groups of aspects can roughly be subdivided into five subjects to consider in a transferability assessment of health economic analysis, namely: outcomes of the clinical study, methodological choices made in the health economic analysis, epidemiological situation, characteristics of the general society, and actual regulations and policies of the healthcare system.

2.1. Clinical study outcomes

Depending on the clinical case and choices made in the study design of a clinical trial, several outcomes may have an effect on the methodological choices made in a subsequent health economic analysis and its transferability, of which two important aspects are highlighted below.

2.1.1. Intervention and comparator

Since an intervention's cost-effectiveness is always related to the alternatives included in the analysis, the transferability of a health economic analysis to a particular setting depends on the interventions currently used, i.e. the current standard of care. In other words: the alternatives compared in the study may not be similar to the actual standard of care in a setting which the results are transferred to. The number and type of comparators that should be selected in a health economic analysis is often described in national guidelines for economic evaluations in healthcare. European countries vary in their recommendation regarding the number of alternatives that should be included in a health economic analysis, ranging from only the most efficient alternative (e.g. Portugal) to all relevant alternatives (e.g. France) (2,3). If one or more comparators have not been included in the trial(s), the scope of the existing health economic analysis may need to be extended by supplementing relevant clinical and economic evidence from other reliable sources (e.g. network meta-analyses) to enable transferability of results.

2.1.2. Health state valuation

A commonly used general questionnaire to evaluate a patient's functioning and well-being is the Euroqol-5-Dimensions (EQ-5D). The EQ-5D questionnaire comprises questions on a patient's health state in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The subjective measurement of the perceived health status of the patient enables to calculate utilities (i.e. health state preference values), using a prespecified value set that reflects the strength of preferences of the general public for the health states. Value sets are country-specific and are therefore not generalisable between countries. For the three-level variant of EQ-5D (EQ-5D-3L), value sets are available for many countries. This is in contrast to the newer five-level variants for both adults (EQ-5D-5L) and children (EQ-5D-Y), for which value sets

are not available yet for many countries. Adjustment of health state utilities may be needed to gain relevant quality of life estimates.

Differences in population's health state preferences may introduce cross-country differences in utility values. The norms and beliefs of health among a particular population are shaped by several factors, including the healthcare system in place, cultural factors, and geography. These and other factors impact an individual's health opportunities and challenges, which may result in heterogeneity of the relative importance of the different EQ-5D-5L dimensions. For example, in countries with well-established domestic care facilities, the dimension 'self-care' may be deemed less important than other dimensions. Alternatively, 'mobility' may be deemed more important than other dimensions in a country with insufficient infrastructure for immobilized individuals. Also, the willingness to trade-off quality for quantity of life in Time-Trade-Off measurements may be influenced by norms and beliefs that are held among a population. Moreover, the marginal effect of moving from one severity level to another may differ per country (4).

2.2. Health-economic methodologies

Besides results of the clinical trial(s) that serve as input parameters in the health economic analysis, methodological choices made in trial-based and model-based analyses are core items when assessing the transferability of health economic analyses.

2.2.1. Model structure

The model structure embodies the health states and pathways and their interaction and is dependent on the type of model used. Where time is an important factor in the specified decision problem of the analysis, a time-dependent model (e.g. Markov model) is useful. Where time is deemed less important and alternative events throughout the clinical course are transparent, a decision tree would be sufficient (5).

The model structure used in a health economic analysis is largely based on the clinical course of patients. Due to differences between countries in clinical practice patterns and healthcare resource availability, the clinical course or natural history of a disease may not be represented by the model structure. This is mainly applicable to a discrete-event simulation (DES), which generally encompasses the explicit modelling of the specific patient pathway. Decision trees represent the clinical pathway in an explicit way as well, albeit to a lesser extent in general. Transferability across countries may therefore be complicated for DES and extensive decision trees, but less complicated for Markov models, which generally represent a more straightforward sequencing of health outcomes.

Besides natural history, the alternative interventions included in the analysis may also affect the model structure, as the mode of action and side effects of alternatives may open up other pathways in the model. Consequently, in addition to varying health outcomes when transferring the analysis, the associated costs to each specific health outcome should be considered as well.

2.2.2. Time horizon

The duration over which health outcomes and costs are calculated is an important decision in health economic modelling. In case of chronic conditions, longer time horizons are applicable, whereas a shorter time horizon may be of use in diseases without direct long-term costs and consequences, such as acute respiratory infections. A long time horizon likely involves the extrapolation of costs and effects in certain health states and the discounting of these costs and effects. In most national guidelines on economic evaluations, the time horizon is recommended to be based on the natural course of the disease and the expected health effects of the intervention. Overall, a lifetime horizon is advocated more or less explicitly (6,7). Therefore, a short time horizon may impede transferability across countries, as several input parameters may need adjustment or additional input when transferring to countries requiring a longer time horizon. An essential parameter that would need adjustment when altering the time horizon of the analysis is the discount rate for costs and health effects, which is shortly explained in the next paragraph.

2.2.3. Cost calculation

The type of costs included and the way costs are calculated are essential elements to take into account when assessing the transferability of health economic analyses. First, the costing approach that has been used should be considered. There are several ways to calculate costs, depending on the level of accuracy. As stated by Tan et al., “the level of accuracy is determined by the identification of cost components (gross costing versus micro costing) and the valuation of cost components (top-down versus bottom-up costing)” (8). Considering costs of hospital services for example, the number and type of services included in a diagnosis-treatment related group (DRG) in one country can differ substantially from another country, making it arduous to include similar cost components as applied in the initial analysis.

Second, the type of costs included is also dependent on the perspective of the analysis. Most national guidelines call for a “healthcare perspective” or “payer’s perspective”, in which the base case analysis considers only the direct (medical and/or non-medical) costs and health effects that affect only patients. Analyses from a “societal perspective” include indirect medical and non-medical costs and health benefits to all individuals. Examples of indirect non-medical costs are transportation costs to the healthcare facility and productivity loss resulting from patients’ reduced efficiency or inability to work because of morbidity or mortality. Indirect medical costs are future medical costs of remaining alive due to the life-prolonging treatment under assessment.

The method to calculate productivity losses may also vary across countries. Productivity loss, referring to the monetary valuation of a reduction in productivity of both paid and unpaid work, can be calculated in different ways. The human capital approach is a general method to calculate productivity costs by counting hours not worked as hours lost. Alternatively, the friction cost method is used in the Netherlands, which takes an employer’s perspective and calculates the hours lost until the vacancy is filled by another employee (9). Depending on a country’s labour system and its recommendations for

health economic evaluations, the productivity loss calculation may or may not be easily applied to the target setting.

Finally, a common technique in health economic analyses is the discounting of future costs and benefits. Discounting is used in analyses with a time horizon of more than one year. However, recommended discount rates are different across countries and mostly vary between 1.5% and 5% (6). Health economic results with discounted costs and effects may therefore need adjustment before being transferred to a specific setting.

2.3. Epidemiology

Apart from the characteristics of the clinical study and subsequent health economic analysis, country-specific prevalence and incidence estimates may be of interest to assess for transferability reasons. Prevalence of a specific type of cancer may be a decisive factor in for instance the adoption and efficient organisation of proton beam therapy, which may therefore be accomplished differently across countries. In case of infectious diseases, risk of getting a disease and incidence in one country may be higher than in the other. A sound example of this is the impact of temperature on respiratory disease cases and subsequent healthcare resource use (e.g. emergency department visits) (10). Not only colder temperature, but also dew point and consistent humidity were found to influence the transmission of viruses causing respiratory infections such as respiratory syncytial virus (RSV) and influenza viruses A and B (11).

Also, disease severity may vary across settings. An intervention may appear to be cost-effective in one setting because the costs prevented by the intervention are higher in countries with many severe influenza cases, whereas the opposite is true for a setting with a lower incidence and less severe cases. An example of this are the hospitalizations for RSV, which were found to be highly variable across six European countries (Denmark, England, Finland, Norway, the Netherlands, and Scotland) in the period 2006 to 2018 (12). Substantial discrepancies between countries may subsequently affect the transferability of health economic analyses of RSV vaccines.

2.4. Society

2.4.1. Demography

Regarding societal characteristics, a country's demography can be an essential part of the volume measurement in a health economic analysis. The size of the population potentially benefiting from the intervention is especially important to calculate the budget impact. Further, population density and socioeconomic status may affect the applicability of an intervention in a setting. For instance, when diagnostic tests are to be paid out of pocket by the patient, the implementation of the test may be delayed in those parts of a city or region with a low socioeconomic status on average. Also ethnicity may play a role in transferring health economic results, as for instance adverse events of the studied intervention may be more frequent among a certain ethnic population, resulting in higher healthcare costs than considered in the initial health economic analysis (13).

A population's age structure is of importance as well when assessing transferability of health economic research. Due to increased life expectancies and low fertility levels, many countries have an ageing population, as can be seen, for instance, in Italy (14). Age structure is among others related to household structures and the level of interaction among individuals. Mainly in case of infectious diseases, this may affect the spread and prevention of disease in different ways. Whereas in old population age structures the transmission of infectious diseases may be lower, the burden of disease may be higher (15). Furthermore, a country's background mortality is an important parameter in many health economic models as well, especially when a lifetime horizon is used. Background mortality is used in the calculation of remaining life years and QALYs, thereby affecting the cost-effectiveness of the intervention. Life expectancy is a country-specific measure and it may have a substantial impact on health economic results in countries with a relatively low life expectancy, depending on the decision problem at hand.

2.4.2. Culture

Differences across countries may also be found in the general health seeking behaviour of a population. Health seeking behaviour is related to the prevention and control of diseases and may be explained by the timing and frequency of the consultation as well as the presence of comorbidities and the severity of symptoms (16,17). A recent systematic review and meta-analysis including 10 studies across 8 countries found that health seeking behaviour was determined by among others age, sex, educational status, residency, economic status, and health insurance (18). A further cultural aspect involves patient expectations and perceptions that may play a role in the prescribing of antibiotics, although evidence base for differences across settings is limited (19). Related to this aspect is the attitude towards antibiotics of prescribers. The point prevalence audit study of consecutive respiratory tract infection consultations in general practices in 13 European countries, performed within the Value-Dx project, revealed wide variations between countries in the percentage of consultations resulting in an antibiotic prescription (20).

In addition, health seeking behaviour changed during the COVID-19 pandemic and may have retained since to some extent. Three waves of public surveys among the England population between March 2020 (pre-pandemic) and March 2022 revealed that self-care actions increased among individuals with respiratory tract infections. Several changes in the work-life environment (e.g. working from home) since the pandemic as well as an increased awareness of respiratory symptoms may have influenced health seeking behaviour. Also the way individuals seek healthcare may have changed since the pandemic, which was indicated by a shift towards remote consultations (21). The consistency of these findings across countries may be of particular interest when assessing the transferability of health economic analyses in the context of respiratory infections.

2.5. Healthcare governance

A final theme relating to the transferability of health economic analyses is the wider regulatory and organisational context to which the results of the analysis are applied. Despite many differences in the way healthcare is organized at a national level across countries, a common structure can be identified, often referred to as the 'Healthcare Triangle' (Figure 1)(22). The triangle shows three categories of actors and their interactions that represent the basis of many healthcare governance systems.

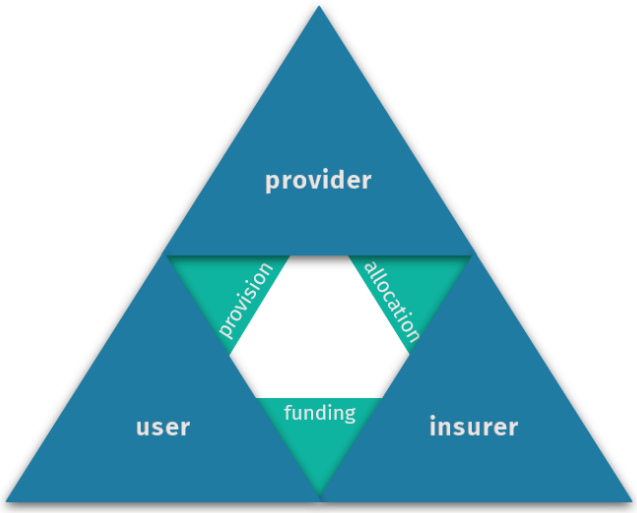

Figure 1 The 'Healthcare Triangle' showing the main actors in healthcare and their interactions, adapted from (23).

Countries have developed and applied health governance in different ways. Basically, health governance types in Europe are built on a either a Social Health Insurance (SHI) model or a National Health Service (NHS) model (24). For example, Germany, Belgium, Switzerland, and the Netherlands originally applied a SHI system, which means that the resident population pays fees to a fund that in turn covers healthcare costs. Nowadays, countries combine both system models, in which many competing insurers are available that reimburse healthcare providers' activities. In other countries, such as the UK, Italy and Spain, the NHS is providing care and is being financed through general taxation (25).

The particular health governance system in place is an important factor in the way healthcare is organised. The underlying system may affect healthcare provision, health seeking behaviour, funding and remuneration, and more. Consequently, costs included in a health economic analysis may differ between countries. For instance, remuneration of healthcare providers in the hospital can be performed on a fee-for-service basis or can be included in the lump sum of healthcare services, as is often seen in a diagnosis-related group system (26). Further, the GP may act as a gate-keeper to secondary care (e.g. in the Netherlands), whereas in other countries healthcare specialists are also providing primary care (e.g. in Belgium) (27). Such differences may influence among others the clinical pathway and associated economic inputs in a health economic analysis of a primary care intervention. Also the payments to be made by patients in addition to the funded amount, the so called 'out-of-pocket' costs, are applicable in general or in specific situations in certain countries. These and other variations may affect the cost calculation when transferring the health economic analysis across countries.

Lastly, some countries compare the incremental cost-effectiveness ratio (ICER) to a prespecified cost-effectiveness threshold in the decision making on pricing and reimbursement. Such thresholds represent the maximum cost per health outcome that a health system is willing to pay, which were found to vary widely across countries (28). This may mean that an intervention is deemed cost-effective in one country, while it is deemed not cost-effective in another country, purely because of different willingness-to-pay thresholds.

Aspects described here do not encompass the complete inventory of determinants that may play a role in the transferability of health economic analyses across countries. Moreover, the impact of each aspect on the transferability probably differs per use case. Health economists should therefore identify which aspects apply to their specific research problem and should incorporate adaptation possibilities in the analysis accordingly. An early transferability assessment of the health economic model used in Value-Dx is described in Chapters 4 and 5, which is preceded by a description of the model itself in Chapter 3.

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

3.1. Overview model

To assess the long-term health-economic effects of improved diagnostics for community-acquired acute respiratory tract infections (CA-ARTI) at the first point of care, a model called MERIAM (Modelling the Economics of Respiratory tract Infections and AMr) was built. MERIAM consists of three modules:

- the demographic module, used to simulate the population over a long time horizon;
- the consultation module, used to simulate patients consulting a healthcare professional in Primary Care for an acute respiratory tract infection;
- the AMR forecasting module, used to forecast AMR levels.

The demographic module contains a representative sample of the population in the country to which the analysis is applied. The consultation module uses incidence data to simulate the healthcare-seeking behaviour for CA-ARTI of a subset of individuals from the demographic module and their outcomes, including diagnostics, costs and antibiotic consumption. The AMR module uses antibiotic consumption data to forecast AMR levels. In the following paragraphs, each module is briefly explained. Detailed descriptions of the modules are provided in deliverable 5.5.

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.

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

- Mortality
- Ageing
- Fertility
- Migration

It is assumed that the population changes are made on January 1 of each year. This improves the efficiency of the model calculations. 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: centennials were not included in the model. Ageing is straightforward in that it increases the age with 1 every year. Data on births are used from the Eurostat population projections. The number of babies born is related to the population aged 15-45. 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.

3.3. Consultation module

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 (29). 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 (30). 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 based on the 10% threshold as applied by the ECDC (31).

3.3.2. 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 (32). 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).

3.3.3. Consultation decision tree

A decision tree was developed to model the patient journey as per the clinical algorithm of PRUDENCE. Figure 2 provides a schematic overview of the decision tree.

All patients present with CA-ARTI are classified as having a positive COVID-19 test or a negative COVID-19 test. In case of a positive COVID-19 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-19 test, a distinction was made between in and outside the influenza 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 case of cough during the influenza season, patients were tested with the Afinion CRP test or the Veritor influenza A/B test;
- In case of sore throat during the influenza season, 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;
- Outside the influenza season, patients with a sore throat were tested with a Veritor GAS test.

In all cases, patients could receive standard-of-care which could include tests performed as part of standard clinical procedures. Each branch ended with the decision to prescribe antibiotics or not. Subsequently, patients continued to the post consultation Markov model.

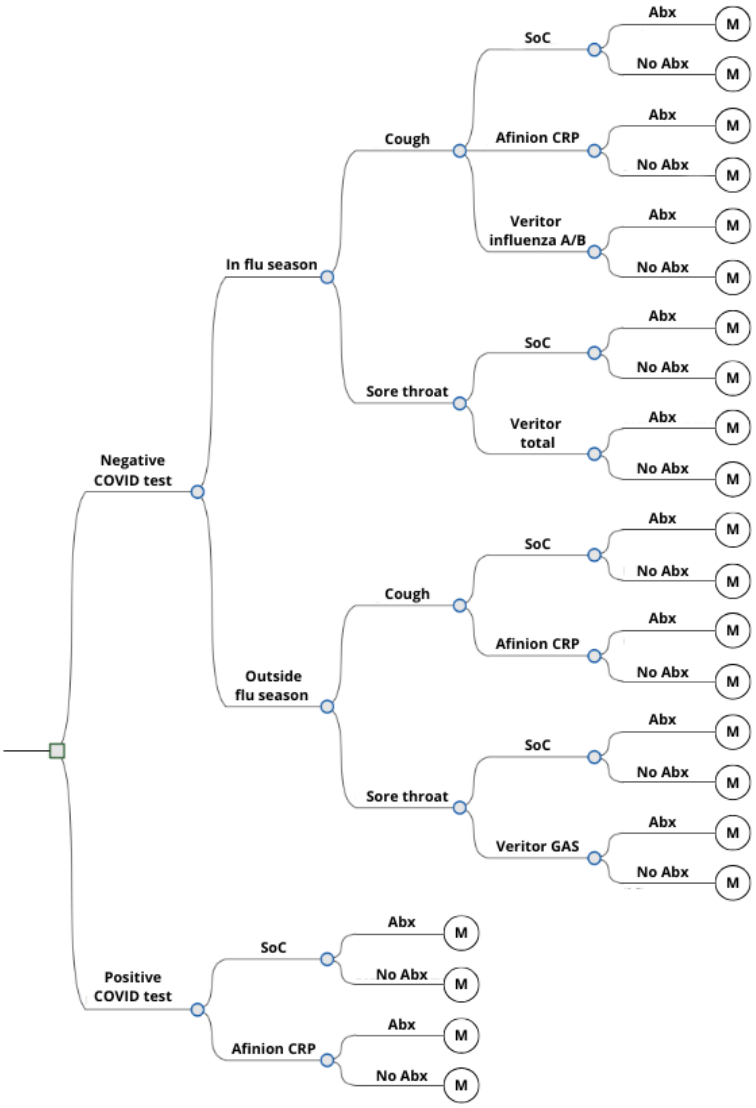

Figure 2 Decision tree used in the consultation module of the MERIAM model.

3.3.4. Post-consultation follow-up

For the post-consultation follow-up, a Markov model was developed consisting of the health states "sick" and "healthy" (Figure 3). 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, i.e. patients could not get sick again within the 28 day time horizon after they became healthy.

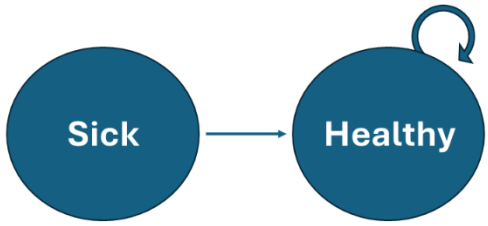

Figure 3 Schematic representation of the post-consultation Markov model.

3.4. Antimicrobial resistance forecasting

The AMR module 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 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:

- 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. The mechanisms to attain and retain resistance may differ between various pathogens. As the aim was to assess the impact of diagnostics for all CA-ARTIs in the population, which can be caused by various pathogens, a mechanistic dynamic transmission model was considered an inviable strategy. A statistical forecasting method, comparable to the methods used by Hashiguchi et al. was used instead (33). Further details regarding the modules can be found in Deliverable 5.5.

4. Generalizability using public data

4.1. Demographics

Using the demographic module from MERIAM, it is straightforward to create datasets representing the various countries. In Figure 4 and Figure 5, the age and sex distributions are shown for many countries in the years 2024, 2034, and 2044, based on a representative sample of 100,000 individuals in 2024. This shows that across most of the European countries, ageing will be a concern. There are some major changes though, as some countries are expected to shrink in population size, while others are expected to grow. This may affect the sustainability of the health system, as it may be young healthy people who are leaving, while the elderly in need of healthcare stay behind. This seems to be especially relevant for South-Eastern Europe. This is a relatively straightforward way to explore differences across countries with certain age-dependent effects. Instead of having all parameters in a health-economic analysis exactly tailored to a specific country, more general age-dependent and/or sex-dependent parameters can be used to come with country-specific estimates.

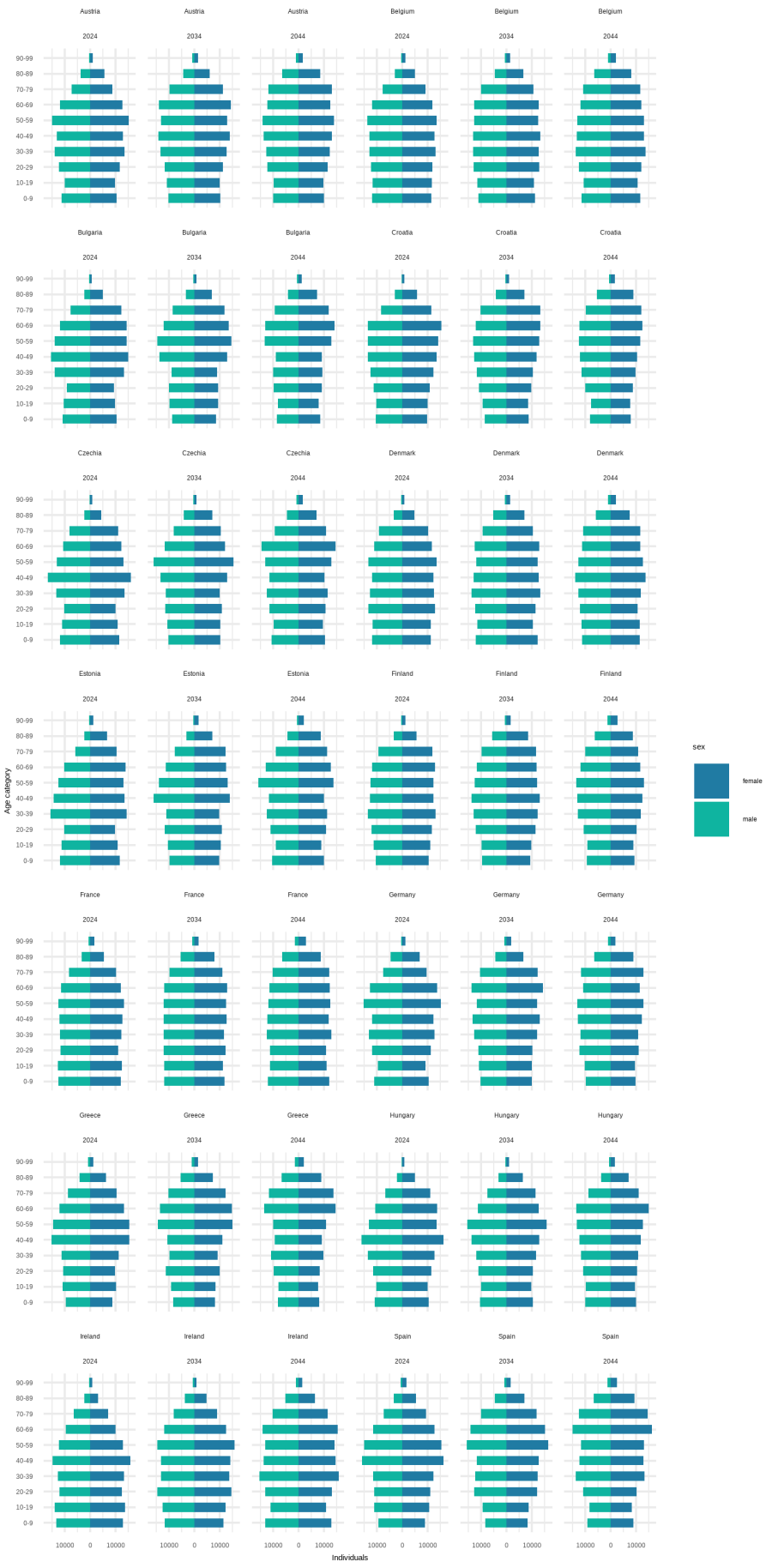

Figure 4 demographic changes in the period 2024 - 2044 in various European countries.

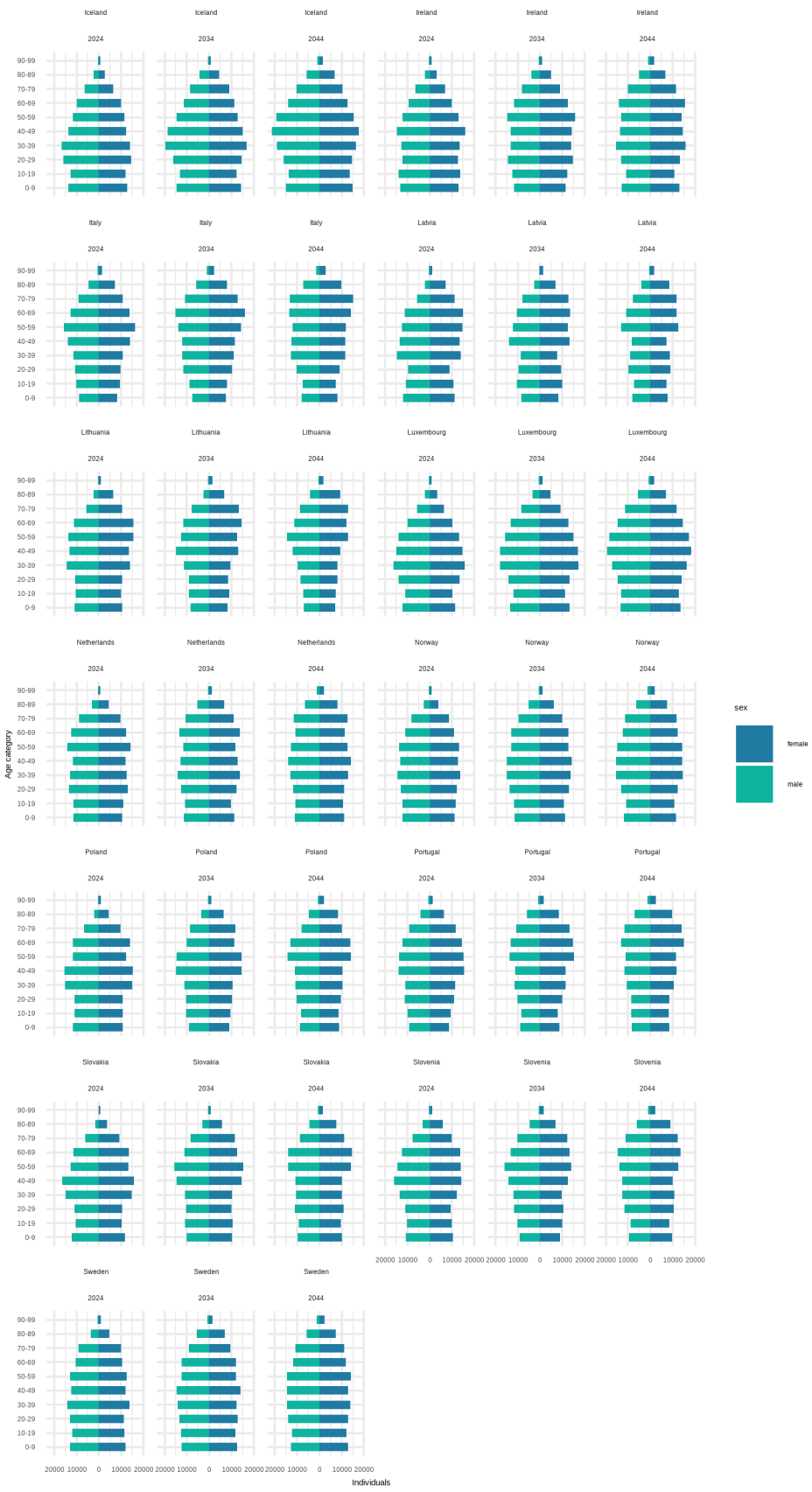

Figure 5 demographic changes in the period 2024 - 2044 in various European countries.

4.2. Incidence

4.2.1. ECDC surveillance data

The requested incidence data from the TESSy database regarding ARI and ILI revealed a substantial level of scarcity of available data. Age-specific incidence data for the full season was available for less than half of the 27 EEA-countries (see Table 1 for ARI incidence and Table 2 for ILI incidence).

Table 1 Countries with age-specific incidence data of acute respiratory infection (ARI) available for at least one full season (seasons 2019-2020, 2020-2021, and 2021-2022 were excluded because of the COVID-19 pandemic). Blank boxes indicate no data available for the full season.

Country	2010-2011	2011-2012	2012-2013	2013-2014	2014-2015	2015-2016	2016-2017	2017-2018	2018-2019	2022-2023	Total
Belgium	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
Bulgaria	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
Czechia			✓			✓	✓	✓	✓	✓	6
Germany	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
Latvia	✓										1
Netherlands							✓	✓	✓		3
Romania	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
Slovenia	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
Slovakia	✓	✓	✓	✓	✓	✓	✓	✓	✓		9
Spain										✓	1
Total	**7**	**6**	**7**	**6**	**6**	**7**	**8**	**8**	**8**	**7**	

Table 2 Countries with age-specific incidence data of influenza-like illness (ILI) available for at least one full season (seasons 2019-2020, 2020-2021, and 2021-2022 were excluded because of the COVID-19 pandemic). Blank boxes indicate no data available for the full season.

Country	2010-2011	2011-2012	2012-2013	2013-2014	2014-2015	2015-2016	2016-2017	2017-2018	2018-2019	2022-2023	Total
Belgium	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
Czechia			✓			✓	✓	✓	✓	✓	6
Denmark										✓	1
Estonia	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
Ireland	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
Latvia	✓										1
Netherlands	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
Norway											1
Poland	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
Portugal	✓	✓	✓	✓	✓	✓	✓	✓	✓		9
Romania	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
Slovenia	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
Slovakia	✓	✓	✓	✓	✓	✓	✓	✓	✓		9
Total	**10**	**9**	**10**	**9**	**9**	**10**	**10**	**10**	**10**	**10**	

As the dataset contained many gaps in both ARI and ILI incidence, ARI and ILI were combined (hereafter referred to as 'ARI+ILI'). The ARI+ILI incidence was calculated per

week per age category and could be used as proxy-estimate of incidence in EEA countries. Even after the combination of ARI+ILI incidence, 73.9% of the age-specific incidence data per country per week was lacking (54,396 of 73,592 objects were removed from the dataset due to no data available). An example of output for a specific season and age category is shown in Figure 6, including the two exponential models.

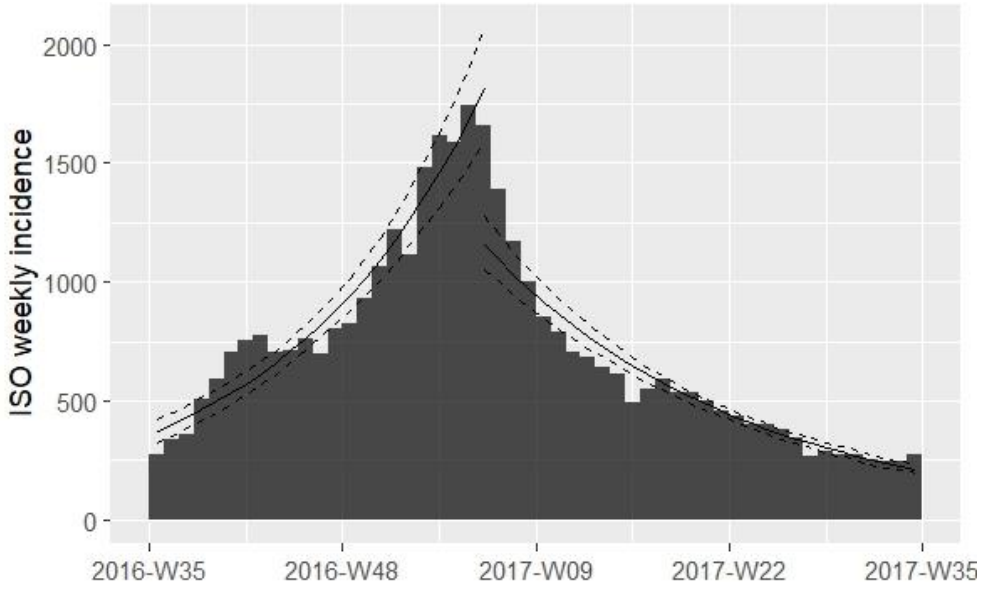

Figure 6 Weekly incidence of ARI+ILI cases and modelled incidence in season 2016-2017 for age group 15-64. Abbreviations: ISO = International Organization for Standardization.

4.2.2. Exploration of incidence data

Incidence data were available for 10 seasons, all starting at week 35. As displayed in Figure 7, weekly incidence of ARI+ILI peaked to approximately 2,000 cases per 100,000 in more than half of the seasons. In most seasons, a relatively large reduction was visible around the end of the calendar year, which may be due to lower healthcare seeking behaviour during Christmas holidays in Europe. Remarkably, average incidence in the 2022-2023 season was lowest, which may be due to various consequences of the COVID-19 pandemic, including a shift in diagnostic classification of respiratory infections as well as a lingering transmission of infections as a whole. It is important to consider that each season may include a different number of countries and that ARI and ILI incidence is not consistently present for each country. The seasons per country for both ARI and ILI incidence are visible in Figure 8.

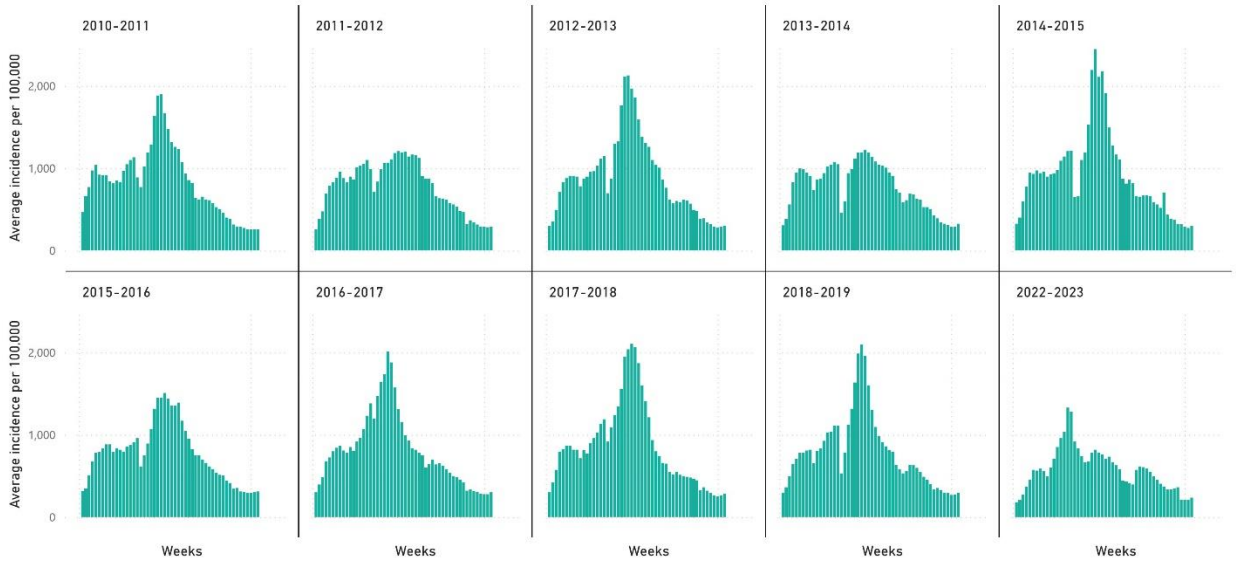

Figure 7 Average weekly incidence per 100,000 of acute respiratory infections and influenza-like illness per season.

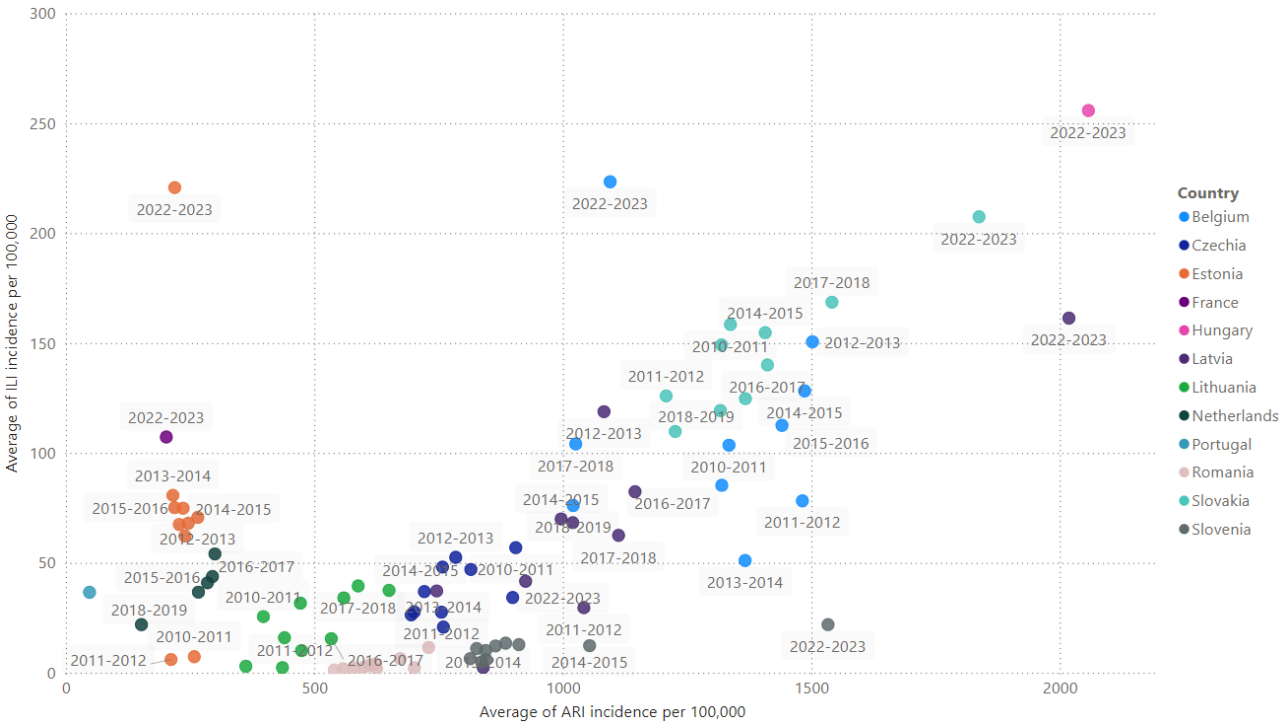

Figure 8 Average incidence per 100,000 of acute respiratory infections and influenza-like illness per country.

With regard to the most recent season before the COVID-19 pandemic (i.e. 2018-2019), ARI cases are present throughout the season, as shown by the weekly incidence per country in Figure 9. In contrast, ILI incidence demonstrated more seasonality (Figure 10). Also, in countries with both ARI and ILI incidence data available in the selected season, ILI incidence was lower in most cases.

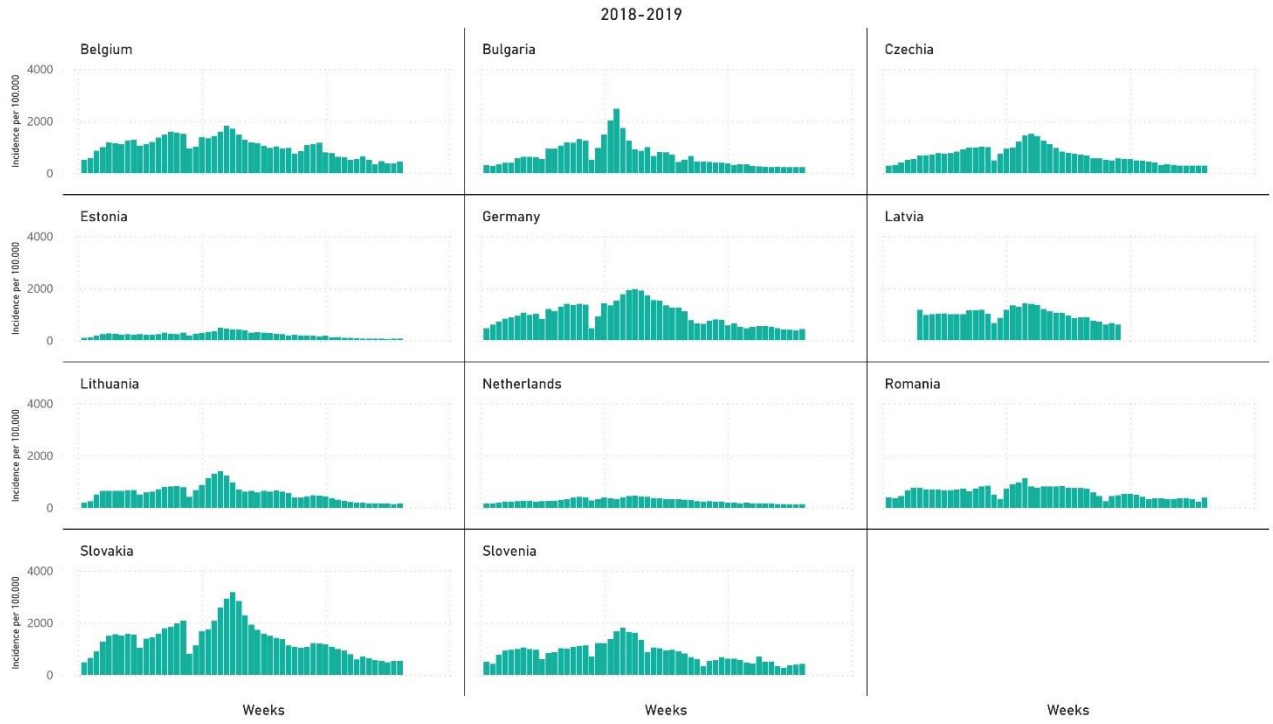

Figure 9 Average weekly incidence per 100,000 of acute respiratory infections per country in season 2018-2019.

Figure 10 Average weekly incidence per 100,000 of influenza-like illness per country in season 2018-2019.

4.2.3. Emergency Department visits

Several data registries and surveillance system databases were found reporting Emergency Department (ED) visits of patients with respiratory infections. The number of ED visits can be used for the health economic analysis on the ADEQUATE trial. However, the definition of medical diagnosis or syndrome differed across data sources and could not always be exactly derived. The German registry AKTIN reports ARI, ILI and severe ARI (SARI) cases per day for different age groups. The French SurSaUD® – Emergency and Death Health Surveillance reported ARI attendances in emergency departments, where ARI involved acute lower respiratory tract infection, suspicion of COVID-19, influenza, acute bronchitis, pneumopathy, or bronchiolitis. The Norwegian registry provided ED consultations of patients with infections of the respiratory passages, including ear infections. In Spain, the Registry of Specialized Health Activity (RAE-CMBD) publishes an interactive data portal in which the number of contacts via the ED can be extracted. The relevant diagnosis can be selected with ICD-10 codes. For the United Kingdom (UK), weekly bulletins were published by the Emergency Department Syndromic Surveillance

System (EDSSS). However, the EDSSS puts the caveat to the data that it should be used to monitor trends rather than to estimate numbers of 'cases'.

Despite the differences in diagnosis definitions, national coverage, time period ranges, and more, the ED sources mentioned here were deemed the best publicly available to estimate the number of patients with cough or a sore throat that enter the ER. An overview of databases per country with partly relevant data is displayed in Table 3.

Table 3 Overview of publicly available data sources reporting the number of cases related to acute respiratory infections and influenza-like illness.

Country	Name / title	Period start	Period end	Diagnosis definition	Age groups	Aggregation levels
Germany	AKTIN – Emergency Department Data Registry	1/1/2019	now	ARI, ILI, SARI	00+, 0-4, 5-9, 10-14, 15-19, 20-39, 40-59, 60-79, 80+	date, ED type, age group, syndrome
UK	Emergency Department Syndromic Surveillance System (EDSSS)	2014	now	ARI, ILI, Pneumonia	0-1, 1-4, 5-14, 15-44, 45-64, 65+	Date, diagnosis, age group, region
France	Surveillance syndromique - SURSAUD®	2020	now	ICD-10 codes J09-J18, J20-J22U07.1, U07.10, U07.11, U07.12, U07.14, U07.15, U04.9, B34.2, B97.2	0-4, 5-14, 15-64, 65+	department, week, age group
Norway	table no. 10903: Emergency Primary Health Care consultations, by age, sex and diagnosis	2014	2022	Infections of the respiratory passages, incl. ear infections	0-5, 6-15, 16-19, 20-29, 30-49, 50-66, 67-79, 80-89, 90+	year, age group
Spain	RAE-CMBD	2018	now	ICD-10 codes J01 - J22	Five-year groups	year, age group
Spain	MBDS-AAE	2004	2015	ICD-10 codes J01 - J22	Five-year groups	year, age group

4.3. Hypothetical example AMR forecasting

As mentioned in deliverable 5.5, a 28% reduction in BSP prescriptions was measured in the ADEQUATE paediatric trial. In Figure 11, we present a purely theoretical scenario where these results could be extrapolated to the full scope of national BSP prescriptions based on MERIAM. for the countries not included within the PRUDENCE and ADEQUATE trials. In line with our assumptions, a reduction in AMR is then simulated in all countries.

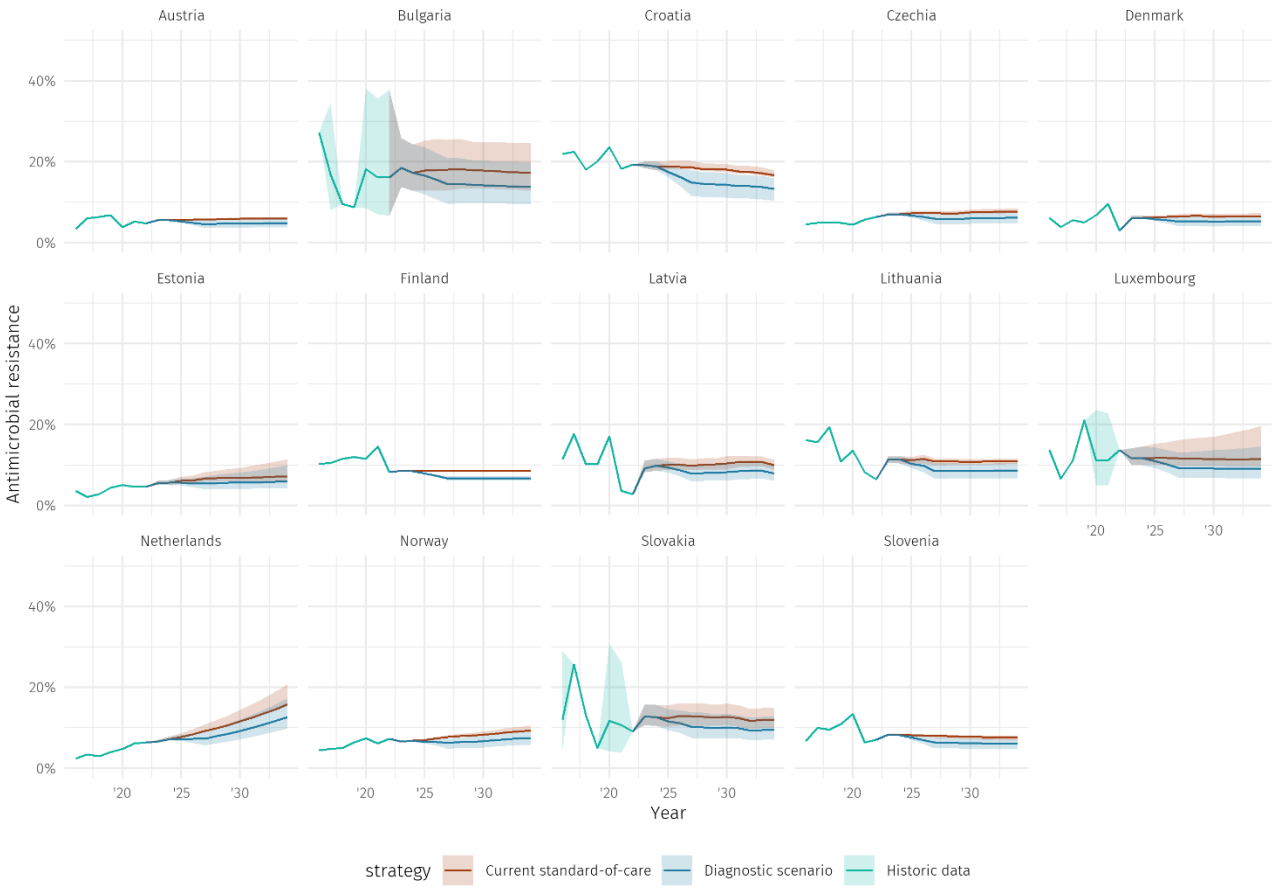

Figure 11 forecasts of antibiotic resistance of Streptococcus pneumoniae against broad-spectrum penicillin (BSP). Historic data based on data collected in the TESSy database (29), diagnostic scenario based on a purely theoretical scenario assuming a 28% reduction in all BSP prescriptions.

5. Inter-country variation in trial results

A transferability assessment of the health economic analysis to other countries than the ones participating in a clinical study is helped by the identification of those variables which values vary substantially across study countries. Substantial variation in results already detected among participating countries may indicate the need for parameter adjustments when transferring the analysis to non-participating countries. Country-specific values of several variables that serve as input parameters in the health economic model were obtained from the PRUDENCE trial. The differences across countries and their estimated impact on the transferability of health economic results are discussed hereafter. Variability was measured by calculating the mean absolute deviation (MAD), interquartile range (IQR) and Quartile Coefficient of Dispersion (QCD). An overview of all variables and their statistical measures of dispersion is provided in Table 6.

Mean absolute deviation (MAD): the average of absolute deviations between each country-specific value and the mean (here: weighted average).

Interquartile range (IQR): the difference between the first quartile (25%) and the third quartile (75%) of values. The IQR measures the spread of the middle 50% of the data and ignores large outliers of the data.

Quartile Coefficient of Dispersion (QCD): the difference between the first and third quartiles divided by the sum of the first and third quartiles. The QCD is a relative measure and results in a value between 0 and 1, where a higher QCD indicates greater variability. The QCD is unitless, enabling comparison across datasets on different scales.

5.1. Disease-related characteristics

5.1.1. Disease severity

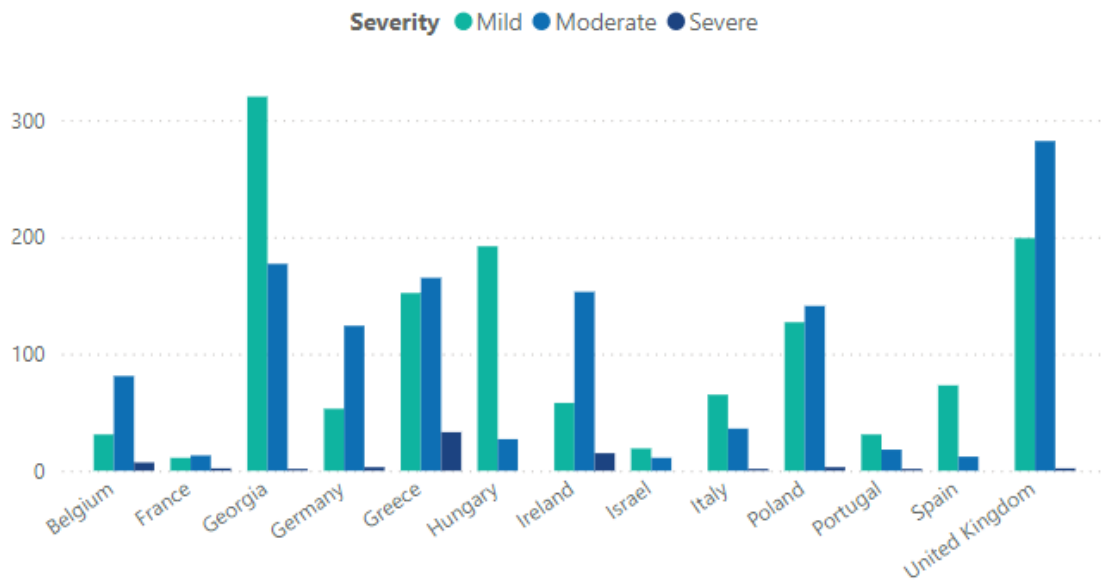

Figure 12 Number of patients per level of disease severity per country in the PRUDENCE trial.

Severity of disease was based on the general practitioner's (GP) clinical judgement and was categorised into mild, moderate and severe disease. On average, the majority of patients had mild disease (52.4%), followed by moderate (44.8%) and severe disease (2.8%). The variation of disease severity across countries was substantial (see Figure 12 and Table 4). Countries deviated on average 17.3% from the mean in the mild category, 15.2% in the moderate category, and 2.9% in the severe category. Some countries had more than two-third of patients in the mild or moderate disease category. Severe disease was highest in Greece with a rate of almost one in ten (9.4%). Remarkably, severe disease was not reported in Spain, Hungary, and Israel.

Table 4 Distribution of disease severity per country in the PRUDENCE trial.

COUNTRY	MILD	MODERATE	SEVERE	NO. PATIENTS
BELGIUM	0.261	0.681	0.059	119
GERMANY	0.294	0.689	0.017	180
SPAIN	0.859	0.141	0.000	85
FRANCE	0.423	0.500	0.077	26
GEORGIA	0.643	0.355	0.002	498
GREECE	0.434	0.471	0.094	350
HUNGARY	0.877	0.123	0.000	219
IRELAND	0.257	0.677	0.066	226
ISRAEL	0.633	0.367	0.000	30
ITALY	0.637	0.353	0.010	102
POLAND	0.469	0.520	0.011	271
PORTUGAL	0.620	0.360	0.020	50
UNITED KINGDOM	0.412	0.584	0.004	483
MEAN	**0.524**	**0.448**	**0.028**	

5.1.2. Cough

The probability of cough was grouped by influenza season. Both during the influenza season as well as outside the influenza season the weighted averages of the probability of cough were almost similar (0.597 against 0.651, respectively). Data revealed low variability in the probability of cough during an influenza season (MAD = 0.110; QCD = 0.09). However, outside the influenza season, the probability was more variable across countries (MAD = 0.211; QCD = 0.34).

5.1.3. Influenza

The probability of influenza on average was 0.462. Across countries, the probability deviated on average 0.170 from the mean, indicating moderate variability. This finding is supported by a QCD of 0.314. Patients diagnosed with COVID-19 were excluded from the calculation of the probability of influenza. The weighted average of influenza probability was mainly elevated by Georgia and Greece (average probabilities of 0.625 and 0.618 and 20.1% and 12.8% of total number of patients, respectively). In contrast, the average probability of influenza was mainly lowered by the probabilities of the UK and Poland.

5.1.4. COVID-19

A large variability across countries was found in the probability of COVID-19. Compared to the average probability of 0.059, the MAD and IQR were high (MAD = 0.064; IQR = 0.115). The QCD of 0.695 supported this finding. COVID-19 probability was highest in Hungary (0.251). Especially the absence of COVID in Georgia (19% of total patients) resulted in a low average.

When interpreting this input parameter and comparing it to the probability of influenza, the COVID incidence at the time of inclusion, the availability of COVID-19 tests, the care pathways and clinical protocols for suspected COVID-19 patients, and more should be taken into account.

5.2. Clinical outcomes

5.2.1. Duration of disease

Time to return to usual daily activities was reported by patients participating in the PRUDENCE trial. In Israel, Italy, and Portugal, the inclusion took place in long term care facilities (LTCFs) only. In other countries - France, Ireland, and Spain -, patients visiting the GP as well as patients in LTCFs were included. Therefore, the results were stratified by setting, i.e. GP and LTCF (Figure 13). The weighted average in time to return was 5.9 days for the GP setting and 4.6 days for the LTFC setting. The number of days that patients reported to be sick varied per country, ranging from 3.2 days in Spain to 9.4 in France for the GP setting (MAD: 2.6 days), and 2.4 days in Italy to 11.6 days in Israel for the LTFC setting (MAD: 0.3 days).

It is however unplausible to consider the study setting as a confounding factor on the duration of disease, especially because both Israel and Italy report the highest and lowest values in time to return, respectively. It should be clear from these country-specific outcome that there may be substantial differences in the duration of disease,

which will impact the outcome of the health economic analysis and thereby its transferability.

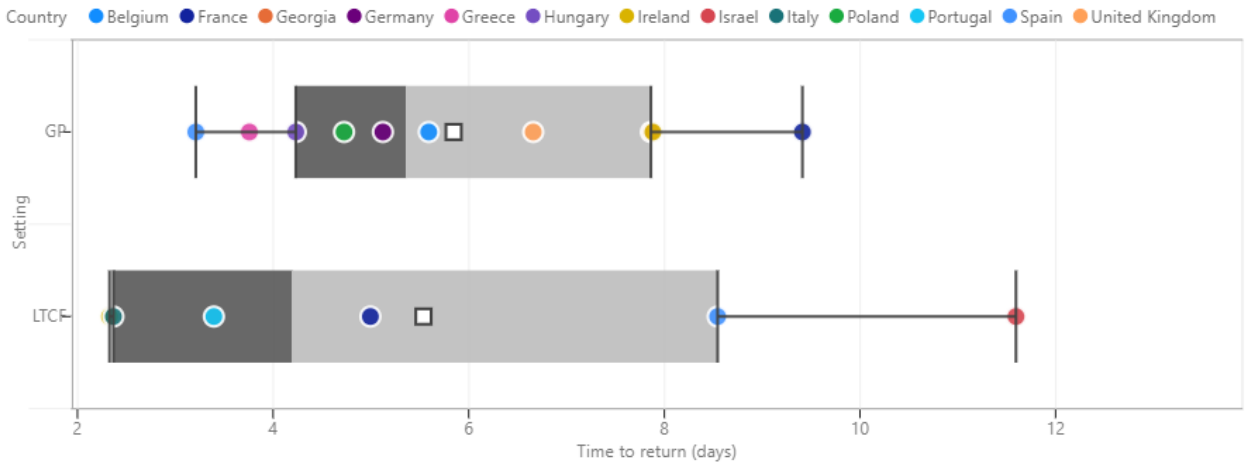

Figure 13 Average time to return in days per study setting per country in the PRUDENCE trial. Abbreviations: GP = general practice; LTCF = long term care facility.

5.2.2. Antibiotics prescribed

The probability of antibiotics prescribed was considerably different across countries (Figure 14). The lowest probability was 0.100 in Israel, against 0.686 in Ireland. Weighted average probability for all patients in the trial was 0.464, which was positively influenced by high-weighting probabilities of Ireland and the UK. A MAD of 0.131, an IQR of 0.180, and a QCD of 0.209 indicate low variability across countries, although the impact on judicious antibiotic prescribing and AMR may be alarming for some countries.

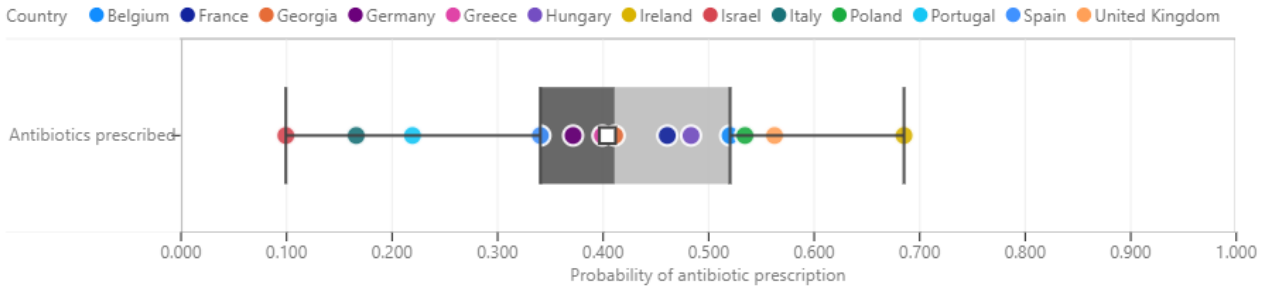

Figure 14 Average probability of antibiotic prescription per country in the PRUDENCE trial.

5.3. Resource use

5.3.1. Diagnostics used

The type of diagnostic tests performed at the GP (i.e. point-of-care) or in the laboratory mainly included X-ray imaging, white blood cell (WBC) counting, and COVID-19 testing (Figure 15). X-ray imaging appeared to be frequently applied in Israel, France, and Georgia, whereas this type of diagnostic was not used in Belgium, Italy, and Portugal. X-ray imaging was on average performed in 11.1% of cases. WBC counting was mainly performed in the laboratory (average = 6.4%): a WBC-POC test was only used in Georgia (average = 5.8%) and the UK (average = 0.2%). COVID-19 tests were more often performed as POC test (average = 2.5%) than in the laboratory (average = 0.7%). Other types of diagnostics were used in 8.1% of cases, on average. Apart from the 'Other' category, inter-country variability was considered high for all types of diagnostics (QCD values >= 0.837).

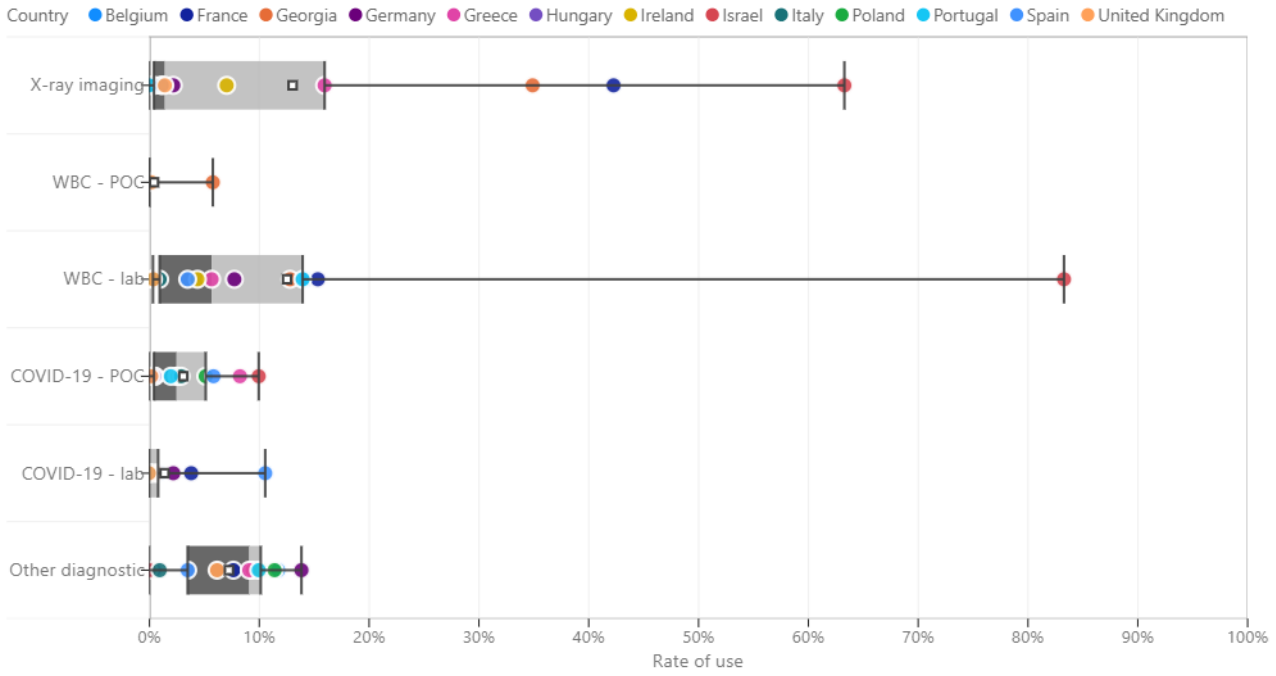

Figure 15 Average rate of diagnostic used per country in the PRUDENCE trial.

5.3.2. Medication prescribed

Medication prescribed by the GP was subdivided into six groups: medical inhalers, antiviral medication, antihistamines, paracetamol, cough suppressants, and other medication (Figure 16). Paracetamol was most frequently prescribed (average = 43.5%), followed by cough suppressants (average = 23.6%), medical inhalers (average = 17.4%), antihistamines (average = 13.3%), and antiviral medication (average = 2.9%). Other types of medication were prescribed in 16.8% of patients, on average. Inter-country variability was considered substantial when observing both MAD and QCD values. Weighted averages of cough suppressants, antihistamines, and antiviral medication were mainly elevated by Georgia. For all types of medication, the UK had a lowering effect on the weighted average. This may be correlated to a high probability of antibiotics prescribed in the UK (see 5.2.2). The weighted average of other types of medication prescribed was especially elevated by Poland.

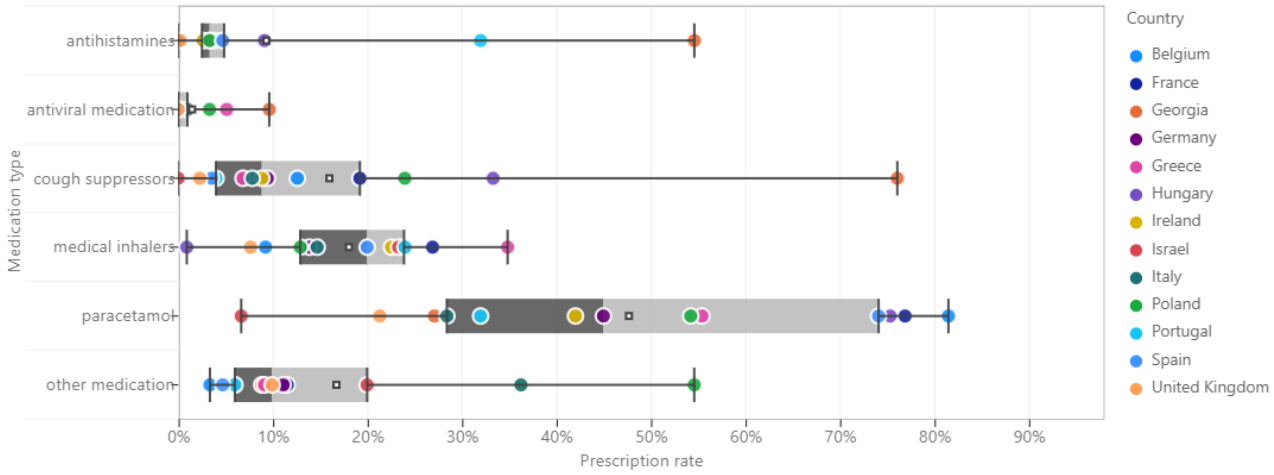

Figure 16 Average prescription rate of antibiotics per country in the PRUDENCE trial.

5.3.3. Primary care visits

Patients reported on average 2.3 GP contact moments (or: consultations) in the past two weeks. Variability across countries was moderate, considering a MAD of 1.3 visits and a QCD of 0.477. Mean number of GP consultations per patient was highest in Georgia (n=5.6), followed by Italy (n=3.4) and Hungary (n=2.8). The setting in which patients were included may have influenced the number of GP consultations per patient. Remarkably, in the GP setting in Ireland and the UK, the mean number of self-reported GP consultations per patient was less than 1. A possible explanation may be that the patient does not count a teleconsultation as a physical visit to the GP office. Moreover, patients in Italy were included in the LTCF setting only though reported 3.4 GP consultations on average.

Frequency rates of other contacts or consultations in outpatient care were below 0.5, indicating one consultation for every two patients or more. QCD values of the other types of outpatient care consultations were between 0.719 and 1.

5.3.4. Secondary care

Outpatient and inpatient care in the hospital was rare for patients in the trial. The length of stay was calculated as the difference in days and nights between the admission date and the discharge date. Weighted averages ranged between 0 and 0.1 for X-ray imaging in the hospital, number of days in the intensive care unit (ICU) and in the general ward, and number of nights in the general ward. While the mean number of nights per patient in the general ward was between 0 and 0.12 for other countries, patients included in Israel (n = 30) spent on average 6.4 nights per patient in the general ward, This was probably due to the fact that patients in Israel were included in LTCFs only.

Although weighted averages of X-ray imaging in the hospital and days and nights in the general ward and ICU were low, these types of healthcare resources should not be neglected, as healthcare costs in secondary care are generally high in comparison to other healthcare costs. This issue is also addressed in the discussion part of deliverable 5.3.

5.3.5. Societal costs

Societal costs were expressed in hours spent in informal care and hours missed of paid work, as well as the out-of-pocket (OOP) costs of daycare treatment and medication. The mean number of hours missed per individual due to informal care was 0.5 hour and ranged between 0 and 2 across countries. The mean number of hours missed of paid work per patient were 8.2 hours and varied substantially across countries. On average per patient, zero hours of paid work were missed in Portugal, against 23 hours of paid work missed in Germany.

Average OOP costs per patient for daycare treatment amounted EUR 0.33 (currency year: 2023). OOP costs per patient for medication was EUR 7.81, on average. OOP costs for medication were especially high in Germany, Poland, and Hungary, amounting EUR 19.00, 19.23, and 22.42, respectively. In some countries, the mean OOP costs for medication were zero. The statistical measures of dispersion indicate that costs were highly variable across countries (see Table 6).

5.4. Quality of life

EQ-5D-5L scores obtained in the trial (aggregated over all countries and both treatment arms) were translated into country-specific utilities by using country-specific value-sets. The utility estimates were calculated for the countries with an EQ-5D-5L values set available, including Germany, the UK, France, Italy, Spain, Poland, Belgium, Portugal, Hungary, and Ireland (n=10). To represent the impact of CA-ARTI, a *dis*utility was calculated by taking the difference in utility values between the first day that the QoL was measured and the day of return to usual activities, derived from the final moment of QoL measurement. Average disutility values per country are shown in Table 5.

Despite the fact that EQ-5D-5L scores as input for each value set were identical, the country-specific output deviated on average 0.027 from the weighted average disutility (0.157). Poland had the lowest disutility value, which differed 0.123 from the highest disutility value for the UK. A QCD of 0.093 was calculated, indicating relatively limited variability across countries. Nonetheless, the transformation of disutility values in QALYs and subsequent incorporation in a health economic analysis may have substantial impact on the outcome of the cost-utility ratio.

Table 5 Disutility values per country with an EQ-5D value set available.

COUNTRY	AVERAGE	MILD DISEASE	MODERATE DISEASE	SEVERE DISEASE
POLAND	0.096	0.069	0.125	0.174
FRANCE	0.108	0.075	0.141	0.200
PORTUGAL	0.146	0.110	0.182	0.254
HUNGARY	0.151	0.109	0.194	0.267
GERMANY	0.151	0.113	0.190	0.262
ITALY	0.162	0.120	0.205	0.287
SPAIN	0.167	0.137	0.197	0.274
BELGIUM	0.180	0.144	0.217	0.297
IRELAND	0.192	0.148	0.236	0.336
UNITED-KINGDOM	0.219	0.188	0.250	0.341
AVERAGE	**0.157**	**0.121**	**0.194**	**0.269**
MAD	**0.027**	**0.026**	**0.027**	**0.038**
MEDIAN	**0.156**	**0.116**	**0.196**	**0.271**
IQR	**0.030**	**0.033**	**0.031**	**0.038**
QCD	**0.093**	**0.131**	**0.077**	**0.069**

ABBREVIATIONS: IQR = INTER-QUARTILE RANGE; MAD = MEAN ABSOLUTE DEVIATION; QCD = QUARTILE COEFFICIENT OF DISPERSION.

Table 6 Overview of statistical measures of dispersion per parameter used in the health economic model of the PRUDENCE trial. Abbreviations: GP = general practitioner; HCRU = healthcare resource use ; ICU = intensive care unit; IQR = interquartile range ; LTCF = long term care facility; MAD = mean absolute deviation; POC = point-of-care; QCD = quartile coefficient of dispersion ; QOL = quality-of-life; WBC = white blood cell counting.

TOPIC	VARIABLE GROUP	VARIABLE NAME	VARIABLE UNIT	(WEIGHTED) AVERAGE	MAD	MEDIAN	IQR	QCD
CLINICAL OUTCOME	Time to return (days)	Time to return (days) - GP	days	5.9	2.6	5.4	3.2	0.269
CLINICAL OUTCOME	Time to return (days)	Time to return (days) – LTCF	days	4.6	0.3	4.2	5.0	0.489
CLINICAL OUTCOME	Antibiotics prescribed	Antibiotics prescribed	probability	0.464	0.131	0.412	0.180	0.209
DISEASE	Disease severity	mild	rate	52.4%	17.3%	46.9%	22.5%	0.215
DISEASE	Disease severity	moderate	rate	44.8%	15.2%	47.1%	22.9%	0.243
DISEASE	Disease severity	severe	rate	2.8%	2.9%	1.1%	5.7%	0.934
DISEASE	Cough	Cough - influenza season = N	probability	0.597	0.211	0.588	0.356	0.344
DISEASE	Cough	Cough - influenza season = Y	probability	0.651	0.110	0.623	0.116	0.093
DISEASE	Influenza	Influenza	probability	0.462	0.170	0.546	0.299	0.314
DISEASE	COVID-19	COVID-19	probability	0.059	0.064	0.055	0.115	0.695
HCRU	Medication prescribed	medical inhalers	rate	17.4%	7.6%	20.0%	11.0%	0.298
HCRU	Medication prescribed	antiviral medication	rate	2.9%	2.9%	0.0%	1.0%	1.000
HCRU	Medication prescribed	antihistamines	rate	13.3%	13.2%	3.3%	2.3%	0.317
HCRU	Medication prescribed	paracetamol	rate	43.5%	20.1%	45.0%	45.7%	0.446
HCRU	Medication prescribed	cough suppressors	rate	23.6%	17.2%	8.9%	15.2%	0.656
HCRU	Medication prescribed	other medication	rate	16.8%	12.4%	9.9%	14.0%	0.538
HCRU	Diagnostics used	X-ray imaging	rate	11.1%	15.3%	1.5%	15.5%	0.944
HCRU	Diagnostics used	WBC - POC	rate	1.1%	1.4%	0.0%	0.0%	n/a
HCRU	Diagnostics used	WBC - lab	rate	6.4%	10.6%	5.7%	13.0%	0.869
HCRU	Diagnostics used	COVID-19 - POC	rate	2.5%	2.4%	2.5%	4.7%	0.837
HCRU	Diagnostics used	COVID-19 - lab	rate	0.7%	1.6%	0.0%	0.8%	1.000
HCRU	Diagnostics used	Other diagnostic	rate	8.1%	3.8%	9.1%	6.7%	0.485
HCRU	Outpatient care	Accident and emergency	frequency rate	0.02	0.03	0.03	0.04	1.000
HCRU	Outpatient care	General practitioner	frequency rate	2.27	1.28	1.18	1.48	0.477
HCRU	Outpatient care	Out of hours service	frequency rate	0.05	0.08	0.02	0.05	0.719
HCRU	Outpatient care	Paediatrician	frequency rate	0.06	0.06	0.01	0.10	1.000
HCRU	Outpatient care	Pharmacy	frequency rate	0.48	0.42	0.56	0.67	0.922
HCRU	Outpatient care	Specialist	frequency rate	0.26	0.57	0.10	0.34	0.844
HCRU	Hospital care	X-ray in the hospital	frequency rate	0.02	0.04	0.02	0.01	0.388
HCRU	Hospital care	Hospital nights	frequency rate	0.10	0.55	0.02	0.04	0.519
HCRU	Hospital care	ICU days	frequency rate	0.00	0.01	0.00	0.00	n/a

HCRU	Hospital care	Hospital days	frequency rate	0.02	0.02	0.01	0.04	1.000
COSTS	Societal costs	Mean number of hours missed due to informal care	hours	0.5	0.4	0.5	0.7	0.818
COSTS	Societal costs	Mean number of hours missed of paid work	hours	8.2	5.6	5.1	6.5	0.487
COSTS	Societal costs	Out-of-pocket costs paid to daycare	EUR (2023)	0.33	0.38	0.09	0.64	1.000
COSTS	Societal costs	Out-of-pocket costs paid for medication	EUR (2023)	7.81	7.07	2.47	9.25	0.947
QOL	EQ-5D-5L	average	disutility	0.157	0.027	0.156	0.030	0.093
QOL	EQ-5D-5L	mild disease	disutility	0.121	0.026	0.116	0.033	0.131
QOL	EQ-5D-5L	moderate disease	disutility	0.194	0.027	0.196	0.031	0.077
QOL	EQ-5D-5L	severe disease	disutility	0.269	0.038	0.271	0.038	0.069

6. Generalizability of costs

6.1. Example using Spanish and British data

To explore the accuracy and applicability of an existing method that can be used in the transferability of health economic analyses, a cross comparison was made between costs used for Spain and the UK with purchasing power parities (PPPs). The current exploratory analysis included unit costs that were applied in the trial-based economic evaluation (Deliverable 5.3). These involve direct healthcare costs per capita in terms of consumption of antibiotics and other types of medication, diagnostic tests, hospitalisation, and medical visits. The web-based Cost Converter tool of the Campbell & Cochrane Economics Methods Group (CCEMG) and Evidence for Policy and Practice Information (EPPI) Centre (v.1.7, released in January 2024) was used to convert costs between the two countries (34). The tool offers two sources for PPP values, one from the International Monetary Fund (IMF) and the other from the Organisation for Economic Cooperation and Development (OECD). Although the tool first calculates price-year adjusted cost estimates, this was not necessary in our case. PPP values for price year 2022 are displayed in Table 7.

Table 7 PPP values applied. Derived from the CCEMG-EPPI Cost Converter tool (34).

Country	OECD PPP value (2022)	ICF OECD to target country	IMF PPP value (2022)	ICF IMF to target country
UK	0.651253998279572	0.89	0.694999992847443	1.09
Spain	0.578808009624481	1.13	0.639999985694885	0.92

Abbreviations: ICF = Implied Conversion Factor; IMF = International Monetary Fund; OECD = Organisation for Economic Cooperation and Development; PPP = Purchasing Power Parity; UK = United Kingdom.

Cost converted estimates of Spain and UK original values are displayed in Table 8 and Table 9, respectively. On average, differences between the converted costs and the original estimates ranged between -16.4% and +23.5%. When interpreting these results, it should be noted that original estimates for both countries may have been identified, measured, and valued in different ways. The cost components included may be unsimilar and the method used to calculate costs for the resources used may have varied. The sources and methods used for the cost calculation are described in deliverable 5.3. Despite substantial differences shown here, the use of PPP appears to be an efficient method to convert costs between countries, compared to the labour- and time-intensive option to calculate country-specific costs for each component.

Table 8 PPP converted cost estimates of Spain original estimates per cost component and their percentual differences.

	Antibiotic consumption	Consumption of other medications	Costs for diagnostic tests	Hospitalization costs	Costs for medical visits and others	average difference
Original estimate Spain (EUR)	3.27	6.37	6.69	53.98	40.97	
OECD PPP converted estimate (EUR) from original estimate UK (GBP)	2.21	4.58	6.34	58.29	31.02	
% difference from original	-32.4%	-28.1%	-5.2%	8.0%	-24.3%	-16.4%
IMF PPP converted estimate (EUR) from original estimate UK (GBP)	2.29	4.74	6.57	60.4	32.14	
% difference from original	-30.0%	-25.6%	-1.8%	11.9%	-21.6%	-13.4%

Table 9 PPP converted cost estimates of UK original estimates per cost component and their percentual differences.

	Antibiotic consumption	Consumption of other medications	Costs for diagnostic tests	Hospitalization costs	Costs for medical visits and others	average difference
Original estimate UK (GBP)	2.49	5.15	7.13	65.59	34.9	
OECD PPP converted estimate (GBP) from original estimate Spain (EUR)	3.68	7.17	7.53	60.74	46.1	
% difference from original	47.8%	39.2%	5.6%	-7.4%	32.1%	23.5%
IMF PPP converted estimate (GBP) from original estimate Spain (EUR)	3.55	6.92	7.26	58.62	44.49	
% difference from original	42.6%	34.4%	1.8%	-10.6%	27.5%	19.1%

6.2. Lessons in the ALIC^{4}E trial

A recent comparable health economic evaluation was performed alongside the ALIC^{4}E trial (35). The trial was performed in 15 European countries, consisting of 21 networks covering 209 primary care practices over three consecutive winters (Q4 2015–Q2 2018). The cost-effectiveness analysis (CEA) of adding oseltamivir to usual primary care in ILI patients was supplemented by country-specific analyses. All country-specific costs were expressed in 2018 euro values and converted where needed, using PPPs. The list price of the intervention (i.e. oseltamivir) were made country-specific by using PPPs.

Direct and indirect costs originated from an earlier descriptive analysis of costs alongside the same multinational clinical trial (27). The cost analysis identified country-specific healthcare resources by sending out templates to all participating countries in the research network. This was supplemented by contextual information regarding the healthcare system and reimbursement policies, using phone interviews with members of the research network. Then, costs were collected from public data sources (e.g. national tariffs) and grey and white literature. Where cost data were unavailable, assumptions were made, which were discussed and validated with health economists in the UK, Belgium, and Sweden. The cost analysis used four different perspectives to show the sensitivity to different assumptions and approaches.

The methodological choices and findings of the cost analysis could be of interest to the health economic evaluation in the context of both the ADEQUATE and PRUDENCE trial. Several unit costs measured in the cost analysis of Li et al. are similar to the current

health economic analysis. Examples of these are the costs for visiting the GP, the paediatrician, and the accident and emergency department. Moreover, the average salary per hour was shown per country. The cost data as presented by Li et al. could serve as a reference point for cost data in the current health economic analyses, or could be directly applied after inflation correction for the cost components with identical resource units. As also mentioned in the cost analysis, the inclusion of over-the-counter (OTC) medication costs is important to consider, depending on the perspective of the analysis. For the patient perspective, the OTC medication costs impacted a large proportion of direct costs. Moreover, the actual reimbursement regulations that apply to a particular country may be a contributing factor to the costs, of which OTC medication costs are an example (see also paragraph 2.5). A similar effect on the cost-effectiveness outcomes in the context of ADEQUATE and PRUDENCE may be deemed plausible.

Remarkably, the ICER was not only expressed in costs per QALY, but also in costs per day of faster recovery. As QALY evaluation was surrounded by uncertainties and challenging to derive among certain population groups (e.g. very young children), the ICER in costs per day of faster recovery may be a proper alternative and not less informative to clinicians and healthcare decision-makers than the costs per QALY.

The ALIC^{4}E CEA employed both the healthcare payers' and societal perspectives and provided cost-effectiveness estimates for those countries with data available for more than 90 patients per treatment arm. The use of multiple perspectives, i.e. including direct costs only or both direct and indirect costs, increases the transferability of the analysis across countries.

7. Conclusions

7.1. Summary of findings

The current task identified several issues that probably impact the transferability of the health economic analysis to other countries than the ones participating in PRUDENCE and ADEQUATE. In the first place, age-specific incidence data of ARI and ILI reported in primary care appeared to be limitedly available for many countries in the past decade. It was not possible to calculate the age-specific incidence data from the ECDC TESSy database for the majority of EEA countries. After combining ARI and ILI incidence, age-specific incidence data per country per week was not available for almost 75% of the data. Besides incidence data reported in Primary Care facilities, some publicly available national data sources of ARI and ILI incidence in Emergency Departments were found. Although age-specific data was available for a small number of countries, definitions of diagnosis were found to be inconsistent when comparing between countries, which limits the external validity of data and related transferability. In the context of long-term care facilities no incidence data was found.

Secondly, the PRUDENCE trial results were substantially different across participating countries, especially for healthcare resource use and costs. It is essential to carefully interpret the inter-country variation as presented here. The trial was not powered to detect country differences in outcomes. Moreover, each statistical measure of dispersion used here provides a limited view of tendency and spread of the data. Therefore, the measured outcomes need a detailed look per parameter to attain a proper interpretation of inter-country variability. In general, most input parameters of the health economic model may need adjustment before being applied to another country. Nonetheless, the inter-country variation as described here indicates the relevance to perform country-specific health economic analyses.

Finally, the use of PPPs for cost conversion between countries can be considered efficient. Bearing in mind the efforts needed to calculate country-specific costs, this method may be the best available in the transferability of health economic analyses.

7.2. Recommendations

The results of the current task raise several points of consideration that may need attention in future analyses. As ARI and ILI incidence is lacking or limitedly available for some countries that participated in PRUDENCE and ADEQUATE, the analysis in the context of the trial is hampered and also affects the transferability to many non-participating countries. A first step to close the gap regarding this type of data may be to start an enquiry for alternative sources of incidence data not included in the TESSy database at the national health agency or authority of the country to which the analysis is applied. Alternatively, country-specific evidence regarding incidence data may be derived from scientific literature. However, as there is almost no literature available reporting on CA-ARTI incidence, we recommend to use the average incidence of EEA countries as a proxy

for a country's incidence in the health economic analysis. In all cases, evidence should be discussed with epidemiological experts. .

Further research is needed to identify patterns of ARI and ILI incidence across countries. Similarity may be detected by focusing on seasonality, for example, which enables the clustering of countries. This way, a country with no or low data availability of incidence can apply data of a cluster with the most plausible comparability of incidence data.

Similarly, a cluster analysis of the PRUDENCE trial data may be a useful addition to the current analysis of inter-country variation. Clusters of countries can be based on a single parameter or multiple parameters. However, the clustering of countries probably brings along several uncertainties. For example, the number of patients per country in PRUDENCE differs substantially, which may impact the stability of the clusters. Moreover, a prespecified combination of parameters to identify clusters is probably complicated and may induce subjectivity. Therefore, a certain cluster analysis would be exploratory in nature and its outcome could serve as a starting point in the identification of missing data for one or more input parameters. This way, countries not included in the trial may explore their affiliation with one of the clusters, which increases the transferability of the health economic analysis on the potential of diagnostics in terms of AMR prevention.

In conclusion, the work done in this task emphasizes the importance of a country-specific approach to estimating the cost-effectiveness of diagnostics. Not only because of vast between-country differences in potentially many of the input parameters, but also because implementation of diagnostic tests in clinical practice is far from straightforward as demonstrated by the social science research team in WP4, and will not follow the same process in all countries. Therefore, transferring the results of the health economic models to other settings warrants careful study of, among others, local incidence numbers, consultation behaviour, and cost parameters, but also of the logistic and social implications of introducing point-of-care tests in a certain GP practice or ER.

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Supplementary Materials

Analyzing weekly incidence of ARI and ILI cases using R

Introduction: This document describes the cleaning and preparation process and subsequent data analysis of incidence data of cases with Acute Respiratory Infections (ARI) and Influenza-like Illness (ILI). Incidence data was requested from The European Surveillance System (TESSy) database of the European Center for Disease Control (ECDC). Data from countries that are within the European Union (EU) and European Economic Area (EEA) were selected. Data was shared by the ECDC in .CSV file format and entailed the sum of cases (i.e. nominators) and the sum of the population included in the database (i.e. denominators) per country on a weekly basis in the period 2009W53 - 2024W07. Incidence data were provided in total numbers as well as per age group. Data was categorized in four age groups:

0-4 years

5-14 years

15-64 years

65 years and over

The data cleaning and preparation of data is described in stage 1 and includes the imputation of missing values and the preparation of data frames that serve as input for the data analysis (stages 2-5). Data from four 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 is converted into an incidence object and modeled using the Incidence package. Two exponential models will be created for each year, one where the number of cases increases over time and one where the number cases decrease. This way, an annual peak is created in the influenza season. The function fit_optim_split() from the incidence package is used to automatically determine the peak of the influenza season.

STAGE 1: DATA CLEANING AND PREPARATION

Step 1.1: impute data in the source file outside the R environment. Calculate ARI_Denominator00-04 and ILI_Denominator00-04 for Slovakia (ReportingCountry = 'SK') in DateUsedForStatisticsISO '2013W24':

1) calculate average ARI and ILI incidence of 2013W23 and 2013W25;
2) calculate ARI and ILI denominators based on ARI and ILI cases 2013W24 and the calculated ARI and ILI incidence;
3) calculate average of both denominators.

Step 1.2: delete values of ARI denominators and ARI cases for Denmark (ReportingCountry = DK). ARI cases were not recorded but still filled as '0' for all years and can therefore be removed.

Step 1.3: save data file as 'INFLCLINAGGR.csv' in your working directory.

Step 1.4: load data file 'INFLCLINAGGR.csv', rename age-specific column names, add missing rows based on date values and add time-specific columns.

```
setwd("C:/Users/clazi/OneDrive - UMCG/Documenten/R working directory")
ECDC_inc_raw <- read_csv("INFLCLINAGGR.csv",  show_col_types = FALSE)

ECDC_inc <- ECDC_inc_raw %>%
  rename(ARI_0 = `ARINumberOfCases`, ARI_1 = `ARI00-04`, ARI_2 = `ARI05-
14`, ARI_3 = `ARI15-64`, ARI_4 = `ARI65+`,
         ARI_Denom_0 = `ARI_DenominatorNumberOfCases`, ARI_Denom_1 = `AR
I_Denominator00-04`, ARI_Denom_2 = `ARI_Denominator05-14`, ARI_Denom_3 =
`ARI_Denominator15-64`, ARI_Denom_4 = `ARI_Denominator65+`,
         ILI_0 = `ILINumberOfCases`, ILI_1 = `ILI00-04`, ILI_2 = `ILI05-
14`, ILI_3 = `ILI15-64`, ILI_4 = `ILI65+`,
         ILI_Denom_0 = `ILI_DenominatorNumberOfCases`, ILI_Denom_1 = `IL
I_Denominator00-04`, ILI_Denom_2 = `ILI_Denominator05-14`, ILI_Denom_3 =
`ILI_Denominator15-64`, ILI_Denom_4 = `ILI_Denominator65+`) %>%

  mutate(Date = week2date(DateUsedForStatisticsISO)) %>%
  group_by(ReportingCountry) %>%
  pad_by_time(.date_var = Date, .by = "auto") %>%

  mutate(DateUsedForStatisticsISO2 = date2week(Date),
         DateUsedForStatisticsISO = substr(DateUsedForStatisticsISO2,1,8
),
         across(c(ARI_Denom_1:NumberOfPhysicians), ~na.approx(.x, na.rm
= FALSE, maxgap = 2)),
         ReportingCountry = na.locf(ReportingCountry, fromLast = T),
         DateWeek = date2week(Date,numeric = T),
         DateYear = substr(DateUsedForStatisticsISO,1,4),
         DateYear = as.numeric(DateYear),
         DateWeek = as.numeric(DateWeek)) %>%
  mutate(Season = if_else(DateWeek > 34, str_c(DateYear, "-", DateYear+1
), str_c(DateYear-1, "-", DateYear)),
         YearWeek = ifelse(DateWeek<10, paste(DateYear, paste('0', DateW
eek, sep = ""), sep = "-"), paste(DateYear, DateWeek, sep = "-"))) %>%
```

```
  filter(!ReportingCountry %in% c("CY", "FI","LU", "MT")) %>%
  select(ReportingCountry, YearWeek, Season, DateYear, DateWeek, Date, A
RI_Denom_1:ILIUnk)

## pad applied on the interval: week
```

Step 1.5: create a subset for ARI incidence, remove rows with empty denominator values, calculate the sum of denominator values for each row and remove redundant rows, i.e. rows with sum of denominators = 0

```
ECDC_inc_ARI <- ECDC_inc %>%
  select(ReportingCountry:ARIUnk) %>%
  filter_at(vars(ARI_Denom_1:ARI_Denom_4), all_vars(!is.na(.))) %>%
  group_by(ReportingCountry, Date) %>%
  mutate("ARI_Denom_sum" = sum(c_across(ARI_Denom_1:ARI_Denom_4), na.rm
= T)) %>%
  filter(ARI_Denom_sum > 0)
```

Step 1.6: calculate the sum of denominators and nominators by week and calculate incidence per 100.000 inhabitants per week. The message about missing grouping variables (ReportingCountry) can be ignored.

```
ECDC_inc_ARI_2 <- ECDC_inc_ARI %>%
  select(YearWeek:Date, ARI_Denom_1:ARI_Denom_4, ARI_1:ARI_4) %>%
  group_by(YearWeek, Season, DateYear, DateWeek, Date) %>%
  summarise_at(vars(ARI_Denom_1:ARI_4), sum, na.rm = TRUE) %>%
  mutate(ARI_1 = (100000*ARI_1)/ARI_Denom_1,
         ARI_2 = (100000*ARI_2)/ARI_Denom_2,
         ARI_3 = (100000*ARI_3)/ARI_Denom_3,
         ARI_4 = (100000*ARI_4)/ARI_Denom_4) %>%
  select(YearWeek:Date, ARI_1:ARI_4)

## Adding missing grouping variables: `ReportingCountry`
```

Step 1.7: repeat step 1.5 and 1.6 for ILI incidence

```
ECDC_inc_ILI <- ECDC_inc %>%
  select(ReportingCountry:Date, ILI_Denom_1:ILIUnk) %>%
  filter_at(vars(ILI_Denom_1:ILI_Denom_4), all_vars(!is.na(.))) %>%
  group_by(ReportingCountry, Date) %>%
  mutate("ILI_Denom_sum" = sum(c_across(ILI_Denom_1:ILI_Denom_4), na.rm
= T)) %>%
  filter(ILI_Denom_sum > 0)

ECDC_inc_ILI_2 <- ECDC_inc_ILI %>%
  select(YearWeek:Date, ILI_Denom_1:ILI_Denom_4, ILI_1:ILI_4) %>%
  group_by(YearWeek, Season, DateYear, DateWeek, Date) %>%
  summarise_at(vars(ILI_Denom_1:ILI_4), sum, na.rm = TRUE) %>%
  mutate(ILI_1 = (100000*ILI_1)/ILI_Denom_1,
         ILI_2 = (100000*ILI_2)/ILI_Denom_2,
         ILI_3 = (100000*ILI_3)/ILI_Denom_3,
         ILI_4 = (100000*ILI_4)/ILI_Denom_4) %>%
  select(YearWeek:Date, ILI_1:ILI_4)
```

```
## Adding missing grouping variables: `ReportingCountry`
```

Step 1.8: join ARI and ILI incidence data frames to one data frame containing the mean incidence for ARI and ILI per week per age group

```
ECDC_mean_inc_ARI_ILI <- inner_join(ECDC_inc_ARI_2, ECDC_inc_ILI_2, by =
c('YearWeek', 'Season', 'DateYear', 'DateWeek', 'Date'))
```

Step 1.9: calculate incidence based on present values

```
ECDC_true_inc_ARI_ILI <- ECDC_inc %>%
  select(-contains(c("_0", "Unk"))) %>%
  mutate(ARI_1 = if_else(is.na(ARI_Denom_1), NA, if_else(ARI_Denom_1 ==
'0', NA, (100000*ARI_1)/ARI_Denom_1)),
         ARI_2 = if_else(is.na(ARI_Denom_2), NA, if_else(ARI_Denom_2 ==
'0', NA, (100000*ARI_2)/ARI_Denom_2)),
         ARI_3 = if_else(is.na(ARI_Denom_3), NA, if_else(ARI_Denom_3 ==
'0', NA, (100000*ARI_3)/ARI_Denom_3)),
         ARI_4 = if_else(is.na(ARI_Denom_4), NA, if_else(ARI_Denom_4 ==
'0', NA, (100000*ARI_4)/ARI_Denom_4)),
         ILI_1 = if_else(is.na(ILI_Denom_1), NA, if_else(ILI_Denom_1 ==
'0', NA, (100000*ILI_1)/ILI_Denom_1)),
         ILI_2 = if_else(is.na(ILI_Denom_2), NA, if_else(ILI_Denom_2 ==
'0', NA, (100000*ILI_2)/ILI_Denom_2)),
         ILI_3 = if_else(is.na(ILI_Denom_3), NA, if_else(ILI_Denom_3 ==
'0', NA, (100000*ILI_3)/ILI_Denom_3)),
         ILI_4 = if_else(is.na(ILI_Denom_4), NA, if_else(ILI_Denom_4 ==
'0', NA, (100000*ILI_4)/ILI_Denom_4))) %>%
  select(ReportingCountry:Date, ARI_1:ARI_4, ILI_1:ILI_4)
```

Step 1.10: calculate the sum of ARI and ILI incidences as EU/EEA average and per country.

```
ECDC_inc_ARLI <- ECDC_mean_inc_ARI_ILI %>%
  mutate(ARLI_1 = (ARI_1+ILI_1),
         ARLI_2 = (ARI_2+ILI_2),
         ARLI_3 = (ARI_3+ILI_3),
         ARLI_4 = (ARI_4+ILI_4)) %>%
  select(YearWeek:Date, ARLI_1:ARLI_4)

ECDC_inc_ARLI_country <- ECDC_true_inc_ARI_ILI %>%
  mutate(ARLI_1 = (ARI_1+ILI_1),
         ARLI_2 = (ARI_2+ILI_2),
         ARLI_3 = (ARI_3+ILI_3),
         ARLI_4 = (ARI_4+ILI_4)) %>%
  select(ReportingCountry:Date, ARLI_1:ARLI_4)
```

Step 1.11: write output to GitHuBDesktop. The first two data frames contain the weekly incidence of ARI and ILI together, in which the first is grouped by week only and the second by week and country. The third data frame contains the weekly incidence of ARI and ILI separately and is grouped by week and country.

```
write_vc(ECDC_inc_ARLI
         , file = "data_input/incidence_modelling/ECDC_inc_ARLI"
         , root = repo)

##           337a16cd4567e0152b6c3d41a2b6463c8f89f71c
## "data_input/incidence_modelling/ECDC_inc_ARLI.tsv"
##           46c0ff469da3db3063a418df10f2896fa0557953
## "data_input/incidence_modelling/ECDC_inc_ARLI.yml"

write_vc(ECDC_inc_ARLI_country
         , file = "data_input/incidence_modelling/ECDC_inc_ARLI_country"
         , root = repo)

##                   42205de20435cd8e7bbe877c950cb0496f68a222
## "data_input/incidence_modelling/ECDC_inc_ARLI_country.tsv"
##                   8eac540757b82f4ac63a622bcfa105734ba79d7b
## "data_input/incidence_modelling/ECDC_inc_ARLI_country.yml"

write_vc(ECDC_true_inc_ARI_ILI
         , file = "data_input/incidence_modelling/ECDC_inc_ARI_ILI_count
ry"
         , root = repo)

##                       141a418d67a1bdcd5901b88891fb20fcf98df643
## "data_input/incidence_modelling/ECDC_inc_ARI_ILI_country.tsv"
##                       30221b970a45a37c75146878f75f5e7a6c4ee50d
## "data_input/incidence_modelling/ECDC_inc_ARI_ILI_country.yml"
```

END OF STAGE 1

STAGE 2: Model ARI+ILI incidence (EU/EEA average)

Step 2.1: load incidence data of stage 1 from the GitHubDesktop repository if stage 1 has not been executed in your current session

```
ECDC_inc_ARLI <- read_vc(file = "data_input/incidence_modelling/ECDC_inc
_ARLI.tsv", root = repo)
```

Step 2.2: create a pivot table, exclude incomplete seasons (2009-2010, 2023-2024) and pandemic season (2019-2020, 2020-2021, 2021-2022), and nest by season and age category

```
av_inc_ARLI <- ECDC_inc_ARLI %>%
  pivot_longer(cols = c("ARLI_1", "ARLI_2","ARLI_3", "ARLI_4"),
               names_to = "AgeCat",
               values_to = "IncidenceRate") %>%
  filter(!Season %in% c('2009-2010', '2019-2020', '2020-2021', '2021-202
2', '2023-2024'))

nested_av_ARLI <- av_inc_ARLI %>%
  group_by(Season, AgeCat) %>%
  nest()
```

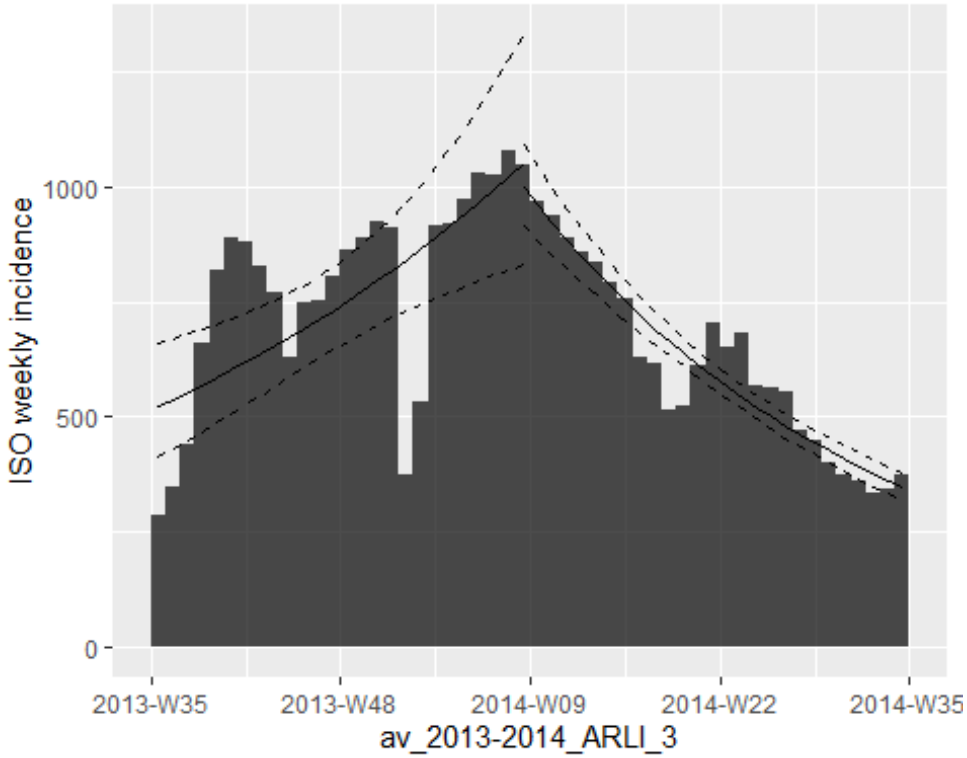
Step 2.3: calculate incidence model by season and age category

```
ARLI_model <- nested_av_ARLI %>%
  mutate(object = map(data, ~as.incidence(.x$IncidenceRate, dates = .x$D
ate)),
         name = str_c("av", '_', Season, '_', AgeCat),
         model = map(object, ~fit_optim_split(.x, window = .x$timespan/2
)),
         plot = map2(object, model, ~plot(.x, labs(name), fit = .y$fit))
)
```

Step 2.4: view one plotted incidence model as an example of output

```
ARLI_model$plot[15]

## [[1]]
```



Step 2.5: save model_output as .rds file in GitHubDesktop

END OF STAGE 2

STAGE 3: Model ARI+ILI incidence per country

Step 3.1: load country-specific ARI+ILI incidence output generated in stage 1 from your GitHubDesktop repository if stage 1 has not been executed in your current session

```
ECDC_inc_ARLI_country <- read_vc(file = "data_input/incidence_modelling/
ECDC_inc_ARLI_country.tsv", root = repo)
```

Step 3.2: Create a pivot table

```
cy_inc_ARLI <- ECDC_inc_ARLI_country %>%
  pivot_longer(cols = c("ARLI_1", "ARLI_2","ARLI_3","ARLI_4"),
               names_to = "AgeCat",
               values_to = "IncidenceRate") %>%
  na.omit(IncidenceRate)
```

Step 3.3: exclude rows containing NA values. These rows pertain to the countries and weeks with missing data on ARI and ILI cases. Nest data by country, season, and age category for countries with data for full seasons

```
nested_cy_inc_ARLI <- cy_inc_ARLI %>%

  group_by(ReportingCountry, Season, AgeCat) %>%
  filter((ReportingCountry %in% c("BE", "SI", "SK") & !Season %in% c('20
09-2010', '2019-2020', '2020-2021', '2021-2022', '2023-2024')) |
         (ReportingCountry == "CZ" & Season %in% c('2015-2016', '2016-20
17', '2017-2018', '2018-2019', '2022-2023')) |
         (ReportingCountry == "LV" & Season %in% c('2016-2017', '2017-20
18', '2018-2019', '2022-2023')) |
         #(ReportingCountry == "NL" & Season %in% c('2015-2016', '2016-2
017', '2018-2019')) |
         (ReportingCountry == "NL" & Season %in% c('2016-2017', '2018-20
19')) |
         (ReportingCountry == "RO" & Season %in% c('2010-2011', '2013-20
14', '2014-2015', '2018-2019'))) %>%
  nest()
```

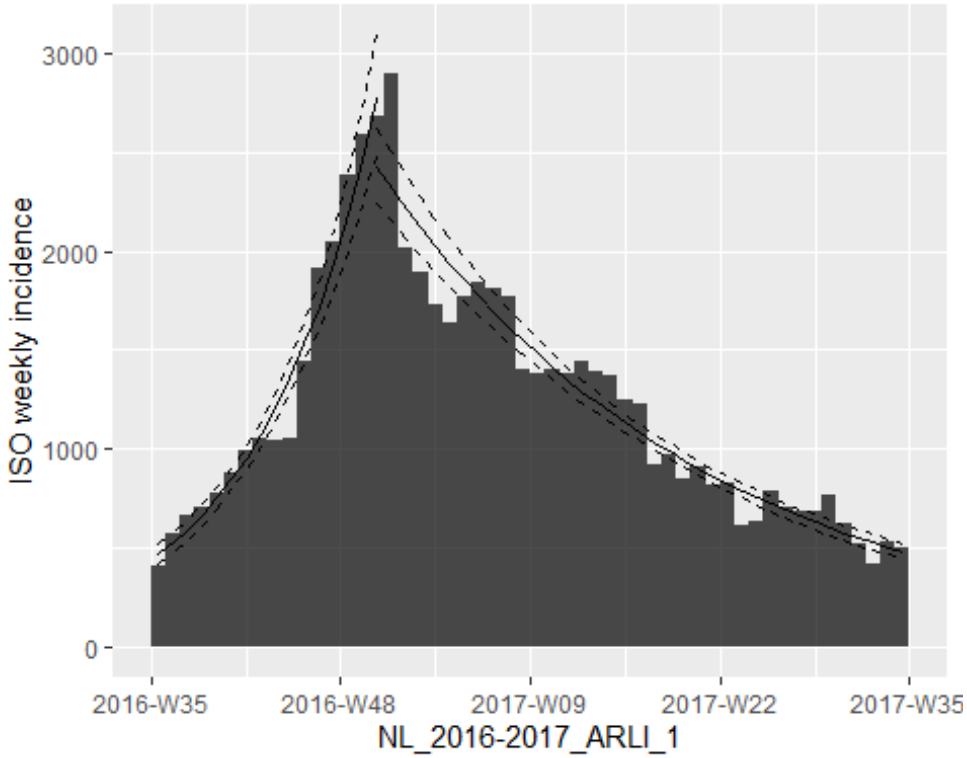
Step 3.3: calculate ARI+ILI incidence model by country, season and age category

```
ARLI_model_country <- nested_cy_inc_ARLI %>%
  mutate(object = map(data, ~as.incidence(.x$IncidenceRate, dates = .x$D
ate)),
         name = str_c(ReportingCountry, '_', Season, '_', AgeCat),
         model = map(object, ~fit_optim_split(.x, window = .x$timespan/2
)),
         plot = map2(object, model, ~plot(.x, labs(name), fit = .y$fit))
)
```

Step 3.4: view one plotted incidence model as an example of output

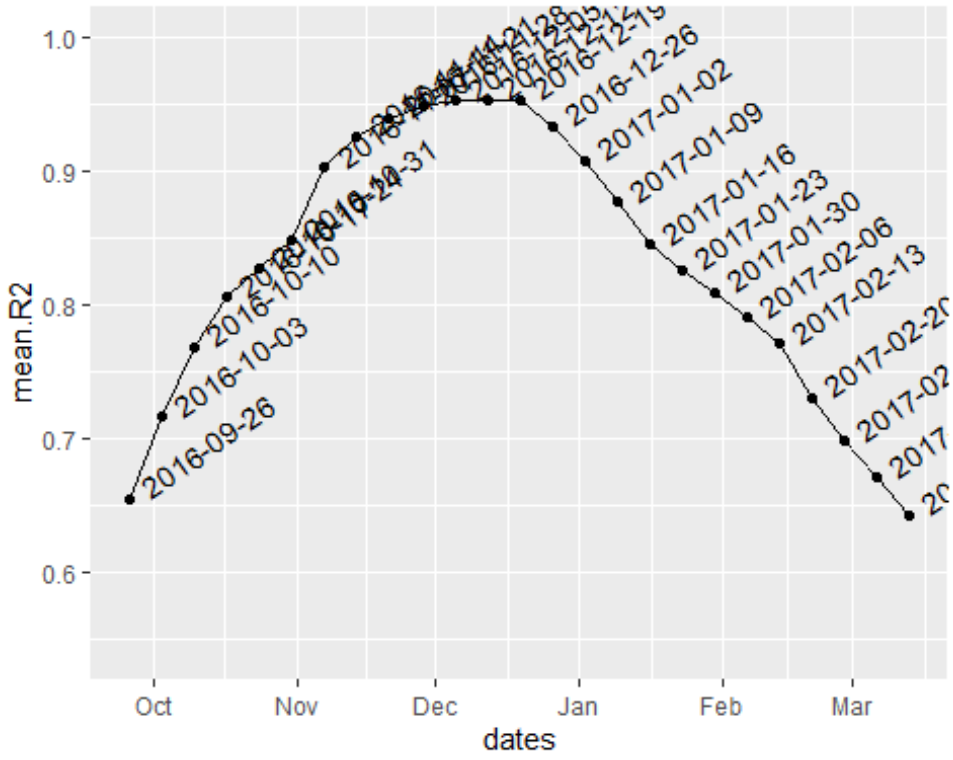
```
ARLI_model_country$plot[77]; ARLI_model_country$model[77]

## [[1]]
```




```
## [[1]]
## [[1]]$df
##         dates   mean.R2
## 1  2016-09-26 0.6550860
## 2  2016-10-03 0.7159727
## 3  2016-10-10 0.7681471
## 4  2016-10-17 0.8057510
## 5  2016-10-24 0.8270014
## 6  2016-10-31 0.8481171
## 7  2016-11-07 0.9026291
## 8  2016-11-14 0.9261439
## 9  2016-11-21 0.9397315
## 10 2016-11-28 0.9485367
## 11 2016-12-05 0.9524318
## 12 2016-12-12 0.9533964
## 13 2016-12-19 0.9532181
## 14 2016-12-26 0.9331955
## 15 2017-01-02 0.9075634
## 16 2017-01-09 0.8765359
## 17 2017-01-16 0.8446025
## 18 2017-01-23 0.8257338
## 19 2017-01-30 0.8089818
## 20 2017-02-06 0.7905181
## 21 2017-02-13 0.7706254
## 22 2017-02-20 0.7303961
## 23 2017-02-27 0.6982189
## 24 2017-03-06 0.6706416
## 25 2017-03-13 0.6424947
##
## [[1]]$split
```

```
## [1] "2016-12-12"
##
## [[1]]$fit
## <list of incidence_fit objects>
##
## attr(x, 'locations'): list of vectors with the locations of each inci
dence_fit object
##
## 'before'
## 'after'
##
## $model: regression of log-incidence over time
##
## $info: list containing the following items:
##   $r (daily growth rate):
##       before        after
##  0.016947835 -0.006405799
##
##   $r.conf (confidence interval):
##                2.5 %       97.5 %
## before  0.015168822  0.018726847
## after  -0.006945323 -0.005866274
##
##   $doubling (doubling time in days):
##   before
## 40.89886
##
##   $doubling.conf (confidence interval):
##           2.5 %   97.5 %
## before 37.01356 45.69552
##
##   $halving (halving time in days):
##    after
## 108.2062
##
##   $halving.conf (confidence interval):
##          2.5 %  97.5 %
## after 99.80056 118.158
##
##   $pred: data.frame of incidence predictions (53 rows, 6 columns)
##
## [[1]]$plot
```



Step 3.5: save model_output as .rds file in GitHubDesktop

```
setwd("C:/Users/clazi/OneDrive - UMCG/VALUE-Dx - Teamkanaal/Tasks/task 5
.6/Incidence_rds/Country-specific")
walk2(ARLI_model_country$model, ARLI_model_country$name, function(x, nam
e){
  write_rds(x, file = str_c(name, '.rds'))
})
```

END OF STAGE 3

STAGE 4: Model ARI incidence per country

Step 4.1: load country-specific incidence output of stage 1 from GitHubDesktop if stage 1 has not been executed in your current session

```
ECDC_inc_ARI_country <- read_vc(file = "data_input/incidence_modelling/ECDC_inc_ARI_ILI_country.tsv", root = repo)
```

Step 4.2: create a pivot table and nest by country, season, and age category

```
cy_inc_ARI <- ECDC_inc_ARI_country %>%
  select(ReportingCountry:ARI_4) %>%
  pivot_longer(cols = c("ARI_1", "ARI_2","ARI_3","ARI_4"),
               names_to = "AgeCat",
               values_to = "IncidenceRate")
```

Step 4.3: exclude rows containing NA values. These rows pertain to the countries and weeks with missing data on ARI cases. Nest data by country, season, and age category for countries with specific seasons that have complete data

```
nested_cy_inc_ARI <- cy_inc_ARI %>%
  na.omit(IncidenceRate) %>%
  group_by(ReportingCountry, Season, AgeCat) %>%
  filter((ReportingCountry %in% c("BE", "BG", "DE", "SI", "SK") & !Season %in% c('2009-2010', '2019-2020', '2020-2021', '2021-2022', '2023-2024')) |
           (ReportingCountry == "CZ" & Season %in% c('2015-2016', '2016-2017', '2017-2018', '2018-2019', '2022-2023')) |
           (ReportingCountry == "NL" & Season %in% c('2016-2017', '2017-2018', '2018-2019')) |
           #(ReportingCountry == "ES" & Season == '2022-2023') |
           (ReportingCountry == "RO" & Season %in% c('2010-2011', '2013-2014', '2018-2019'))
           ) %>%
  nest()
```

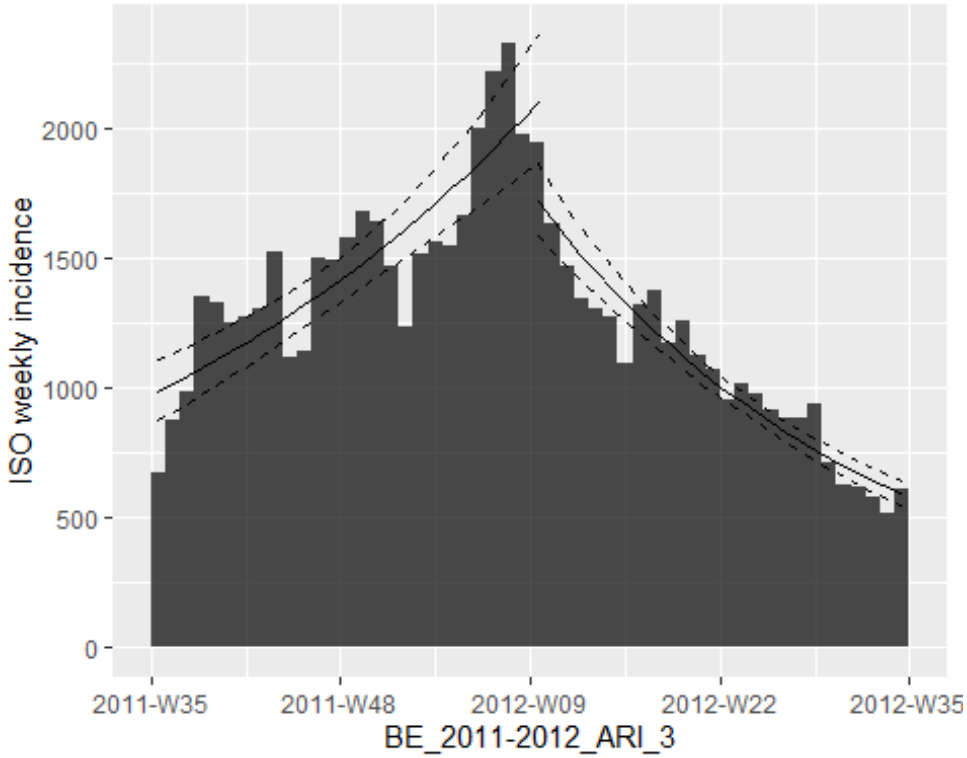
Step 4.4: calculate ARI incidence model by country, season, and age category

```
ARI_model_country <- nested_cy_inc_ARI %>%
  mutate(object = map(data, ~as.incidence(.x$IncidenceRate, dates = .x$Date, interval = 7)),
         name = str_c(ReportingCountry, '_', Season, '_', AgeCat),
         model = map(object, ~fit_optim_split(.x, window = .x$timespan/2)),
         plot = map2(object, model, ~plot(.x, labs(name), fit = .y$fit))
)
```

Step 4.5: view first plotted incidence model as an example of output

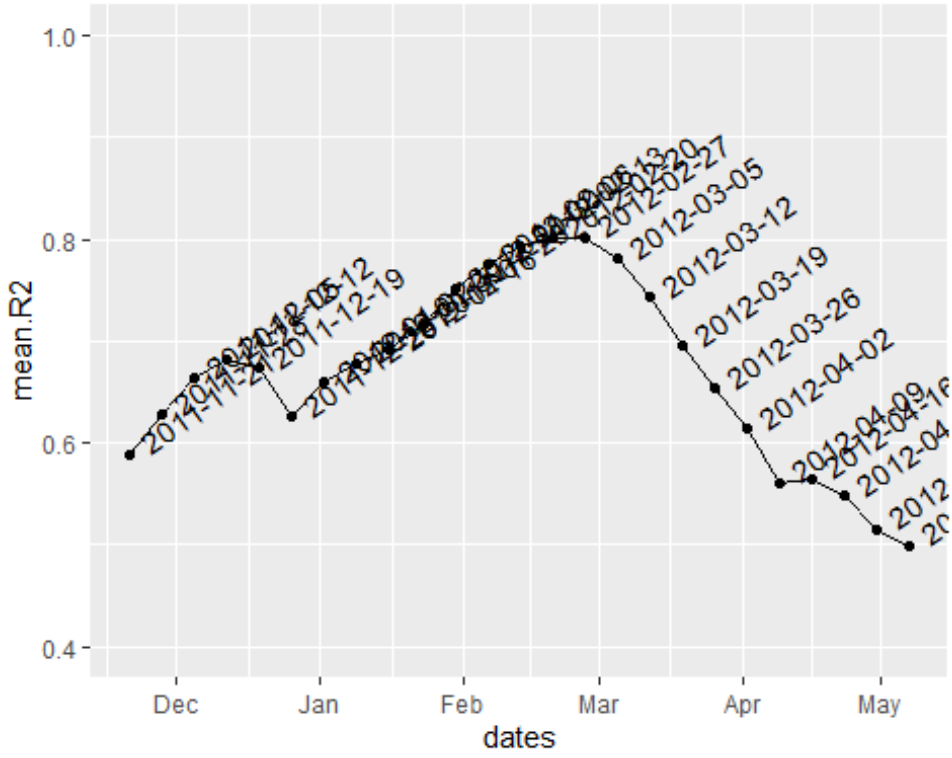
```
ARI_model_country$plot[7]; ARI_model_country$model[7]

## [[1]]
```




```
## [[1]]
## [[1]]$df
##         dates   mean.R2
## 1  2011-11-21 0.5887219
## 2  2011-11-28 0.6274573
## 3  2011-12-05 0.6636478
## 4  2011-12-12 0.6824688
## 5  2011-12-19 0.6736540
## 6  2011-12-26 0.6256558
## 7  2012-01-02 0.6588654
## 8  2012-01-09 0.6783932
## 9  2012-01-16 0.6911795
## 10 2012-01-23 0.7160025
## 11 2012-01-30 0.7503178
## 12 2012-02-06 0.7742560
## 13 2012-02-13 0.7924632
## 14 2012-02-20 0.8003074
## 15 2012-02-27 0.8018231
## 16 2012-03-05 0.7809087
## 17 2012-03-12 0.7428385
## 18 2012-03-19 0.6952208
## 19 2012-03-26 0.6531629
## 20 2012-04-02 0.6139687
## 21 2012-04-09 0.5610762
## 22 2012-04-16 0.5644696
## 23 2012-04-23 0.5484750
## 24 2012-04-30 0.5148274
## 25 2012-05-07 0.4996756
##
## [[1]]$split
```

```
## [1] "2012-02-27"
##
## [[1]]$fit
## <list of incidence_fit objects>
##
## attr(x, 'locations'): list of vectors with the locations of each inci
dence_fit object
##
## 'before'
## 'after'
##
## $model: regression of log-incidence over time
##
## $info: list containing the following items:
##   $r (daily growth rate):
##       before        after
##  0.004163462 -0.006124198
##
##   $r.conf (confidence interval):
##                2.5 %       97.5 %
## before  0.003059690  0.005267234
## after  -0.006925962 -0.005322434
##
##   $doubling (doubling time in days):
##   before
## 166.4834
##
##   $doubling.conf (confidence interval):
##           2.5 %   97.5 %
## before 131.5961 226.5416
##
##   $halving (halving time in days):
##    after
## 113.1817
##
##   $halving.conf (confidence interval):
##          2.5 %   97.5 %
## after 100.0796 130.2312
##
##   $pred: data.frame of incidence predictions (53 rows, 6 columns)
##
## [[1]]$plot
```



END OF STAGE 4

STAGE 5: Model ILI incidence per country

Step 5.1: load country incidence output of stage 1 from GitHubDesktop if stage 1 has not been executed in your current session

```
ECDC_inc_ILI_country <- read_vc(file = "data_input/incidence_modelling/ECDC_inc_ARI_ILI_country.tsv", root = repo)
```

Step 5.2: create a pivot table and nest by country, season, and age category

```
cy_inc_ILI <- ECDC_inc_ILI_country %>%
  select(ReportingCountry:Date, ILI_1:ILI_4) %>%
  pivot_longer(cols = c("ILI_1", "ILI_2","ILI_3","ILI_4"),
               names_to = "AgeCat",
               values_to = "IncidenceRate")
```

Step 5.3: exclude rows containing NA values. These rows pertain to the countries and weeks with missing data on ILI cases. Nest data by country, season, and age category for a specific country of interest

```
nested_cy_inc_ILI <- cy_inc_ILI %>%
  na.omit(IncidenceRate) %>%
  group_by(ReportingCountry, Season, AgeCat) %>%
  filter((ReportingCountry %in% c("BE", "CZ", "IE", "NL", "NO", "PL") & Season %in% c('2015-2016', '2016-2017', '2017-2018', '2018-2019', '2022-2023')) |
           (ReportingCountry == "EE" & Season %in% c('2015-2016', '2016-2017', '2018-2019', '2022-2023')) |
           (ReportingCountry == "RO" & Season %in% c('2017-2018', '2018-2019', '2022-2023')) |
           (ReportingCountry == "SI" & Season %in% c('2016-2017', '2018-2019', '2022-2023')) |
           (ReportingCountry == "SK" & Season %in% c('2015-2016', '2017-2018', '2018-2019', '2022-2023'))) %>%
  nest()
```

Step 5.3.2: zoom in on influenza season by selecting week 40 to week 20

```
nested_cy_inc_ILI <- nested_cy_inc_ILI %>% mutate(data = map(data, ~ head(., 33)))
```

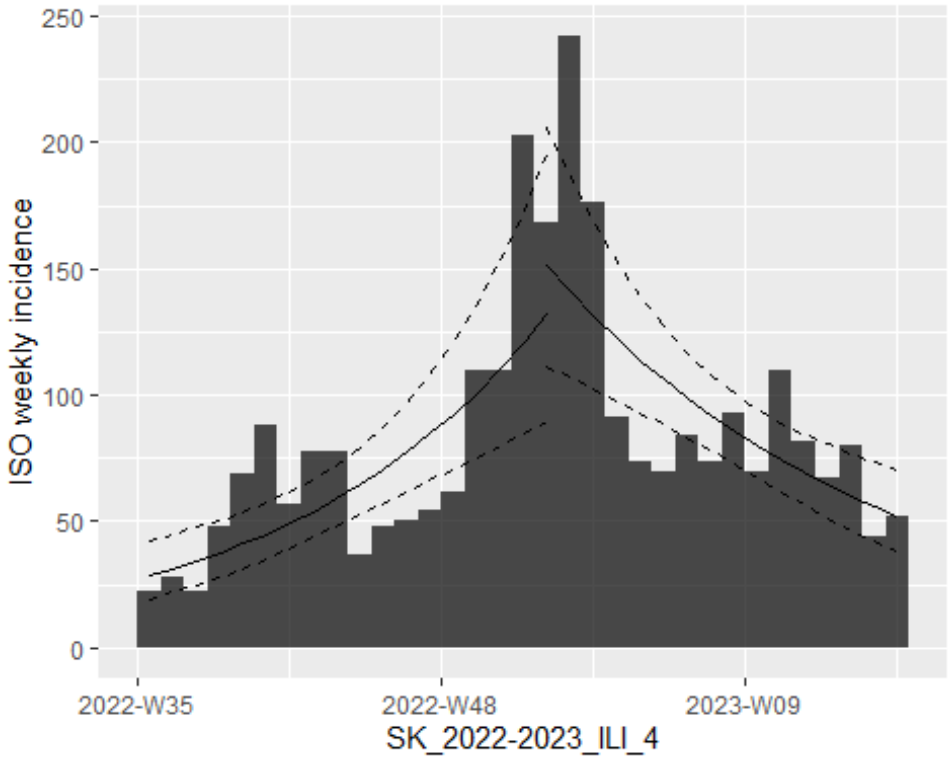
Step 5.4: calculate ILI incidence model by country, season and age category

```
ILI_model_country <- nested_cy_inc_ILI %>%
  mutate(object = map(data, ~as.incidence(.x$IncidenceRate, dates = .x$Date)),
         name = str_c(ReportingCountry, '_', Season, '_', AgeCat),
         model = map(object, fit_optim_split),
         plot = map2(object, model, ~plot(.x, labs(name), fit = .y$fit))
)
```

Step 5.5: view one plotted incidence model as an example of output

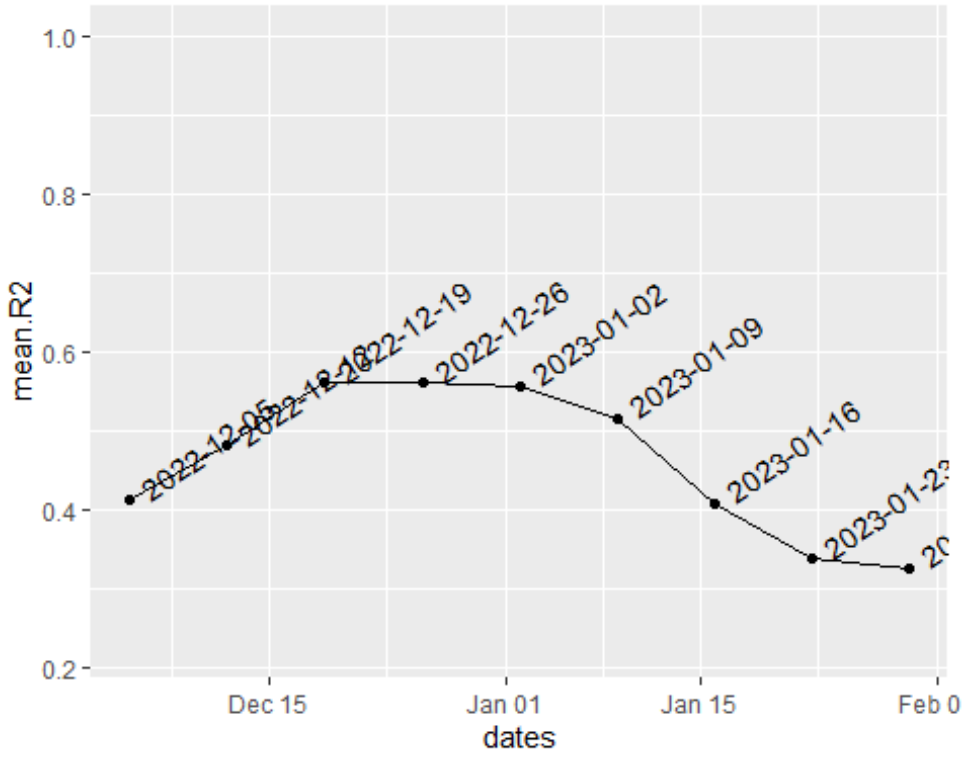
```
ILI_model_country$plot[176]; ILI_model_country$model[176]
```

```
## [[1]]
```




```
## [[1]]
## [[1]]$df
##        dates   mean.R2
## 1 2022-12-05 0.4123543
## 2 2022-12-12 0.4808756
## 3 2022-12-19 0.5607192
## 4 2022-12-26 0.5610707
## 5 2023-01-02 0.5569520
## 6 2023-01-09 0.5161664
## 7 2023-01-16 0.4078284
## 8 2023-01-23 0.3376766
## 9 2023-01-30 0.3256446
##
## [[1]]$split
## [1] "2022-12-26"
##
## [[1]]$fit
## <list of incidence_fit objects>
##
## attr(x, 'locations'): list of vectors with the locations of each inci
dence_fit object
##
## 'before'
## 'after'
##
## $model: regression of log-incidence over time
##
## $info: list containing the following items:
```

```
##   $r (daily growth rate):
##      before       after
##  0.01283809 -0.01019348
##
##   $r.conf (confidence interval):
##                2.5 %       97.5 %
## before  0.007256843  0.018419341
## after  -0.015170354 -0.005216616
##
##   $doubling (doubling time in days):
##   before
## 53.99145
##
##   $doubling.conf (confidence interval):
##           2.5 %   97.5 %
## before 37.63149 95.51635
##
##   $halving (halving time in days):
##    after
## 67.99904
##
##   $halving.conf (confidence interval):
##         2.5 %  97.5 %
## after 45.6909 132.873
##
##   $pred: data.frame of incidence predictions (34 rows, 6 columns)
##
## [[1]]$plot
```



END OF STAGE 5

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