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Health econometric studies into the determinants of antibiotic consumption and the cost-effectiveness of adult influenza and pneumococcal vaccination strategies

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2. **Blommaert, A.**, Bilcke, J., Vandendijck, Y., Hanquet, G., Hens, N., & Beutels, P. (2014). Cost-effectiveness of seasonal influenza vaccination in pregnant women, health care workers and persons with underlying illnesses in Belgium. Vaccine, 32(46), 6075-6083. (CHAPTER 8)

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4. Coenen, S., Gielen, B., **Blommaert, A.**, Beutels, P., Hens, N., & Goossens, H. (2014). Appropriate international measures for outpatient antibiotic prescribing and consumption: recommendations from a national data comparison of different measures. Journal of Antimicrobial Chemotherapy, 69(2), 529-534. (NOT COVERED)

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1. Beutels P., Vandendijck Y., Willem L., Goeyvaerts N., **Blommaert, A.**, Van Kerckhove K., Bilcke J., Hanquet G., Neels P, Thiry N., Liesenborgs J., Hens N. Vaccinatie tegen seizoensinfluenza: prioritair de kinderen of andere doelgroepen? Deel II: Kosten-effectiviteitsanalyse Health Technology Assessment (HTA). Brussel: Federaal Kenniscentrum voor de Gezondheidszorg (KCE). 2013. KCE Reports 204As. D/2013/10.273/40.

2. Beutels P., **Blommaert, A.**, Hanquet G., Bilcke J., Thiry N., Sabbe M., Verhaegen J., De Smet F., Callens M., & Van Damme P. Kosteneffectiviteit van 10- en 13-valent geconjugeerde pneumokokkenvaccins bij kinderen. Health Technology Assessment (HTA). Brussel: Federaal Kenniscentrum voor de Gezondheidszorg (KCE). 2011. Reports 155A. D/2011/10.273/19

List of abbreviations

AMINOPEN	E. coli resis- tance against aminopenicillins
ATC	Anatomical Therapeutic Chemical
BAPCOP	Belgian Antibiotic Policy Coordination
CEPH	E.Coli resistance against 3rd generation cephalosporins
DDD	Daily defined dosage
DID	number of DDDs per 1,000 inhabitants per day (DID)
E. coli	Escherichia coli
EARSS	European Antimicrobial Resistance Surveillance System
EN	Elastic Net penalty function
ESAC	European Surveillance of Antimicrobial Consumption
FAOSTAT	Food and Agriculture Organisation statistical database
FLUORO	E. Coli resistance against fluoroquinolones
GEE	Generalized Estimating Equations
GP	General Practisioner
ICER	Incremental Cost-Effectiveness Ratio
ILI	Influenza Like Illness
IPD	Invasive Pneumococcal Disease
LASSO	Least Adaptive Shrinkage and Selection Operator
LNR	Lead National Representatives
MCP	Minimax Concave Penalty
MI-GEE	Multiple Imputation Generalized Estimating Equations
OECD	Organisation for Economic Co-operation and Development
OSCAR	Octagonal Shrinkage and Clustering Algorithm
PCV13	13 valent conjugate pneumococcal vaccine

PGEE	Penalized Generalized Estimating Equations
PGLS	Penalized Generalized Least Squares
PLMM	Penalized Linear Mixed Model
PNSP	S. pneumoniae resistance against resistance against penicillins
PNSP	joint resistance of S. pneumoniae against penicillins and macrolides
PPV23	23 valent polysaccharide pneumococcal vaccine
QALY	Quality-Adjusted Life Years
RE-EM trees	Random Effects Expectation Maximization regression trees
S. pneumoniae	Streptococcus pneumoniae
SCAD	Smoothly Clipped Absolute Deviation penalty
SCAD_$L2$	Smoothly Clipped Absolute Deviation penalty combined with ridge penalty
WHO	World Health Organization

Part I

Introduction

Pneumococcal treatment and prevention

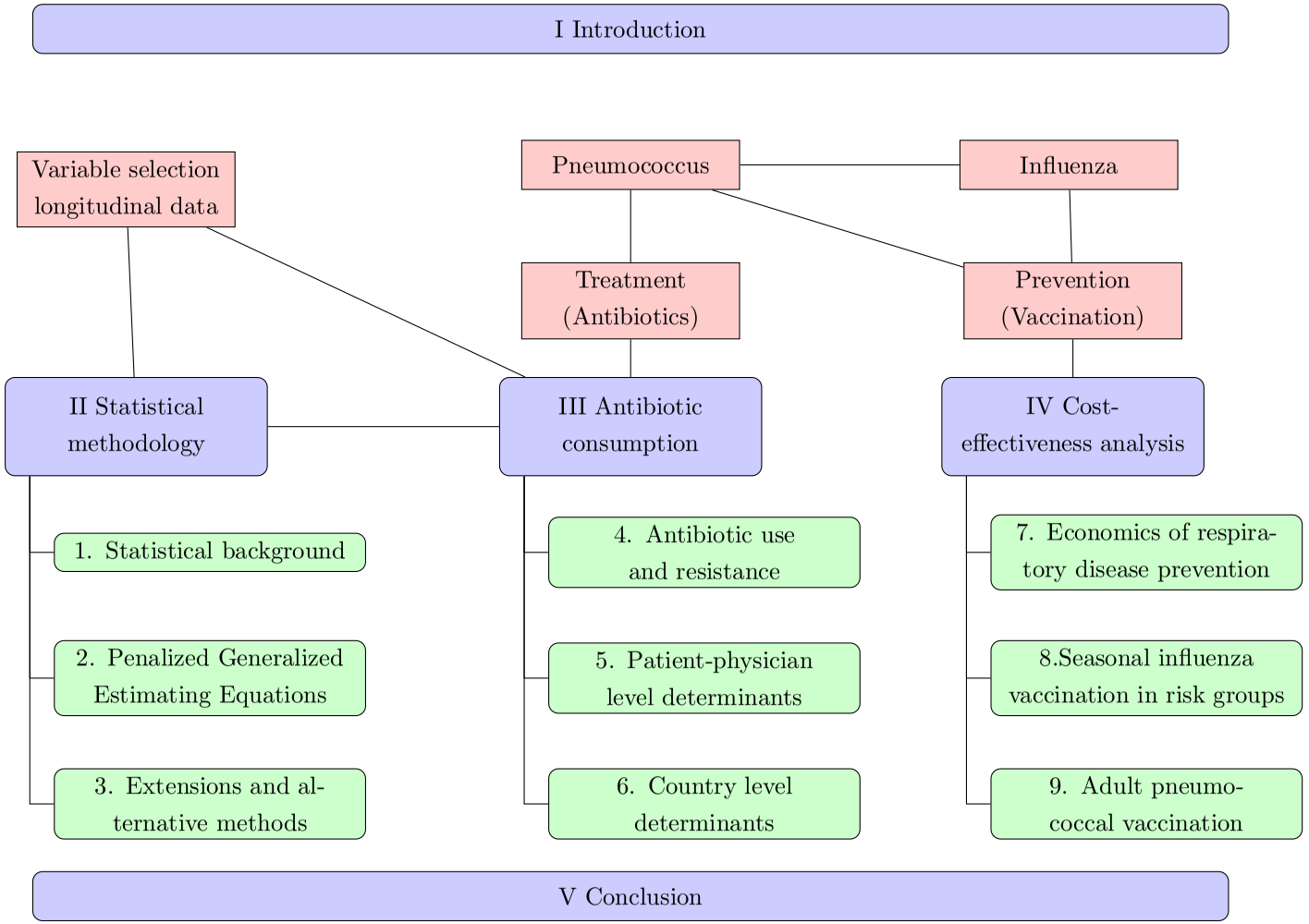
Streptococcus pneumoniae or *pneumococcus* is a bacterial pathogen that can cause invasive (meningitis, bacteremia) and non-invasive (otitis media) disease affecting children and adults worldwide. Over 90 different serotypes of the pneumococcus are distinguished on the basis of the bacterium's outer surface on which the human immune system reacts distinctively. These serotypes compete with each other and other pathogens to colonise the nasospherix of human hosts. Colonisation is usually asymptomatic but important, because it is the engine of transmission of the pneumococcus which occurs by exchange of droplets in the air. A small percentage of these colonisations result in disease. *Influenza disease* caused by the influenza virus is a key risk factor for the transition from asymptomatic carriage to pneumococcal disease. Pneumococcal disease causes a significant morbidity and mortality burden in the elderly population. Vaccination and antibiotic treatment are used to prevent or alleviate the disease burden. Since pneumococcal vaccines contain only a limited proportion of circulating serotypes, vaccine protection is strongly dependent on the serotype distribution. Both antibiotics and vaccination affect the competition between serotypes to colonise the nasospherix and hence transmission dynamics. This thesis focuses on the treatment and prevention of pneumococcal disease from a statistical and economics point of view by investigating the broader context of determinants of antibiotic consumption, statistical methodology for variable selection in longitudinal data and the cost-effectiveness of influenza and pneumococcal vaccination programs in adult risk groups. The next section overviews the thesis build up in more detail.

Overview thesis

Figure 1 summarises the thesis' buildup into five large parts investigating the treatment (antibiotics) and prevention (vaccination) of pneumococcal disease by focusing on finding determinants of antibiotic consumption and resistance, developing statistical methodology for finding these determinants in longitudinal data and assessing the cost-effectiveness of both influenza and pneumococcal vaccination. This first part briefly introduces the following parts. A more in depth introduction is provided in each part separately.

Antibiotics are the only real treatment option for bacterial infections such as pneumococcal disease. Because of historic antibiotic use, bacteria have evolved to be increasingly resistant to more and more antibiotic classes. Even though large differences between antibiotic consumption and resistance figures across countries have

Figure 1: Overview subjects (pink nodes), parts (blue nodes) and chapters (green nodes) or this Thesis



been observed, the determining factors of these differences are largely unknown as are the reasons for the choice of the specific antibiotic class used/prescribed. In Part III we set out to identify determinants of total antibiotic use, quality of prescribing and resistance focusing on all antibiotics in outpatient use, not limited to the treatment of pneumococcal disease. After giving background information on antibiotic consumption and resistance in Chapter 4, we document prescriber and patient characteristics associated with the choice between amoxicillin and broader spectrum alternatives (co-amoxiclav or moxifloxacin) in recent years in Belgium (Chapter 5). In Chapter 6 we zoom out to the country level, the level for which health care policy differs due to political choices and socioeconomic differences. We search for determining factors of total antibiotic use, relative use of antibiotic subgroups and resistance out of a large set of factors characterising the agriculture, culture, demography, disease burden, education, health care organisation and socioeconomics of a country.

In our statistical analysis of antibiotic consumption data, such as mining for determinants of differences of antibiotic consumption between countries, we encountered the statistical problem of variable selection for longitudinal data under multicollinearity and time dependent covariates: *longitudinal data* means the response variable is measured several times for each subject, implying within subject observations to be possibly correlated; *multicollinearity* means that several of the exploratory variables contain overlapping information; *time dependent covariates* mean that covariates such as gross domestic product vary from year to year. In Part II we review existing methodology for dealing with these issues (Chapter 1) and propose new methodology (Chapter 2): Focusing on retrieving the most important cross-sectional associations we propose Penalized Generalized Estimating Equations (PGEE) using penalty functions combining sparsity and grouping effect properties in order to eliminate irrelevant and select highly correlated determinants together. In Chapter 3 alternative methods and possible extensions to PGEE are discussed. The statistical part is included first, even though chronologically it came second to the antibiotic use part, because it provides some background on the statistical methodology used in the other thesis parts.

In Part IV we shift focus from the empirical study of the treatment of infectious diseases with antibiotics using statistical models to the assessment of the cost-effectiveness of the prevention of influenza and pneumococcal disease by vaccination, using simulation models. In Chapter 7 we provide biomedical background information on influenza and pneumococcal disease and introduce the foundations of cost-effectiveness analysis.

Current influenza vaccination policy in Belgium prioritises risk groups with in-

creased vulnerability for influenza complications such as pregnant women, persons with underlying illnesses as well as persons who come into contact with them, such as health care workers. In Chapter 8 we evaluate this policy from a health care payer's perspective by cost-effectiveness analysis in the three specific target groups above, while accounting for effects beyond the target group.

For pneumococcal disease, a recent trial demonstrated the 13 valent conjugate pneumococcal vaccine (PCV13) to be effective against invasive and non-invasive pneumococcal disease in the adult population. PCV13 might therefore be considered as an alternative to the 23 valent polysaccharide vaccine (PPV23), which does not provide protection against non invasive pneumococcal disease. In Chapter 9 we explore influential factors for the cost-effectiveness of vaccinating adults over 50, with either PCV13 or PPV23 alone, or with a combined strategy using both PCV13 and PPV23.

Part V gives an overall conclusion, points out main limitations of this thesis together with recommendations for future research.

Part II

Statistical methodology

Chapter 1

Statistical background

In applied data analysis in this thesis we aim to find the determining factors of antibiotic consumption and resistance. Mining for determinants of differences of antibiotic consumption between countries and over time is one example. Dependency between observations within a country and selection of the most important covariates are two statistical issues paramount in such analyses. The current Part II lays out the existing techniques we use in the applications and new methodological developments to better tackle similar data analyses in future work. In this first chapter we start with explaining basic statistical concepts for two reasons. First for setting the scene of penalization methods which we seek to incorporate in longitudinal data analysis via Generalized Estimating Equations (GEE). Second to explain the concept of GEE to perform regression analysis for longitudinal data, the technique used in applications in Part III.

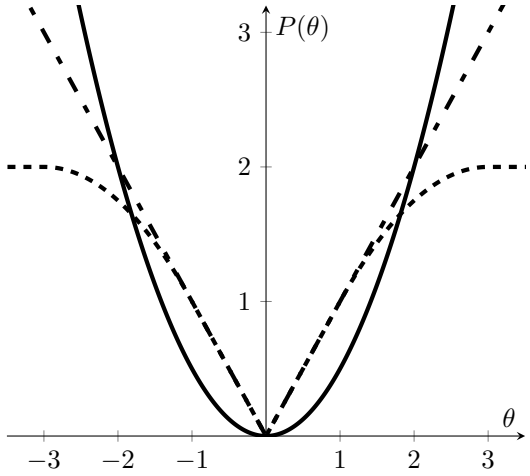
1.1 Model selection by penalization

A main aim of statistical analysis is to explain variability in an outcome variable by means of covariates. Regression is a way to investigate the influence of such covariates by constructing a model connecting the mean of the outcome variable with the covariates and fitting it to data by optimizing some goodness of fit measure. Taking the likelihood function as goodness of fit measure is a popular approach, of which ordinary least squares regression is a special case. When confronted with a large number of potential covariates, selecting which variables to and not to include might strongly improve a model's interpretability and accuracy. Various methods exist such as significance testing, using information criteria and penalization methods. Penalization methods are particularly interesting because of their simplicity in use for high dimensional problems and their increased accuracy and stability of selection compared with significance testing or using information criteria. Equation 1.1 displays how penalization can be included in the likelihood setting.

$$L^P(\boldsymbol{\beta}) = L(\boldsymbol{\beta}) - P(\boldsymbol{\beta}), \tag{1.1}$$

with $L(\boldsymbol{\beta}) = \sum \log(p(x_i|\boldsymbol{\beta}))$ the log-likelihood of the parameter vector, e.g. a vector of regression coefficients $\boldsymbol{\beta}$. $p(x_i|\boldsymbol{\beta})$ is the probability density function of observation x_i. The second part, $P(\boldsymbol{\beta})$, is the penalty function which is a function of $\boldsymbol{\beta}$ only, not of the data. Model estimation can then be performed by maximizing this entire penalized log-likelihood, $L^P(\boldsymbol{\beta})$, in terms of $\boldsymbol{\beta}$ yielding an estimate $\hat{\boldsymbol{\beta}}$. Maximizing the first term is searching for the parameter vector making the observed data most

Figure 1.1: Sketch of different penalty functions: The Ridge (——), Lasso (- - -) and SCAD (- - -)



likely to having been observed (therefore maximum likelihood). The second term pulls this optimum away towards a region which has additional desirable properties such as smaller, more stable or fewer regression coefficients.

The bias variance trade-off explains why a penalized estimator might estimate the true parameter vector $\boldsymbol{\beta}_T$ more precisely. The mean squared error of prediction (MSE) is a measure for how close the estimate is in expectation to its true value:

$$\mathrm{MSE}(\hat{\boldsymbol{\beta}}) = \mathrm{E}(\boldsymbol{\beta}_T - \hat{\boldsymbol{\beta}})^2 = \mathrm{Bias}^2(\hat{\boldsymbol{\beta}}) + \mathrm{Var}(\hat{\boldsymbol{\beta}}),$$

with $\mathrm{Bias}(\hat{\boldsymbol{\beta}}) = \mathrm{E}(\hat{\boldsymbol{\beta}}) - \boldsymbol{\beta}_T$ the bias, measuring the expected deviation of the estimate from the true value; and $\mathrm{Var}(\hat{\boldsymbol{\beta}})$ the variance of the estimate, measuring how much an estimate varies from its expected value. Maximum likelihood estimation is unbiased meaning $\mathrm{Bias}^2(\hat{\boldsymbol{\beta}}) = 0$. Adding a penalty to the objective function makes the resulting estimator no longer unbiased but hopes to eventually have a smaller MSE-value by reducing the variance of the estimator more than the increase in the bias squared.

Figure 1.1 displays some possible options for the choice of the penalty function for a single parameter θ. The Least Adaptive Selection and Shrinkage Operator (LASSO, P_{L1}, [5]) uses the L_1 norm of the parameter vector, penalized smaller coefficients therefore less and can put parameters exactly equal to zero. The ridge penalty uses the L_2 norm and is unable to set parameters to zero but is useful under collinearity of the covariates. The Smoothly Clipped Absolute Deviation penalty (SCAD, P_{SCAD},

[1]) is a modification of the LASSO where smaller coefficients are penalized the same as the LASSO but for larger ones the penalty does not increase together with the coefficient's size, resulting in less bias in the final estimate.

$$P_{L_1}(\boldsymbol{\beta}) = \sum_{j=1}^{p} |\beta_j| \,,$$

$$P_{L_2}(\boldsymbol{\beta}) = \sum_{j=1}^{p} |\beta_j|^2 \,,$$

$$P_{SCAD}(\boldsymbol{\beta}) = \sum_{j=1}^{p} f_{SCAD}(|\beta_j|),$$

$$f_{SCAD}(\theta) = \int_0^{\theta} \left\{ I\left(\theta \leq \lambda_1\right) + \frac{(a\lambda_1 - \theta)_+}{(a-1)\lambda_1} I(\theta > \lambda_1) \right\} d\theta.$$

These penalty functions can be combined such as in the the Elastic net which sums the LASSO and Ridge penalty to inherit properties of both [7].

1.2 Longitudinal data and Generalized Estimating Equations

When subjects are measured over time, observations are not independent but clustered within subjects and standard regression techniques such as generalized linear models cannot be applied because their underlying assumptions are violated; regression techniques for these longitudinal data should take into account the hierarchy of the clustering of measurements within subjects. A possible way to go about this is by formulating a full likelihood, parameterizing dependency between covariates by taking up subject specific effects. In the popular mixed effects model, these subject specific effects, called random effects, are specified as random draws from a probability distribution (see [3]). Generalized Estimating Equations (GEE, [2, 6]) is an alternative and ingenious way to account for clustering without specifying a full likelihood, by tweaking the score equations of a Generalized Linear Model (GLM, [4]) so these can be applied to correlated and consequently longitudinal data.

Consider a random sample of n subjects. Y_{it} is the measured response for subject i at time t with $t = 1, \ldots, T_i$. $\boldsymbol{X}_{it} = (X_{1it}, \ldots, X_{pit})$ is a vector of p covariates measured at the same time as the response. Observations within a subject are correlated, observations of different subjects are assumed independent. The relation between the

mean response and the covariates, $\mathrm{E}(Y_{it}|\boldsymbol{X}_{it}) = g^{-1}(\boldsymbol{\beta}^T\boldsymbol{X}_{it})$, parametrized by the vector of regression coefficients $\boldsymbol{\beta}$ can be estimated by solving the equation (GEE):

$$\sum_{i=1}^{n} \boldsymbol{D}_i^T V_i^{-1}(\boldsymbol{Y}_i - \boldsymbol{\mu}_i) = \mathbf{0}. \tag{1.2}$$

With $\boldsymbol{\mu}_i = g^{-1}(\boldsymbol{\beta}^T\boldsymbol{X}_{it})$; $\boldsymbol{D}_i = \boldsymbol{D}_i(\boldsymbol{\beta}) = \partial\boldsymbol{\mu}_i(\boldsymbol{\beta})/\partial\boldsymbol{\beta}$; $V_i = U_i^{1/2}W(\boldsymbol{\alpha})U_i^{1/2}$ the working covariance matrix; $W(\boldsymbol{\alpha})$ is the working correlation matrix, parameterised by parameter vector $\boldsymbol{\alpha}$, U_i is a diagonal matrix with diagonal elements $\mathrm{Var}(Y_{it}|\boldsymbol{X}_{it})$.

Without the working correlation matrix, these would just be the score equations of a GLM. The working correlation matrix specifies the association between observations within the same subject. Liang and Zeger [2], Zeger and Liang [6] showed that even if this working correlation matrix is an incorrect correlation matrix then asymptotically:

$$\sqrt{N}(\hat{\boldsymbol{\beta}} - \boldsymbol{\beta}) \sim \mathrm{N}(\mathbf{0}, I_0^{-1}I_1I_0), \tag{1.3}$$

with N the number of observations,

$$I_0 = \sum_{i=1}^{n} \boldsymbol{D}_i^T V_i^{-1}\boldsymbol{D}_i$$

and

$$I_1 = \sum_{i=1}^{n} \boldsymbol{D}_i^T V_i^{-1} Var(\boldsymbol{Y}_i) V_i^{-1}\boldsymbol{D}_i.$$

It should be noted that GEE is not a likelihood method because only the first moment of the regression relation needs to be correctly specified, the variance is treated as a nuisance parameter. Modifications of the GEE method exist, specifying higher order moments or parameterising dependencies differently (see [3] for details).

Given the asymptotic normality result (Equation 1.3), inference can be achieved trough Wald-type tests and confidence intervals. These test are also standardly applied in a stepwise way to achieve model selection. In contrast to mixed models which involves integrating out random effects, GEE (1.2) can be solved by only a small modification to the software for GLMs.

1.3 Penalized Generalized Estimating Equations

GEE is used throughout the applications in this thesis, as a computational efficient way to focus on the problem of variable selection requiring few assumptions. In applications like mining for the determinants of antibiotic consumption in Chapter 6, we

are confronted with a large number of potential predictors of which we want to identify the most important ones. In the following chapters of Part II we look into how penalization methods can be used in combination with GEE. More precisely, in Chapter 2 Penalized GEE with Elastic Net or L2-Smoothly Clipped Absolute Deviation penalization is proposed to simultaneously select the most important variables and estimate their effects for longitudinal Gaussian data when multicollinearity is present. The method is able to consistently select and estimate the main effects even when strong correlations are present. In addition, the potential pitfall of time-dependent covariates is clarified. Both asymptotic theory and simulation results reveal the effectiveness of penalization as a data mining tool for longitudinal data, especially when a large number of variables is present. The method is illustrated by mining for the main determinants of life expectancy in Europe.

In the final chapter of this thesis part we shortly review possible extensions of the proposed PGEE estimator and alternative data mining tools in the longitudinal context.

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Chapter 2

Penalized Generalized Estimating Equations

2.1 Introduction

Longitudinal data appear frequently in biomedical applications. Researchers are often confronted with the problem of determining the impact of different covariates on a response. Correct inference can be obtained by building an appropriate longitudinal model. Molenberghs and Verbeke [19] distinguish three types of model families: marginal models, conditional models and subject-specific models. After the choice of the model family, an optimal set of predictors has to be selected. This can be a tedious task due to a large number of potential covariates. Including irrelevant covariates leads to inefficient inference. Therefore covariate selection is an important part of longitudinal model building, which is the main focus of this chapter.

Variable selection in both the mixed model as a subject-specific model and GEE as a marginal model will be briefly reviewed before turning to penalization methods within the GEE framework.

Within the mixed model framework, Wu [27] advised using significance testing or information criteria such as the Akaike information criterion (AIC) or the Bayesian information criterion for the selection of fixed effects. Information criteria have been further adapted to select both random and fixed effects in Jiang and Liu [15] and Vaida and Blanchard [25]. Liu et al. [18] generalized the idea of cross-validation to mixed models. When the number of covariates becomes large, employing a stepwise search can reduce the computational burden for the selection techniques above. Recently, Jiang et al. [14] have suggested fence methods to put up a barrier between correct and incorrect mixed models.

In this chapter we choose GEE [17] as our inference framework instead of Generalized Linear Mixed Models (GLMM). The GEE approach yields population averaged effects by only specifying the first two moments of the outcome distribution. Its robustness against variance structure misspecification makes the GEE method well suited for our purpose of mean structure selection. Additionally, the problem of time-dependent covariates can be more easily clarified in the GEE context. The results provided in this chapter are generalizable to linear mixed models as well, however this is not addressed here.

Despite the focus of GEE on mean structure estimation, appropriate covariate selection techniques are not well developed in this context. The standard practice for GEE model building is stepwise selection based on Wald-type tests (see for instance 5). More recently some general variable selection techniques have been adapted to the GEE framework. Pan [21] generalized the AIC to the GEE context based on the working independence assumption. Cantoni et al. [3] suggested selection based on

adequacy of prediction as measured by an adapted version of Mallow's C_p. In addition to these direct methods, more computationally intensive methods have been explored. Cantoni et al. [4] combined cross-validation with a Markov Chain Monte Carlo based search. Alternatively, Pan [20] proposed minimizing a bootstrap smoothed cross-validation estimate of the expected predictive bias.

However, all of these methods lack the ability to properly deal with a large number of covariates. Because of the discrete nature of these selection methods, the resulting estimator can become unstable [2]. Moreover, complete subset comparison becomes computationally unfeasible when too many covariates are present, encouraging the use of a stepwise search. The gain in computation time by stepwise procedures comes at the price of suboptimal prediction performance and even higher instability.

In this chapter we revisit the use of penalization within the GEE context to both reduce the computational burden and tackle the problem of instability. Indeed, in ordinary regression and classification problems, penalization methods are well suited and often used for the task of variable selection and regularization. The Least Adaptive Shrinkage and Selection Operator (LASSO, 24), for example, is a penalization method which achieves both subset selection and parameter shrinkage. The continuous nature of the shrinkage leads to stable selection. The LASSO transforms the dimensionality of the subset selection problem into the selection of a single continuous tuning parameter. A major disadvantage of the LASSO is the potentially large bias induced by its shrinkage effect. The Smoothly Clipped Absolute Deviation penalty (SCAD, [8]) is an adaptation to the LASSO which avoids unnecessary bias by using a different rate of penalization depending on the size of the coefficients. Smaller coefficients are penalized in the same manner as with the LASSO, while larger coefficients experience approximately no influence of the penalty.

Penalized Generalized Estimating Equations (PGEE) were conceived by Fu [12] as a framework in which these penalty methods can be applied in the longitudinal context. His asymptotic results were concentrated on bridge penalization [9, 11]. Dziak [6] and Dziak and Li [7] extended this approach by using the SCAD penalty function. Even though their simulation studies display good performance of SCAD penalization for binomial data, we argue in Section 2.3 that their asymptotic results are limited to the Gaussian setting. Recently, Wang et al. [26] have properly underpinned the SCAD penalized GEE with asymptotic theory for a response coming from the exponential family. Moreover, their asymptotic results are constructed in a high dimensional-framework, allowing for the number of covariates p to diverge together with the number of clusters n. Assuming only that this divergence is of the same order as the increase in the number of clusters ($p = O(n)$), whereas in other aforementioned

work p is assumed fixed.

In spite of the achievements of these authors, we believe that in mining for important variables in longitudinal data, two issues are commonplace, often overlooked and could be addressed better: multicollinearity and time-dependent covariates.

In order to deal with the first issue, multicollinearity, we suggest combining a sparse penalty function, namely the LASSO or the SCAD with a ridge part. In ordinary regression the elastic net (EN, [30]) has been proposed as the combination of the LASSO and ridge regression. Recently, the SCAD penalty has also been combined with a ridge part by Zeng [28], an approach to which we refer hence as the SCAD$_{L2}$ penalty. The inclusion of a ridge part, adds the grouping effect to the resulting estimator. This means that highly correlated variables tend to be selected or omitted as a group.

The second issue, time-dependent covariates is often overlooked in this type of longitudinal analysis. Time dependence in GEE will cause bias in the regression coefficients, unless either the cross-sectionallity assumption is satisfied or the working independence matrix is used [23, 22, 5].

In this chapter we study EN and SCAD$_{L2}$ penalization within the framework of PGEE with time-dependent covariates. We show how these methods deal with selection under multicollinearity using both asymptotic theory and simulation studies. We limit ourselves to the Gaussian setting with a fixed number of covariates and present avenues for generalization to the broader exponential family.

The remainder of the chapter is organized as follows. In Section 2.2 we discuss the PGEE estimator with EN or SCAD$_{L2}$ penalty functions. As in Dziak [6] we establish theory by turning to the equivalent penalized generalized least squares problem, but in contrast to Dziak [6] argue that this is only possible for the Gaussian case. The SCAD$_{L2}$ penalty function is shown to be convex under a condition on the tuning parameters. The equivalent penalized least square problem together with the convexity of the penalty function allows us to establish the grouping effect. We demonstrate how the local quadratic approximation algorithm (Fan and Li 2001) can be used to fit such a model. We also address the problem of tuning parameter selection. In Section 2.3 we extend the asymptotic results of Dziak [6] to EN and SCAD$_{L2}$ penalty functions. We show selection consistency, estimation consistency and asymptotic normality. The small sample performance is investigated through simulation studies in Section 2.4. Section 2.5 presents a data example and we end this chapter by discussing our findings.

2.2 Methodology

2.2.1 Penalized GEE

2.2.1.1 PGEE estimators

Consider a random sample of n subjects. Y_{it} is the measured response for subject i at time t with $t = 1, \ldots, T_i$. $\boldsymbol{X}_{it} = (X_{1,it}, \ldots, X_{p,it})$ is a vector of p time-dependent covariates measured at the same time as the response. Observations within a subject are correlated, observations of different subjects are assumed independent.

Without loss of generality and to facilitate the use of penalization, we assume the response to be scaled and the covariates to be standardized.

The cross-sectional influence of the covariates $\boldsymbol{X}_{it}$ on the response Y_{it} is our main interest. We assume Y is generated from a distribution in the exponential family with $\mathrm{E}(Y_{it}|\boldsymbol{X}_{it}) = g^{-1}(\boldsymbol{\beta}^T\boldsymbol{X}_{it})$, where g is a known link-function.

The regression coefficients $\boldsymbol{\beta}$ can be estimated by solving the PGEE [12]:

$$\boldsymbol{S^P}(\boldsymbol{\beta}) = \sum_{i=1}^{n} \boldsymbol{D}_i^T V_i^{-1}(\boldsymbol{Y}_i - \boldsymbol{\mu}_i) - N\dot{\boldsymbol{P}}(\boldsymbol{\beta}) = \boldsymbol{0}. \tag{2.1}$$

With $\boldsymbol{\mu}_i = g^{-1}(\boldsymbol{\beta}^T\boldsymbol{X}_{it})$; $\boldsymbol{D}_i = \boldsymbol{D}_i(\boldsymbol{\beta}) = \partial\boldsymbol{\mu}_i(\boldsymbol{\beta})/\partial\boldsymbol{\beta}$; $V_i = U_i^{1/2}W(\boldsymbol{\alpha})U_i^{1/2}$ the working covariance matrix; $W(\boldsymbol{\alpha})$ is the working correlation matrix, parameterized with parameter vector $\boldsymbol{\alpha}$, U_i is a diagonal matrix with diagonal elements $\mathrm{Var}(Y_{it}|\boldsymbol{X}_{it})$; $\dot{\boldsymbol{P}}(\boldsymbol{\beta}) = \partial P(\boldsymbol{\beta})/\partial\boldsymbol{\beta}$ is the vector derivative of the penalty function. Fu [12] proposed using the bridge penalty: $P(\boldsymbol{\beta}) = \lambda\sum|\beta_j|^\gamma$ with $\lambda \geq 1$. The bridge penalty reduces to the LASSO when $\gamma = 1$ and to the ridge penalty when $\gamma = 2$. Both have interesting properties. The first possesses the sparsity property, which implies irrelevant parameters can be set to zero. The second yields good predictive performance under multicollinearity by the grouping effect, meaning coefficients of correlated covariates tend to be equal. When γ is chosen between one and two, the grouping effect holds, the sparsity property in contrast is lost.

We propose PGEE with a penalty function combining both the sparsity property and the grouping effect:

$$P(\boldsymbol{\beta}) = \lambda_1 P_{L1}(\boldsymbol{\beta}) + \lambda_2 P_{L2}(\boldsymbol{\beta}). \tag{2.2}$$

2.2.1.2 Sparsity

P_{L1} is the part of the penalty function that provides sparsity to the resulting estimator. We explore two possibilities. The LASSO, which uses the $L1$-norm,

$$P_{L1}(\boldsymbol{\beta}) = \sum_{j=1}^{p} |\beta_j| ,$$

and the SCAD penalty:

$$P_{L1}(\boldsymbol{\beta}) = \sum_{j=1}^{p} f_{SCAD}(|\beta_j|);$$

$$f_{SCAD}(\theta) = \int_0^{\theta} \left\{ I(\theta \leq \lambda_1) + \frac{(a\lambda_1 - \theta)_+}{(a-1)\lambda_1} I(\theta > \lambda_1) \right\} d\theta,$$

with $a > 2$, $I(\cdot)$ the indicator function: $I(c) = 1$ if c is true and 0 if c is false; $x_+ = xI(x > 0)$. Both provide the the sparsity property to the proposed PGEE estimator, because these penalties are singular at the origin (see discussion on sparsity in Fan and Li, 2001). The SCAD penalty behaves like the LASSO for small coefficients, whereas the estimator remains approximately unbiased for larger coefficients, because the penalty $f_{SCAD}(\theta)$ is increasing with θ and bounded by a constant.

2.2.1.3 Grouping effect

$P_{L2}(\boldsymbol{\beta}) = \sum_{j=1}^{p} \beta_j^2$ is the ridge part of the penalty function. This provides the grouping effect to the resulting estimator, meaning regression coefficients of highly correlated variables tend to be equal [30].

Theorem 1 (Grouping effect)**.** *If for all subjects i the observed covariate vector $\boldsymbol{x}_{i,l} = \boldsymbol{x}_{i,k}$, with $l, k \in \{1, \ldots, p\}$, then $\hat{\beta}_l = \hat{\beta}_k$, with $\hat{\boldsymbol{\beta}} = (\hat{\beta}_1, \ldots, \hat{\beta}_p)$ the solution of the PGEE (2.1) with EN or $SCAD_{L2}$ penalty.*

To prove the grouping effect, we consider the PGEE as a Penalized Generalized Least Squares problem (PGLS), (see Lemma 2). It is then sufficient to show that the EN and SCAD_{L2} penalty functions are strictly convex in $\boldsymbol{\beta}$. This is satisfied for the EN if $\lambda_2 > 0$. For the SCAD_{L2} this is satisfied if $\lambda_2 > \frac{1}{2(a-1)}$ (see Lemma 3).

Thus choosing $\lambda_2 > \frac{1}{2(a-1)}$ yields the desired grouping effect for the SCAD_{L2} PGEE estimator. Notice that the grouping effect also holds for the non-Gaussian case with an identity working correlation matrix, because in that case, solving the PGEE is equivalent to optimizing a penalized likelihood. And the grouping effect can be proved using the same logic.

Lemma 2 (PGEE as PGLS)**.** *In the Gaussian case, solving the PGEE equations is equivalent to minimizing a PGLS problem.*

Proof Consider the following PGLS problem:

$$Q^P(\boldsymbol{\beta}) = Q(\boldsymbol{\beta}) + NP(\boldsymbol{\beta}), \tag{2.3}$$

with:

$$Q(\boldsymbol{\beta}) = \frac{1}{2n}\boldsymbol{S}^T K^{-1}\boldsymbol{S},$$

$$K = \frac{1}{n}\sum_{n}^{i=1} \boldsymbol{D}_i^T V_i^{-1}\boldsymbol{D}_i = -\frac{1}{n}\frac{\partial \boldsymbol{S}(\boldsymbol{\beta})}{\partial \boldsymbol{\beta}}.$$

This is only valid for the Gaussian case, because otherwise $\boldsymbol{D}_i$ is a function of $\boldsymbol{\beta}$.

$$\frac{\partial Q^p(\boldsymbol{\beta})}{\partial \boldsymbol{\beta}} = -\boldsymbol{S} + N\dot{\boldsymbol{P}}(\boldsymbol{\beta})$$

Solving the PGEE in equation (2.1) is hence equivalent to minimizing the objective function $Q^P(\boldsymbol{\beta})$ in equation (2.3).

Proof (Theorem 1) Suppose $\hat{\beta}_l \neq \hat{\beta}_k$, let us consider $\hat{\boldsymbol{\beta}}^*$ as:

$$\begin{cases} \hat{\beta}_j = \hat{\beta}_k, & \text{if } j \neq k \text{ and } j \neq l \\ \hat{\beta}_j^* = \frac{1}{2}(\hat{\beta}_k + \hat{\beta}_l), & \text{if } j = k \text{ or } j = l \end{cases}$$

Suppose $\boldsymbol{x}_{i,l} = \boldsymbol{x}_{i,k}$ for all subjects i, then $Q(\hat{\boldsymbol{\beta}}) = Q(\hat{\boldsymbol{\beta}}^*)$, because $X_i\hat{\boldsymbol{\beta}} = X_i\hat{\boldsymbol{\beta}}^* = \boldsymbol{D}_i, \forall$ subjects i, with $X_i = (\boldsymbol{x}_{i,1}, \ldots, \boldsymbol{x}_{i,p})$. Since $P(\boldsymbol{\beta})$ is strictly convex, $P(\boldsymbol{\beta}) > P(\boldsymbol{\beta}^*)$. Therefore $\boldsymbol{\beta}$ cannot be the minimizer of $Q^p(\boldsymbol{\beta})$, which is a contradiction. Therefore $\hat{\beta}_l = \hat{\beta}_k$.

Lemma 3 (Convexity of the penalty function)**.** *If $\lambda_2 > \frac{1}{2(a-1)}$, the $SCAD_{L2}$-penalty is strictly convex.*

Proof Given

$$P(\theta) = \lambda_1 \int_0^\theta \left\{ I(\theta \leq \lambda_1) + \frac{(a\lambda_1 - \theta)_+}{(a-1)\lambda_1} I(\theta > \lambda_1) \right\} d\theta + \lambda_2\theta^2,$$

we calculate the second derivative of $P(\theta)$:

$$\ddot{P}(\theta) = \begin{cases} 2\lambda_2, & \text{if } \theta \leq \lambda_1, \\ \frac{-1}{a-1} + 2\lambda_2, & \text{if } \lambda_1 < \theta \leq a\lambda_1, \\ 2\lambda_2, & \text{if } a\lambda_1 < \theta. \end{cases}$$

This second derivative is always positive if:

$$\lambda_2 > \frac{1}{2(a-1)}. \tag{2.4}$$

Under condition (2.4) the SCAD_{L2} penalty function is strictly convex in the parameter vector $\boldsymbol{\beta}$.

In summary, we propose to use the EN (combination of LASSO and RIDGE) and the SCAD_{L2} (combination of SCAD and RIDGE) as the penalty in equation (2.1).

2.2.1.4 Non-naive estimator

Zou and Hastie [30] show empirically that the estimator in equation (2.1) with penalty function (2.2) called the naive estimator can be improved by removing the bias caused by the ridge part. Penalization methods aim at improving prediction performance at a cost of little extra bias for a lower variance. By doing simulations we also observed, that a more beneficial bias-variance trade-off can be realized by removing the ridge-shrinkage by multiplying with the ridge shrinkage factor to get the non-naive PGEE estimator:

$$\hat{\boldsymbol{\beta}}_{\text{non-naive}} = \hat{\boldsymbol{\beta}}_{\text{naive}} * (1 + \lambda_2).$$

We will use this non-naive versus in simulation studies hence called the PGEE estimator.

2.2.1.5 Time dependence

In Section 2.3 we will establish asymptotic properties of the PGEE. These results are only valid if the underlying GEE estimator is consistent. The consistency property of the GEE estimator relies on the estimating equation to be unbiased: $\text{E}\left(\boldsymbol{S}(\boldsymbol{\beta})\right) = 0$. Pepe and Anderson [23] showed that when time-dependent covariates are present, this is not satisfied unless either the full covariate conditional mean (FCCM) assumption is satisfied

$$\mu_{it} = \text{E}(Y_{it}|\boldsymbol{X}_{it}) = \text{E}(Y_{it}|\boldsymbol{X}_{it}\ \boldsymbol{X}_{ij}, j \neq t), \tag{2.5}$$

or the identity working correlation matrix is used: $W(\boldsymbol{\alpha}) = I$.

Using the working independence matrix, which we propose, is a correct inference tool to assess cross-sectional associations, if the FCCM-condition is not met. No additional assumptions are required besides the implied mean structure being correctly specified: $\mu_{it} = \text{E}(Y_{it}|\boldsymbol{X}_{it})$. Nonetheless efficiency can be gained by using all required correct lagged covariates with another working correlation matrix.

2.2.2 Algorithm

Equation (2.1) can be solved with the Local Quadratic Approximation (LQA) algorithm of Fan and Li [8]. We start with an initial estimate $\boldsymbol{\beta}_0 = (\beta_{1,0}, \ldots, \beta_{p,0})$ close to the solution. We thereafter iterate the following algorithm, whereby $\boldsymbol{\beta}_t = (\beta_{1,t}, \ldots, \beta_{p,t})$ expresses the parameter estimate at each iteration step t.

STEP 1 (Remove small values):

If a $\beta_{j,t}$ is close to zero (closer than a predefined threshold), we set $\hat{\beta}_{j,t} = 0$ and remove these variables from the model.

STEP 2 (Quadratic approximation):

We approximate the derivative of the penalty $\dot{\boldsymbol{P}}(\boldsymbol{\beta}) = \left(\dot{P}(|\beta_1|), \ldots, \dot{P}(|\beta_p|)\right)$ as:

$$\dot{P}(|\beta_j|) = \frac{\partial P(|\beta_j|)}{\partial \beta_j} = \frac{\partial P(|\beta_j|)}{\partial |\beta_j|} sgn(\beta_j) \approx \left\{ \frac{\partial P(|\beta_{j,t}|)}{\partial |\beta_{j,t}|} \Big/ |\beta_{j,t}| \right\} \beta_j. \tag{2.6}$$

The penalized generalized estimating equation can hence be approximated by a Taylor series expansion of the GEE part and the approximate derivative of the penalty in (2.6):

$$\boldsymbol{S^P}(\boldsymbol{\beta}) \approx \boldsymbol{S}(\boldsymbol{\beta}_t) + \frac{\partial \boldsymbol{S}(\boldsymbol{\beta}_t)}{\partial \boldsymbol{\beta}} (\boldsymbol{\beta} - \boldsymbol{\beta}_t) - NU(\boldsymbol{\beta}_t) - N\Sigma(\boldsymbol{\beta}_t)(\boldsymbol{\beta} - \boldsymbol{\beta}_t),$$

with

$$\Sigma(\boldsymbol{\beta_t}) = diag\left\{ \frac{\partial P(|\beta_{1,t}|)}{\partial |\beta_{1,t}|}, \ldots, \frac{\partial P(|\beta_{p,t}|)}{\partial |\beta_{p,t}|} \right\}$$

and

$$U(\boldsymbol{\beta}_t) = \Sigma(\boldsymbol{\beta}_t)\boldsymbol{\beta}_t.$$

STEP 3 (Beta update):

We update $\boldsymbol{\beta}$ as follows:

$$\boldsymbol{\beta}_{t+1} = \boldsymbol{\beta}_t - \left\{ \frac{\partial \boldsymbol{S}(\boldsymbol{\beta}_t)}{\partial \boldsymbol{\beta}} - N\Sigma(\boldsymbol{\beta}_t) \right\}^{-1} \{\boldsymbol{S}(\boldsymbol{\beta}_t) - NU(\boldsymbol{\beta}_t)\}, t = 0, \ldots \tag{2.7}$$

We iterate through steps 1 to 3 until convergence. Convergence is reached when the L_2 norm of the change of the parameter vector is smaller than a predefined small constant c:

$$\left\| \boldsymbol{\beta}_t - \boldsymbol{\beta}_{t-1} \right\|_2 < c.$$

Notice that omitting variables in this way, has a similar drawback as backward selection: when during the iteration a parameter hits zero, it can no longer be included into the model in further iterations. The smaller the threshold, the less important this effect will be. Hunter and Li [13] propose a class of Minorize-Maximize (MM) algorithms of which the LQA algorithm is a special case. By using a perturbed version of the LQA, the drawback of not escaping zero can be avoided at the price of requiring more iterations until convergence.

A comparison of different possible algorithms falls outside the scope of this Thesis. We have implemented the LQA algorithm for solving PGEE-problems in the R-software.

2.2.3 Tuning parameter selection

Using a sparse penalization technique strongly reduces the dimensionality of the covariate selection problem. Instead of comparing all subsets of variables, only a limited number of tuning parameters have to be selected. In the case of the EN penalty these are λ_1 and λ_2. In the case of the SCAD$_{L2}$ penalty an additional tuning parameter a is involved. However, we fix $a = 3.7$ as proposed by Fan and Li [8]. To select the remaining tuning parameters, it is useful to reparametrise the penalty function (2.2) as follows:

$$P(\boldsymbol{\beta}) = \lambda \left\{ \alpha P_{L1}(\boldsymbol{\beta}) + (1-\alpha) P_{L2}(\boldsymbol{\beta}) \right\}, \tag{2.8}$$

with $\alpha \in [0, 1]$ the control between sparsity and grouping effect and λ the amount of penalization.

Cross-validation (CV) as proposed in [4] can directly be used to select the tuning parameters. The objective of cross-validation is to select these parameters such that a specific loss function of prediction is minimized (PL), for which the prediction loss of cross-validation (PL$_{CV}$) is an estimator.

The PL$_{CV}$ is calculated by repeatedly splitting up the sample into a test and a training set, fitting a model on the training set and calculating the PL on the test set. We then average the results. Since we are working with repeated measures, the splits should be taken on the subject level rather than on the observation level. If the number of subjects is small, leave-one-subject-out-cross-validation is a suitable choice. We use the approach proposed by [4]:

$$\text{PL}_{CV} = \sum_{i=1}^{n} \frac{(\boldsymbol{y}_i - \hat{\boldsymbol{y}}_i^{[-i]})^T V_i^{-1} (\boldsymbol{y}_i - \hat{\boldsymbol{y}}_i^{[-i]})}{T_i}, \tag{2.9}$$

with $\hat{\boldsymbol{y}}_i^{[-i]}$ the vector of predicted responses of subject i in the model fitted without this

subject, T_i is the number of observations in subject i and V_i the working covariance matrix. In practice the PL_{CV} can be minimized by a grid search. For λ it is convenient to work at a log scale. For α it is sufficient to take a limited number of points within the $[0, 1]$ interval. The standard error of PL_{CV} can be calculated and used to identify a set of plausible models with a PL_{CV} within one standard error of the optimal model.

When one wants to avoid the the computational burden of cross-validation, quasi-generalized cross validation (QGCV) can be used [10]. As CV, QGCV attempts to minimize a PL by using an estimator: PL_{QGCV},

$$\mathrm{PL}_{QGCV} = \frac{Wdev(\lambda, \alpha)}{n\{1 - p(\lambda, \alpha)/N_{df}\}}. \tag{2.10}$$

The numerator in (2.10) is the weighted deviance:

$$Wdev(\lambda, \alpha) = \sum_{i=1}^{n} \boldsymbol{r}_i^T R_i^{-1} \boldsymbol{r}_i.$$

It is based on the vector of deviance residuals $\boldsymbol{r}_i$ of subject i. The longitudinal structure is incorporated by the working correlation R_i. The denominator in (2.10) is a correction for model complexity, with $N_{df} = \sum_{i=1}^{n} \frac{T_i^2}{|R_i|}$ the estimated effective number of observations and $|R_i| = \sum \rho_{ij}$ the sum of the elements of the working correlation matrix R_i. The model complexity is incorporated by an estimate of the effective number of parameters in the penalty model $p(\lambda, \alpha)$. For details see Fu [10].

Notice that in Fu's approach a different prediction loss function is estimated, based on weighted deviance residuals instead of weighted Pearson residuals. In equation (2.9) the ordinary difference between observed and predicted response could be replaced by the deviance residual as well, although this is not proposed in Cantoni et al. [4].

Even though cross-validation is computational intensive, we recommend using this approach instead of the QGCV, because the approximation of the degrees of freedom might not be good when using the working independence matrix. Penalization paths provide an additional useful tool to explore variable importance. The combination of cross-validation and penalization paths is illustrated by a data example in Section 2.5.

2.3 Asymptotic theory

In this section, we establish the asymptotic properties for the naive PGEE estimator, when the number of subjects n goes to infinity. These theorems and their proofs are

adopted from Dziak [6]. For the asymptotic properties to hold, following regularity conditions are required [6]:

Regularity condition 1: $\boldsymbol{S}(\boldsymbol{\beta})$ and $\boldsymbol{K}(\boldsymbol{\beta}) = \frac{1}{n}\sum_{n}^{i=1} \boldsymbol{D}_i^T V_i^{-1} \boldsymbol{D}_i$ have continuous third derivatives in $\boldsymbol{\beta}$.

Regularity condition 2: $\boldsymbol{K}(\boldsymbol{\beta})$ is positive definite with probability approaching one. there exist a non-random function $\boldsymbol{K_0}(\boldsymbol{\beta})$ such that $\|\boldsymbol{K}(\boldsymbol{\beta}) - \boldsymbol{K_0}(\boldsymbol{\beta})\| \xrightarrow{p} 0$ uniformly, and $\boldsymbol{K_0}(\boldsymbol{\beta}) > 0$ for all $\boldsymbol{\beta}$.

Regularity condition 3: The $\boldsymbol{S_i} = \boldsymbol{D}_i^T V_i^{-1}(\boldsymbol{Y}_i - \boldsymbol{\mu}_i)$ have finite covariance for all $\boldsymbol{\beta}$.

Regularity condition 4: The derivatives of $\boldsymbol{K_0}(\boldsymbol{\beta})$ in $\boldsymbol{\beta}$ are $O_p(1)$ for all $\boldsymbol{\beta}$.

Asymptotic properties are derived by turning to the equivalent PGLS problem. (see Lemma 2). This is only possible for the Gaussian case. Collinearity, the main context in which this type of penalization is useful, exerts no influence on these asymptotic results, but if condition (2.5) is not satisfied, the working independence correlation structure is a necessary condition for consistency to hold.

Theorem 4 ($\sqrt{n}$-consistency)**.** *For the EN-penalty with $\lambda_1 = O_p(n^{-1/2})$ and $\lambda_2 = O_p(n^{-1/2})$, or for the SCAD$_{L2}$-penalty with $\lambda_1 = o_p(1)$ and $\lambda_2 = O_p(n^{-1/2})$, under normality and regularity conditions 1-4. there exists a sequence $\hat{\boldsymbol{\beta}}_n$ of solutions to the PGEE equation (2.1) such that $\left\|\hat{\boldsymbol{\beta}}_n - \boldsymbol{\beta}\right\| = O_p(n^{-1/2})$.*

Theorem 4 indicates the asymptotic estimation consistency of the PGEE estimator with EN or SCAD$_{L2}$ penalty when the number of subjects n goes to infinity.

Proof (Theorem 4: $\sqrt{n}$-consistency) For $0 \leq \epsilon \leq 1$, it is sufficient to show that with probability at least $1 - \epsilon$, $\exists$ some large constant C_ϵ, such that a local solution $\hat{\boldsymbol{\beta}}_n$ of $Q^P(\boldsymbol{\beta})$ exist in the interior of the ball $\left\{\boldsymbol{\beta} + n^{-1/2}\boldsymbol{u} : \|\boldsymbol{u}\| \leq C_\epsilon\right\}$,

such that $\left\|\hat{\boldsymbol{\beta}}_n - \boldsymbol{\beta}\right\| = O_p(n^{-1/2})$ will be $O_p(n^{-1/2})$, [8, 6]. The conditions on the tuning parameters make sure, that $Q(\boldsymbol{\beta})$ asymptotically dominates the penalty part.

This result holds if there exists a fixed true underlying vector of regression coefficients $\boldsymbol{\beta}$. The difference in conditions on the tuning parameters for the SCAD part on the one hand and the LASSO and ridge parts on the other can be attributed to the difference in the derivative of the penalty function for the non-zero regression coefficients. In order to achieve $\sqrt{n}$-consistency this rate of penalization must fade away at a high enough rate. Since the derivative of the SCAD is zero for coefficients

larger than $a\lambda_1$, a moderate decrease in penalization is sufficient. For asymptotic results of the SCAD penalty under a diverging number of parameters we refer to Wang et al. [26]. Asymptotic theory in the broader context of penalized estimating function has also been described by Johnson et al. [16], who included results on the EN as an approximate zero-crossing.

The aim of our proposed PGEE estimator is not only to consistently estimate the parameters of a regression model, but also to select the variables for that model. In order to get more insight in the selection properties of this estimator, we partition our vector of regression coefficients into two subgroups:

$$\boldsymbol{\beta} = (\boldsymbol{\beta}_{\mathcal{A}}, \boldsymbol{\beta}_{\mathcal{N}}),$$

with $\mathcal{A} = \{j : \beta_j \neq 0\}$ the vector of indicators of non-zero coefficients, which we want to retain in our model; with $\mathcal{N} = \{j : \beta_j = 0\}$ the vector of indicators of zero coefficients, which we want to omit from our model. We will establish selection consistency in two steps. First we show that all active coefficients $\boldsymbol{\beta}_{\mathcal{A}}$ are retained in Lemma 5. Second we establish conditions under which the zero coefficients $\boldsymbol{\beta}_{\mathcal{N}}$ will be dropped in Lemma 6.

Lemma 5 (Sensitivity)**.** *Under the conditions in Theorem 4 there exists a sequence $\hat{\boldsymbol{\beta}}_n$ such that the active coefficients are included in the model with probability approaching one, i.e., $Pr(\exists j \in \mathcal{A} : \hat{\beta}_j = 0) = o(1)$*

Lemma 5 follows directly from Theorem 4, we omit its proof. We assume that β_j is fixed. And take some small $\epsilon > 0$. Then:

$$\Pr(\exists j \in \mathcal{A} : \hat{\beta}_j = 0) \leq \Pr(\exists j \in \mathcal{A} : \left|\hat{\beta}_j - \beta_j\right| > \epsilon) \leq \Pr(\left\|\hat{\boldsymbol{\beta}} - \boldsymbol{\beta}\right\|^2 > \epsilon^2) = o(1).$$

For the asymptotic estimator to be sparse, we need an additional condition on the strength of tuning parameter λ_1:

$$Nn^{-1/2}\lambda_1 \to \infty, \tag{2.11}$$

as $n \to \infty$.

Let us assume the number of observations N grows proportionally with the number of subjects n. It follows that (2.11) is in conflict with the conditions of Theorem 4 for the EN, but not for the SCAD_{L2}.

Lemma 6 (Sparsity)**.** *For the $SCAD_{L2}$ penalty, under conditions in Theorem 4 and condition (2.11) there exists a sequence $\hat{\boldsymbol{\beta}}_n$ of solutions such that $\hat{\boldsymbol{\beta}}_{\mathcal{A}}$ is $\sqrt{n}$-consistent for $\boldsymbol{\beta}_{\mathcal{A}}$, and that $\hat{\boldsymbol{\beta}}_{\mathcal{N}} = \boldsymbol{\beta}_{\mathcal{N}} = \mathbf{0}$.*

Proof (Lemma 6: Sparsity) Condition (2.11) provides that in a neighborhood where the non-active coefficients are close tho zero, the sparse part has asymptotically still enough influence to put the estimates of the non-active coefficients exactly equal to zero:

$$Q^P(\boldsymbol{\beta}_{\mathcal{A}}, 0) = argmin\left\{Q^P(\boldsymbol{\beta}_{\mathcal{A}}, \boldsymbol{\beta}_{\mathcal{B}})\right\}$$

Theorem 7 (Selection consistency)**.** *Under the conditions of Theorem 4 and condition (2.11) the $SCAD_{L2}$ is asymptotically able to include the active set ($Pr(\exists j \in \mathcal{A} : \hat{\beta}_j = 0) = o(1)$) and to omit the non active set ($\hat{\boldsymbol{\beta}}_{\mathcal{N}} = \boldsymbol{\beta}_{\mathcal{N}} = \mathbf{0}$).*

This follows from Lemma 5 and Lemma 6.

Theorem 8 (Asymptotic normality)**.** *Under the conditions of Theorem 4 there exist a sequence $\hat{\boldsymbol{\beta}}$ of solutions to equation (2.1) such that:*

$$\sqrt{n}\left(\hat{\boldsymbol{\beta}}_{\mathcal{A}} - \boldsymbol{\beta}_{\mathcal{A}}\right) \xrightarrow{L} N(\mathbf{0}, \boldsymbol{\Phi}). \tag{2.12}$$

For details on $\boldsymbol{\Phi}$, see Dziak [6].

We notice this asymptotic normality property allows us to derive standard errors, and therefore to calculate p-values of Wald tests for parameter coefficients. However, no standard errors are provided for the parameters put to zero. Therefore we recommend using the bootstrap to obtain standard errors for all estimates.

2.4 Simulation studies

2.4.1 Aims and setting

We compare the effect of penalization on selection and prediction performance on simulated longitudinal data with multicollinearity and time-dependent covariates, using different penalty functions (LASSO, RIDGE, EN, SCAD and SCAD_{L2}). Two main settings will be investigated:

(1) In Section 2.4.2 we simulate from a cross-sectional longitudinal process and fit a PGEE model with the same time-dependent covariates. In this setting the FCCM-assumption (see equation (2.5)) is satisfied.

(2) In Section 2.4.3 we simulate from a process which includes lagged covariates. The PGEE estimator is used to assess the implied cross-sectional associations between response and covariates. In both cases the working independence matrix will be used. However, this requirement could be relaxed in the first setting.

Table 2.1: Comparison of penalty functions when the cross-sectionality assumption is satisfied. on the basis of prediction performance by model error (ME) with standard error (SE), selection performance (proportion of correct deletions (CD) and proportion of incorrect deletions (ID)) for 1,000 simulations. Tuning parameters are selected using cross-validation, the median tuning parameters are displayed.

Penalty	ME (S.E.)	(λ, α)	C.D.	I.D.
GEE	0.098 (0.006)	-	0.000	0.000
LASSO	0.095 (0.006)	(0.041; 1.000)	0.347	0.000
RIDGE	0.096 (0.005)	(0.010; 0.000)	0.013	0.000
EN	0.095 (0.005)	(0.041; 0.500)	0.333	0.000
SCAD	0.084 (0.006)	(0.079; 1.000)	0.630	0.000
SCAD_{L2}	0.081 (0.006)	(0.170; 0.643)	0.650	0.002

In each case the selection performance will be expressed as the percentage of correct and incorrect deletions. The prediction performance will be measured by the model error (ME, 8):

$$\text{ME}(\hat{\mu}) = (\hat{\boldsymbol{\beta}} - \boldsymbol{\beta})^T \text{E}(XX^T)(\hat{\boldsymbol{\beta}} - \boldsymbol{\beta}). \tag{2.13}$$

The model error is the part of the prediction error which can be influenced by the quality of the estimator $\hat{\mu}$. For a perfect estimator, this quantity is zero. The tuning parameters for the different penalty models will be selected by leave one subject out cross-validation.

2.4.2 Cross-sectional model

We simulated longitudinal datasets with $n = 20$ subjects, $T_i = T = 5$ observations per subject from the following longitudinal process:

$$Y_{it} = \boldsymbol{X}_{it}^T \boldsymbol{\beta} + e_{it}.$$

Y_{it} is the response for subject i at time t, $\boldsymbol{\beta} = (-1, -1, 1, 1, 0.5, 0, 0, 0)^T$; $\boldsymbol{e}_i = (e_{i1}, \ldots, e_{iT})^T$ multivariate normal with a first order autoregressive correlation structure with $\rho = \text{corr}(e_{j,it}, e_{j,it+1}) = 0.7$. $X_{it} \sim \text{N}_8(0, \Sigma)$; Σ is the correlation structure of the covariates at each time point. We use the following structure: $\text{corr}(X_1, X_2) = 0.6$; $\text{corr}(X_3, X_4) = 0.3$. All other correlations between X-variables are set to zero.

Table 2.1 illustrates the impact of penalization on prediction and selection performance. We notice only a small improvement in the ME by ridge, EN or LASSO

penalization. The selection performance of the LASSO is slightly better than the EN, but still only removes about 35% of variables which should be removed.

The SCAD in contrast strongly reduces the ME and achieves a good selection, considering the small sample size. With the inclusion of an additional ridge component, the SCAD_{L2} accomplishes even a further reduction in the ME and a better selection, although the convexity condition ((2.4) in Appendix A) is not satisfied. Also in other settings, we have generally observed SCAD_{L2} penalization to outperform the ordinary SCAD when collinearity is present, even if condition (2.4) is not fulfilled.

The large difference in the ME and selection performance for the EN and the LASSO on the one hand and the SCAD_{L2} and the SCAD on the other, can likely be attributed to the combination of estimation and selection consistency (see Theorem 4 and 7) of the SCAD_{L2} and the SCAD, which is lacking for the EN and the LASSO.

2.4.3 Implied cross-sectional model

2.4.3.1 Data generation

We make two adaptations to the simulation study in Diggle et al. [5]. First we increase the number of time-dependent covariates to twenty. Second multicollinearity is introduced by imposing a correlation structure between the covariates at each time point. The data is simulated from following process:

$$\begin{cases} Y_{it} = \boldsymbol{X}_{it}^T \boldsymbol{\gamma}_1 + \boldsymbol{X}_{it-1}^T \boldsymbol{\gamma}_2 + b_i + e_{it}, \\ X_{j,it} = \rho_j X_{j,it-1} + \epsilon_{j,it}, \ \forall j = 1, \ldots, 20. \end{cases}$$

Both response and covariates have a time-dependent structure. Where i is the indicator of the subject, t is the time indicator, and j indicates the covariate. Here $e_{it} \sim \text{N}(0,1)$, $b_i \sim \text{N}(0,1)$, $\epsilon_{i0} \sim \text{N}(0,1)$, $\epsilon_{j,it} \sim \text{N}(0, 1-\rho_j^2)$ for $t > 0$, all mutually independent. $\boldsymbol{X}_{it} = (X_{1,it}, \ldots, X_{20,it}) \sim \text{N}_{20}(0, \Sigma)$. The covariance structure $\Sigma = diag(\Sigma_1, \Sigma_1, \Sigma_1, I_{11})$ has a block diagonal structure, with

$$\Sigma_1 = \begin{bmatrix} 1 & 0.2 & 0.5 \\ 0.3 & 1 & 0.4 \\ 0.5 & 0.4 & 1 \end{bmatrix}.$$

Notice that we consider two different types of dependence between the X-variables. On the one hand, each covariate for each subject $X_{j,it}$ follows its own autoregressive time evolution. On the other hand, within each subject, at each time point different covariates have a cross-sectional correlation characterized by their covariance structure Σ.

We look at two distinct scenarios:

- Scenario 1:
$$\begin{cases} \boldsymbol{\gamma}_1 = \boldsymbol{\gamma}_2 = \big((2,2,2),(1,1,1),(0.1,0.1,0.1),0,0,\dots\big), \\ \rho_j = 0.5, \forall j = 1,\dots,20. \end{cases}$$
- Scenario 2:
$$\begin{cases} \boldsymbol{\gamma}_1 = \boldsymbol{\gamma}_2 = \big((1,1,1),(1,1,1),(0,0,0),0,0,\dots\big), \\ \boldsymbol{\rho} = (0.3,0.3,0.3,0.6,0.6,0.6,0.5,0.5,\dots). \end{cases}$$

With $\boldsymbol{\rho} = (\rho_1,\dots,\rho_{20})$.

For each scenario, we simulate 100 datasets with 20 subjects and 100 datasets with 100 subjects.

2.4.3.2 Cross-sectional model

Suppose the objective is to assess the cross-sectional associations between Y_{it} and $\boldsymbol{X}_{it}$. We therefore estimate the parameters of the implied cross-sectional model:

$$\mathrm{E}(Y_{it}|\boldsymbol{X}_{it}) = \boldsymbol{X}_{it}^T\boldsymbol{\beta}.$$

The properties of the multivariate normal distribution allow us to calculate the coefficients $\boldsymbol{\beta}$ of this implied model:

$$\boldsymbol{\beta} = \boldsymbol{\gamma}_1 + \boldsymbol{\rho}^T\boldsymbol{\gamma}_1.$$

2.4.3.3 Simulation results

Table 2.2 summarizes different PGEE fits on the 100 simulated datasets for each scenario. SCAD$_{L2}$ penalization yields for all scenarios the best prediction performance of all PGEE estimators. The model error is strongly reduced by using a sparse penalization technique (LASSO, EN, SCAD, SCAD$_{L2}$), especially when only 20 subjects are available. Ridge penalization in contrast improves the model error only modestly. For scenario 2 with 20 subjects, we see that the EN has a smaller model error than the SCAD. The beneficial grouping effect more than compensates for the lack of unbiasedness of the EN in this example. In general we observe the SCAD$_{L2}$ to outperform the SCAD and the EN when strong multicollinearity is present.

In addition the selection performance of the SCAD$_{L2}$ is superior to that of the EN or the LASSO. However, a trade-off between correct deletions and incorrect deletions

is observed. In Table 2.2 we see that ordinary GEE and ridge penalization have sometimes a small percentage of deletions. This is due to the algorithm (see Section 2.2.2), which includes a threshold term.

When we look at the relative bias, we observe the overall sample bias of the first beta coefficient of the SCAD and SCAD$_{L2}$, not to be larger than that of ordinary GEE. For the LASSO and the EN we notice a substantial negative bias.

2.4.4 Extension to binomial data

If we apply the logit transformation to the mean structure of these two scenarios, we can use this quantity as a probability to simulate from the Bernoulli distribution. We simulate data from following longitudinal process, which is a generalized linear mixed model:

$$\begin{cases} X_{j,it} = \rho_j X_{j,it-1} + \epsilon_{j,it}, \ \forall j = 1, \dots, 20, \\ \text{logit}(p_{it}) = \boldsymbol{X}_{it}^T \boldsymbol{\gamma}_1 + \boldsymbol{X}_{it-1}^T \boldsymbol{\gamma}_2 + b_i, \\ Y_{it} \sim Bern(p_{it}), \end{cases}$$

where i indicates the subject, t is the time indicator and j indicates the covariate. The response Y_{it} is generated from the Bernoulli distribution, where the success probability p_{it} is linked by the logit transform to a linear mean structure, with a subject-specific effect $b_i \sim \text{N}(0, 1)$. The covariate process is autoregressive, with $\epsilon_{i0} \sim \text{N}(0, 1)$, $\boldsymbol{X}_{it} = (X_{1,it}, \dots, X_{20,it}) \sim \text{N}_{20}(0, \Sigma)$. The covariance structure $\Sigma = diag(\Sigma_1, \Sigma_1, \Sigma_1, I_{11})$ has a block diagonal structure, with

$$\Sigma_1 = \begin{bmatrix} 1 & 0.2 & 0.5 \\ 0.3 & 1 & 0.4 \\ 0.5 & 0.4 & 1 \end{bmatrix}.$$

Notice that we consider two different types of dependence between the X-variables. On the one hand, each covariate for each subject $X_{j,it}$ follows its own autoregressive time evolution. On the other hand, within each subject, at each time point different covariates have a cross-sectional correlation characterized by their covariance structure Σ.

As in the Gaussian case, we consider two scenarios:

- Scenario 1:
  $$\begin{cases} \boldsymbol{\gamma}_1 = \boldsymbol{\gamma}_2 = \big((2, 2, 2), (1, 1, 1), (0.1, 0.1, 0.1), 0, 0, \dots\big), \\ \rho_j = 0.5, \forall j = 1, \dots, 20. \end{cases}$$

Table 2.2: Comparison of penalty functions when the cross-sectionality assumptions is not satisfied. Comparison on the basis of prediction performance by model error (ME) with standard error (SE), selection performance (proportion of correct deletions (CD) and proportion of incorrect deletions (ID)) and relative bias of the first coefficient for 1,000 simulations. Tuning parameters are selected using cross-validation, the median tuning parameters are displayed.

Penalty	ME (SE)	(λ, α)	CD	ID	Rel. Bias
Scenario 1, 20 subjects					
GEE	6.489 (0.263)	-	0.002	0.000	-0.103
LASSO	4.259 (0.215)	(0.405; 1.000)	0.440	0.169	-0.158
RIDGE	5.593 (0.204)	(0.092; 0.000)	0.002	0.001	-0.182
EN	4.144 (0.193)	(0.405; 0.821)	0.392	0.144	-0.154
SCAD	4.541 (0.287)	(0.425; 1.000)	0.549	0.216	-0.089
SCAD_{L2}	3.744 (0.198)	(0.518; 0.786)	0.500	0.184	-0.088
Scenario 1, 100 subjects					
GEE	0.942 (0.027)	-	0.004	0.001	-0.021
LASSO	0.663 (0.029)	(0.151; 1.000)	0.428	0.099	-0.047
RIDGE	0.934 (0.029)	(0.013; 0.000)	0.011	0.001	-0.036
EN	0.681 (0.030)	(0.193; 0.929)	0.417	0.097	-0.048
SCAD	0.445 (0.026)	(0.287; 1.000)	0.657	0.154	-0.015
SCAD_{L2}	0.438 (0.025)	(0.349; 0.857)	0.662	0.158	-0.019
Scenario 2, 20 subjects					
GEE	3.018 (0.115)	-	0.003	0.000	-0.058
LASSO	1.988 (0.100)	(0.247; 1.000)	0.446	0.003	-0.274
RIDGE	2.463 (0.086)	(0.092; 0.000)	0.006	0.000	-0.246
EN	1.884 (0.086)	(0.316; 0.643)	0.383	0.002	-0.261
SCAD	2.280 (0.147)	(0.287; 1.000)	0.494	0.023	-0.206
SCAD_{L2}	1.626 (0.102)	(0.425; 0.643)	0.431	0.010	-0.202
Scenario 2, 100 subjects					
GEE	0.456 (0.014)	-	0.003	0.000	-0.020
LASSO	0.309 (0.014)	(0.118; 1.000)	0.451	0.000	-0.080
RIDGE	0.449 (0.015)	(0.021; 0.000)	0.006	0.000	-0.046
EN	0.317 (0.015)	(0.151; 0.929)	0.441	0.000	-0.086
SCAD	0.161 (0.010)	(0.235; 1.000)	0.736	0.000	-0.011
SCAD_{L2}	0.150 (0.009)	(0.287; 0.857)	0.722	0.000	-0.029

- Scenario 2:
$$\begin{cases} \boldsymbol{\gamma}_1 = \boldsymbol{\gamma}_2 = \big((1,1,1),(1,1,1),(0,0,0),0,0,\dots\big), \\ \boldsymbol{\rho} = (0.3,0.3,0.3,0.6,0.6,0.6,0.5,0.5,\dots). \end{cases}$$

With $\boldsymbol{\rho} = (\rho_1, \dots, \rho_{20})$.

For each scenario, we simulate 100 datasets with 30 subjects and 100 datasets with 100 subjects. We have chosen for 30 subject as the smallest sample size, because in the case of 20 subjects the problem of quasi-separation made an ordinary GEE fit impossible.

As in the Gaussian case, our interest lies in assessing the cross-sectional associations between Y_{it} and $\boldsymbol{X}_{it}$. We therefore estimate the parameters of the implied marginal cross-sectional model:

$$\mathrm{E}(Y_{it}|\boldsymbol{X}_{it}) = \exp(\boldsymbol{X}_{it}^T\boldsymbol{\beta}).$$

In contrast to the Gaussian case, we cannot give an expression for the implied marginal model. For this reason we will not discuss the relative bias. The proportions of correct and incorrect deletions can in contrast by assessed, because if $\gamma_j = 0$ then $\beta_j = 0$.

Concerning the quality of the fit, following definition of the model error holds:

$$\mathrm{ME} = \mathrm{E}\{E(Y|\boldsymbol{X}_{it}) - \frac{\exp(\boldsymbol{X}_{it}^T\hat{\boldsymbol{\beta}})}{1+\exp(\boldsymbol{X}_{it}^T\hat{\boldsymbol{\beta}})}\}. \tag{2.14}$$

In the absence of a clear expression in terms of the coefficients $\hat{\boldsymbol{\beta}}$, we will use a Monte Carlo estimate of (2.14):

$$\widehat{\mathrm{ME}} = \frac{1}{N}\sum_i\sum_t (p_{ij} - \hat{p}_{ij}),$$

based on a simulated validation set, with a number of subjects of $n = 2000$, five observations per subject, therefore $N = 10000$.

Table 2.3 summarizes different PGEE fits for 100 simulated datasets for each scenario. As in the Gaussian case we observe the SCAD_{L2} gives the best fit. The results in their interpretation are similar to the Gaussian setting, indicating the suitability of these penalty methods outside the Gaussian setting.

2.5 Determinants of female life expectancy in Europe

In health economics, identifying the most influential determinants of health-outcomes is a major research topic. If observations are taken over time, and the number of

Table 2.3: Comparison of penalty functions on a binomial example when the cross-sectionality assumption is not satisfied: prediction performance via the model error (ME) with standard errror (SE) , selection performance (proportion of correct deletions (CD) and proportion of incorrect deletions(ID)).

Scenario 1, 30 subjects				
Penalty	ME(SE)	(λ, α)	CD	ID
GEE	0.1161 (0.0014)	-	0.0036	0.0033
LASSO	0.0956 (0.0006)	(0.0268; 1.0000)	0.5082	0.1978
RIDGE	0.0997 (0.0006)	(0.0210; 0.0000)	0.0173	0.0144
EN	0.0955 (0.0005)	(0.0268; 0.8571)	0.4491	0.1622
SCAD	0.1043 (0.0004)	(0.1301; 1.0000)	1.0000	0.6789
$SCAD_{L2}$	0.0954 (0.0007)	(0.0877; 0.7859)	0.9627	0.4222
Scenario 1, 100 subjects				
GEE	0.0877 (0.0003)	-	0.0155	0.0100
LASSO	0.0842 (0.0002)	(0.0104; 1.0000)	0.3655	0.1077
RIDGE	0.0861 (0.0002)	(0.0069; 0.0000)	0.0236	0.0067
EN	0.0842 (0.0002)	(0.0104; 1.0000)	0.3655	0.1078
SCAD	0.0841 (0.0003)	(0.0720; 1.0000)	0.9382	0.3144
$SCAD_{L2}$	0.0833 (0.0002)	(0.0720; 0.9286)	0.9436	0.3122
Scenario 2, 30 subjects				
GEE	0.1022 (0.0011)	-	0.0064	0.0000
LASSO	0.0832 (0.0006)	(0.0237; 1.0000)	0.4593	0.0167
RIDGE	0.0864 (0.0006)	(0.0291; 0.0000)	0.0179	0.0000
EN	0.0830 (0.0006)	(0.0291; 0.7143)	0.3971	0.0117
SCAD	0.0911 (0.0014)	(0.1301; 1.0000)	0.9071	0.2000
$SCAD_{L2}$	0.0814 (0.0008)	(0.0877; 0.7859)	0.8271	0.0733
Scenario 2, 100 subjects				
GEE	0.0764 (0.0003)	-	0.0064	0.0000
LASSO	0.0727 (0.0002)	(0.0128; 1.0000)	0.4207	0.0000
RIDGE	0.0749 (0.0002)	(0.0104; 0.0000)	0.0186	0.0000
EN	0.0727 (0.0002)	(0.0128; 1.0000)	0.4207	0.0000
SCAD	0.0710 (0.0003)	(0.1068; 1.0000)	0.9829	0.0183
$SCAD_{L2}$	0.0706 (0.0002)	(0.0877; 0.9286)	0.9521	0.0067

Table 2.4: Data availability table of all covariates and response for the different Country-Year combinations, 1 indicates available, 0 non available

Country	1999	2000	2001	2002	2003	2004	2005
Austria	1	1	1	0	1	0	0
Belgium	1	0	0	0	0	0	0
Denmark	0	0	1	0	0	0	0
Estonia	0	0	0	0	1	1	0
Finland	1	1	1	1	0	1	1
France	1	1	1	1	0	0	0
Germany	1	1	1	0	0	0	0
Ireland	1	1	1	0	1	1	0
Italy	1	1	1	0	0	0	0
Netherlands	1	1	1	0	1	0	0
Spain	1	1	1	1	1	0	0
Sweden	1	0	0	1	0	0	0
United Kingdom	1	1	1	1	0	0	0

potential determinants is large, our proposed PGEE estimator can facilitate the selection of the most important ones. Beutels et al. [1] for instance try to search for determinants of antibiotic consumption between European countries and over time. We will use a subset of this original dataset to search for determinants of female life expectancy. All available years between 1999 and 2005 are used in our analysis, for the following 13 countries: Austria, Belgium, Denmark, Estonia, Finland, France, Germany, Ireland, Italy, the Netherlands, Spain, Sweden and the United Kingdom. The data availability is summarized in Table 2.4.

The objective of this study is to find the most important determinants, which could explain observed differences in female life expectancy at birth between countries and over time. A set of 42 potential determinants, having a potential direct or indirect effect on life expectancy, are included. These determinants can be roughly structured into six groups: *death rates* such as the death rate due to pneumonia; *socio-economics* such as GDP per capita and hours in a work week; *culture* such as the four dimensions of Hofstede: Power distance index, Individualism, Masculinity and Uncertainty avoidance; factors that characterize *infectious disease preventions* such vaccination coverage against pertussis; *organization of the health care system* such as hospital beds and *demographics* such as population density. These different covariates are cor-

related, and vary over time. The ordinary GEE estimator is unable to fit a full model, because of the limited number of data points (44) compared to the number of covariates (42). We assess the cross-sectional associations between response and covariates using the PGEE estimator. Both covariates and response are standardized prior to analysis. We employ PGEE with the penalty function parametrized as in equation (2.8). Leave-one-subject-out-cross-validation is then performed on a grid of α and λ values. For α the two extremes 0 and 1 are included. On this grid of tuning parameters the minimum of the PL_{CV} is selected for both the EN and the SCAD_{L2}. For the EN, we find a $\mathrm{PL}_{CV} = 0.0348$ with a standard error of 0.0035. The SCAD_{L2} outperforms the EN with a $\mathrm{PL}_{CV} = 0.025$, with a standard error of 0.0020. For the EN, this minimum is found for the tuning parameters $(\alpha; \lambda) = (2.857\mathrm{E}-4); 3.393\mathrm{E}-4)$. The SCAD_{L2} reaches its optimum at $(\alpha; \lambda) = (0.786; 0.0146)$. In both cases this minimum was significantly different from the two extreme α values. In Table 2.5 the standardized coefficients of both the EN and the SCAD_{L2} are reported. The EN selects 27 out of the 42, whereas the SCAD_{L2} reduces this number further to 20. The order of the standardized coefficients differs only slightly between EN and SCAD_{L2}.

For EN penalization, a shrinkage plot gives some insight into the impact of the different variables on the response. Figure 2.1 displays the shrinkage paths of the ten largest standardized coefficients at the selected fit. We keep α fixed and observe the evolution of standardized coefficients if λ decreases. This shrinkage plot indicates the sensitivity of the fit with respect to λ. If λ increases we see that some variables are excluded from the model such as the percentage children vaccinated against pertussis, whilst others increase their influence such as the infants death. The grouping effect implies that correlated variables are pulled towards each other with increasing penalization. The coefficients of death rates due to ischaemic heart disease and of death rate due to chronic illness, for instance, seem to converge when more penalization is performed. Our simulation studies have shown that this property results in better estimation of the regression parameters under multicollinearity, however no clear grouping structure can be identified using these methods. The shrinkage paths can at most be indicative for any grouping structure in the covariates. The PGEE fit provided a selection of all main determinants of female life expectancy in Europe, even in case of high correlation amongst the different covariates. In this manner, six specific death rates (due to ischaemic hearth disease; chronic diseases, pneumonia; cancer; bronchitis, asthma or emphysema; overall infant mortality) turned out to be the 'big fish' [30] correlated and all predictive for lower average female life expectancy. Besides these identified death rates vaccination against pertussis, working hours per week, level of education, relative humidity and birth rate were all predictive for higher

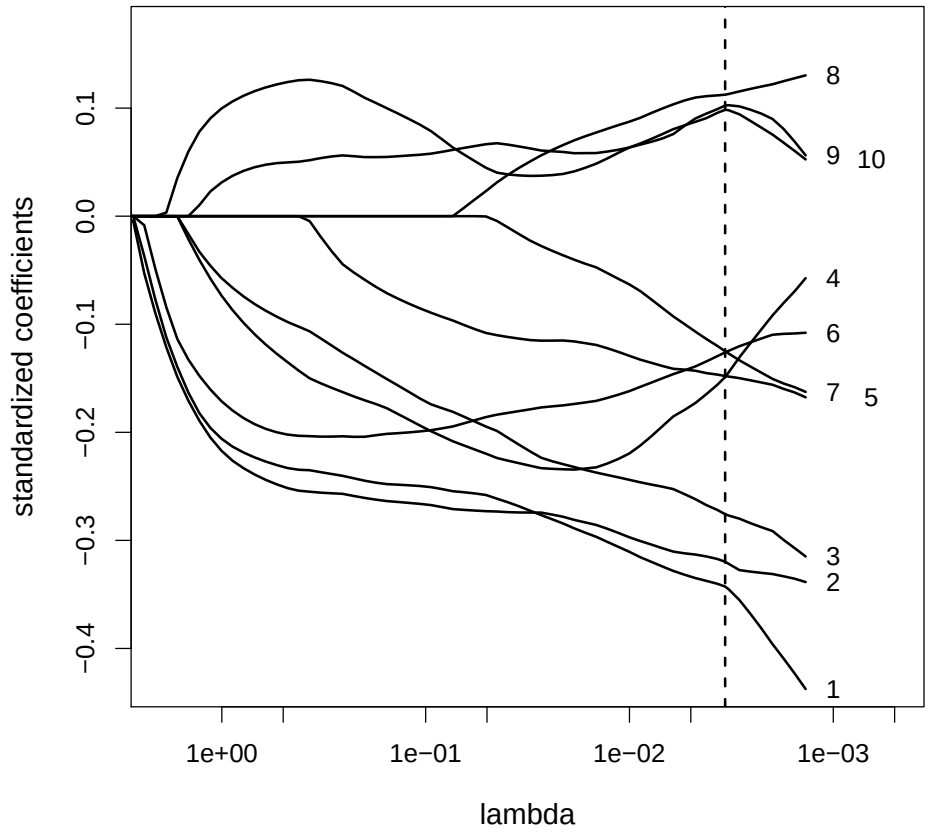

Figure 2.1: EN plot: Standardized coefficients for the ten largest coefficients at optimal (α, λ) combination, as a function of λ. λ is indicated in reverse log-scale. The coefficients are numbered by their ordering of the EN-fit as in Table 2.5

female life expectancy, while alcohol consumption and the percentage of people who believe that most people can be trusted predicted lower average female life expectancy. Penalized estimating equations can generally be applied to identify determinants for health outcomes as illustrated by this case study.

2.6 Discussion

In this chapter we addressed the problem of variable selection in longitudinal data under multicollinearity and time-dependence. We proposed using the PGEE estimator under working independence to identify the most important cross-sectional associations in this context. In order to deal with potential multicollinearity, the use of a penalty function combining both the sparsity and grouping effect was proposed, namely the EN or the SCAD$_{L2}$. We proved the grouping effect as a consequence of the convexity of the penalty function and established the conditions for the SCAD$_{L2}$ to be convex. An additional consequence of this convexity is the avoidance of the multiple roots problem in penalized GEE with the SCAD penalty, mentioned in Wang et al. [26].

Asymptotic theory reveals that both the EN and the SCAD$_{L2}$ penalty functions can achieve a consistent fit, however only the SCAD$_{L2}$ has the additional property of selection consistency. This is also reflected in our simulation studies were the SCAD$_{L2}$ outperformed all other methods (ordinary GEE, LASSO, ridge, EN, SCAD) with respect to prediction performance. Although the SCAD$_{L2}$ displayed overall better prediction performance this might not always be the case. In practice we recommend exploring variable importance using EN-paths and base final inference on the model selected (EN or SCAD$_{L2}$) through cross-validation.

Combining penalty functions has proven beneficial for selection and prediction, however this requires the selection of additional tuning parameters. In our data example we used cross-validation to select these parameters, which is computationally intensive. Establishing appropriate information criteria is crucial to the further development of penalty methods within GEE.

Adaptive versions of the LASSO and the EN [29, 31] have not been considered as alternatives to the SCAD and the SCAD$_{L2}$ in this work. In ordinary regression these penalty methods achieve selection consistency by using adaptive weights to different coefficients within the penalty function. These weights are the inverse of an initial estimate. In this manner larger initial coefficients are penalized less. The asymptotic theory in does not incorporate adaptive versions of the penalty functions with weights

dependent on the data at hand. Moreover in the presence of a large number of covariates, getting a good initial estimate is not feasible. A small simulation study (not included) suggest that the performance of the PGEE with the adaptive EN is only slightly better then the PGEE with the EN penalty, when a small number of potential covariates is present. We have also explored an adaptive SCAD_{L2}, but this performance was generally worse than the ordinary SCAD_{L2}.

We limited ourselves to look for cross-sectional associations in the Gaussian setting with an exploration of the binomial case. The development of asymptotic theory for the non-Gaussian setting and adaptations to the penalty function to incorporate lagged covariates are topics for future research. Asymptotic theory developed in Dziak [6] and extended in this work cannot be employed in the non-Gaussian context because of the absence of an objective function. Asymptotic theory in the broader context of penalized estimating functions has also been described by Johnson et al. [16]. This approach might be fruitful to derive asymptotic properties for the SCAD_{L2}.

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Table 2.5: Standardised coefficients for the PGEE estimator with both EN and $SCAD_{L2}$ penalty function. Both response and covariates were standardised before applying penalization.

	EN fit		$SCAD_{L2}$ fit	
Variable	Order	Stand Coeff	Order	Stand Coeff
Death rate due to ischaemic heart disease	1	-0.343	1	-0.343
Death rate due to chronic diseases	2	-0.320	3	-0.259
Death rate due to pneumonia	3	-0.276	2	-0.284
Death rate due to cancer	4	-0.149	5	-0.144
Death rate due to bronchitis asthma & emphysema	5	-0.148	8	-0.130
Infant deaths per 1000 live births	6	-0.126	9	-0.128
Percentage of urban population	7	-0.125	4	-0.166
Percentage of infants vaccinated against pertussis	8	0.112	13	0.117
Uncertainty Avoidance Index	9	0.102	7	0.136
Death rate of AIDS	10	0.098	6	0.140
Relative humidity (average dew point in degrees Celsius)	11	0.094	16	0.094
Hours worked per week of full time employment	12	0.084	14	0.097
Expectancy of educational level in years	13	0.080	10	0.123
Percentage of people who believe that most people should not be trusted	14	0.076	17	0.090
How strongly people find having experts, not government, make decisions for a country a bad thing	15	-0.071	12	-0.118
Birth rate	16	0.065	11	0.122
Pure alcohol consumption, liters per capita	17	-0.057	15	-0.096

Table 2.5: Standardised coefficients for the PGEE estimator with both EN and $SCAD_{L2}$ penalty function. Both response and covariates were standardised before applying penalization, continued

	EN fit		$SCAD_{L2}$ fit	
Variable	Order	Stand Coeff	Order	Stand Coeff
Women to men ratio	23	0.016	27	0
Private households' out-of-pocket payment on health as % of total health expenditure	24	0.012	36	0
% of people attaining the educational level of upper secondary school	25	-0.006	28	0
Practicing physicians per 100,000	26	-0.004	34	0
Individualism	27	0.000	22	0
Masculinity	28	0	21	0
Power Distance Index	29	0	23	0
Total health expenditure, purchasing power parity in dollar per capita	30	0	24	0
Average number of people per room in an occupied housing unit	31	0	25	0
Death rate due to accidents	32	0	26	0
Standard deviation of absolute humidity	33	0	29	0
How strongly respect for a authority is perceived as a bad thing	34	0	30	0
How strongly atheist versus religious people describe themselves	35	0	31	0
Poverty rate	36	0	32	0
Average Population Density per km^2	37	0	33	0

Table 2.5: Standardised coefficients for the PGEE estimator with both EN and $SCAD_{L2}$ penalty function. Both response and covariates were standardised before applying penalization, continued

	EN fit		$SCAD_{L2}$ fit	
Variable	Order	Stand Coeff	Order	Stand Coeff
Public sector expenditure on health as % of total government expenditure.	38	0	35	0
Hospital beds per 100,000 inhabitants	39	0	37	0
Death rate due to chronic liver disease	40	0	40	0
Death rate due to diabetes Mellitis	41	0	41	0
Death rate due to alcohol abuse	42	0	42	0

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Chapter 3

Extensions and alternative methods

In the previous chapter we studied the properties of Penalized Generalized Estimating Equations to select the most important covariates in longitudinal data analysis under multicollinearity and time dependence. Using penalty functions possessing selection and grouping properties such as the EN and the SCAD$_{L2}$ proved particularly useful to select time dependent covariates on the basis of their cross-sectional association with the response when multicollinearity is present. In this chapter we broaden the scope and discuss new literature, alternative methods and give recommendations for future research to deal with multicollinearity, time dependent covariates and variable selection in longitudinal data analysis. We start exploring extensions of PGEE by clarifying a possible conflict between the grouping effect and conditions for the asymptotic properties to hold, discuss alternative penalty functions possessing the grouping effect, explore the option of group penalization methods to select both time dependent covariates and their time lags and recommend exploring significance testing in PGEE methods for future research. Penalization in the linear mixed model framework and variable selection by regression trees for longitudinal data are discussed as alternative methods to select the most important determinants of a longitudinal response. This overview does not aim to be exhaustive, we rather focus on what we believe to be important new developments and open issues to be investigated in future research.

3.1 Open issues and extending PGEE

3.1.1 Addressing multicollinearity by penalization

The SCAD$_{L2}$ penalty possesses the grouping effect when the penalty function is strictly convex, so when: $\lambda_2 > \frac{1}{2(a-1)}$. However for $\sqrt{n}$-consistency to hold we need the coefficient of the ridge part to go to zero asymptotically (precisely: $\lambda_2 = O_p(n^{-1/2})$). Combining these two conditions yields: $\frac{1}{(a-1)} = O_p(n^{-1/2})$. So a needs to grow with increasing sample size n: $a \geq (C\sqrt{n}+1)$ for a constant C and for some n onwards. If we take a look at the rate of penalization of the SCAD$_{L2}$ in the single parameter case:

$$\dot{P}_{SCAD_{L2}}(\theta) = \begin{cases} \lambda_1 + \lambda_2\theta & \text{if } \theta \leq \lambda_1, \\ \frac{(a\lambda_1-\theta)_+}{2(a-1)\lambda_1} + \lambda_2\theta & \text{if } \lambda_1 < \theta \leq a\lambda_1, \\ 0 + \lambda_2\theta & \text{if } \lambda_2\theta > a\lambda_1, \end{cases}$$

and apply the limit of a going to infinity:

$$\lim_{a\to+\infty} \dot{P}_{SCAD_{L2}}(\theta) = \begin{cases} \lambda_1 + \lambda_2\theta & \text{if } \theta \leq a\lambda_1, \\ 0 + \lambda_2\theta & \text{if } \theta > a\lambda_1. \end{cases}$$

We end up with an EN-penalty for a coefficient θ smaller than $a\lambda_1$ and only a ridge penalty for θ larger than $a\lambda_1$. This boundary below which parameters are penalized as the EN also needs to follow the asymptotic restrictions imposed on λ_1 and a. Perhaps the conditions on the ridge parameter λ_2 and hence on a might be less important as sketched above, since in the non-naive version of the SCAD$_{L2}$ the shrinkage of the ridge part is removed. The robustness of the asymptotic results of the non-naive SCAD$_{L2}$ PGEE estimator to conditions for the grouping effect to hold, require further investigation.

In Chapter 2 we only used the EN and SCAD$_{L2}$ penalty functions, both relying on a ridge component to provide the grouping effect. Naturally every strictly convex penalty function could be plugged in instead of the ridge part. The Octagonal Shrinkage and Clustering Algorithm (OSCAR) uses an alternative strictly convex penalty:

$$P(\boldsymbol{\beta}) = \lambda \left[\sum_{j=1}^{p} |\beta_j| + c \sum_{j<k} max(|\beta_j|, |\beta_k|) \right],$$

which employs a pairwise L_∞-norm in combination with a LASSO part [1] in ordinary least squares regression. Because of the octagonal shape (hence the name) of the constraint region equivalent to the penalty function, the estimator has the tendency to put parameters either to zero (as the LASSO) or exactly equal (if they are highly correlated) and hence possesses the so called exact grouping property. This exact grouping property is a consequence of using the pairwise L_∞-norm, which requires quadratic programming techniques for its solution. In the Gaussian case this penalty function could be implemented within PGEE framework and quadratic programming techniques employed. The properties of the resulting estimator remain to be investigated. A combination of SCAD and pairwise L_∞-norm would be also of interest to investigate in future research.

3.1.2 Time dependent covariates and group penalization

In the previous chapter we explained the issue of time dependent covariates in longitudinal data analysis. PGEE with working independence covariance matrix still allowed us to identify cross-sectional associations, demonstrated by simulation studies (Section 2.4) to work reasonably well even under a limited number of independent data points. However, using a working independence matrix for GEE when the data are far

from independent might not be very efficient [15]. An alternative and possibly more efficient approach to variable selection could be combining variable and lag selection, within the PGEE-framework by modifying the penalty function. We suggest group penalization as a possible way to construct such a penalty function. This would not require the working independence assumption and allow for a more efficient choice of the working correlation matrix.

In the last decade, group penalization methods such as the group LASSO [18], sparse group LASSO [7], group bridge [10] and group Minimax Concave Penality (MCP [3]) and others have been developed, aiming at variable selection at the group level, when a predefined grouping structure is present in the covariates. An application is to select the indicator variables representing a categorical covariate.

We use the group MCP penalty [3] as an illustration as to how these penalties might be put to work to simultaneous select time dependent covariates and their time lags to include in a longitudinal regression model:

$$P(\boldsymbol{\beta}) = \sum_{l=1}^{L} f_2 \sum_{j=1}^{p_l} f_1(\beta_{lm}), \tag{3.1}$$

with f_1 and f_2 two penalty functions, in Breheny and Huang [3] this is the MCP function with the same selection properties as the SCAD function, L is the number of variable groups and p_l the number of variables within a group l. Alternative model formulations are possible including different penalty functions e.g. the LASSO, but the general aim is to penalize variables as a group and possibly also within a group to select the group as a whole and possibly some elements within that group. Note that the meaning of group penalty is distinct from the grouping effect coined in the previous chapter.

Now for PGEE with time dependent covariates we could consider each time dependent covariate as a group of covariates constituted by the measurements at different time points. For example one can take for a time dependent covariate the same measurement time as the response and some previous, lagged measurements identified with their lag, i.e. the time difference with the observed response. The performance of the various group penalties in improving prediction accuracy and selection capability for both time dependent covariates and lag of each time dependent covariate was investigated by simulation studies in [17]. Even though the investigated group penalty methods could improve model prediction accuracy to some extent, variable selection was poor in even the most basic simulation examples. Selecting correct lags together with coefficients might require the development of more appropriate penalty functions. It might be a better idea to reformulate the selection problem by includ-

ing spline components to represent the time dependent covariates and select spline components instead. Alternative penalty functions and selecting spline components remain to be investigated within the PGEE framework. An other issue to investigate would be the bias-variance trade-off using non-independence working correlation matrices in conjunction with coefficient penalization. Depending on the type of study, using the exchangeability assumption instead of independence has been recommended from a bias-variance point of view in unpenalized GEE [15].

3.1.3 Significance testing as alternative to tuning parameter selection

Recently Lockhart et al. [12] routed penalization methods deeper into classical, frequentist statistics by constructing a significance test for LASSO penalized regression. Focused on the linear regression setup, the regression coefficients of a linear model $y = X\boldsymbol{\beta} + \varepsilon$; $\varepsilon \sim N(0, \sigma^2 I)$ can be estimated by LASSO penalized least squares:

$$\hat{\boldsymbol{\beta}} = \text{argmin}\frac{1}{2} \|\boldsymbol{y} - X\boldsymbol{\beta}\|_2^2 + \lambda \|\boldsymbol{\beta}\|_1 . \tag{3.2}$$

Now Lockhart et al. [12] derived the asymptotic distribution of the proposed covariance test statistic (T_k, Equation 3.3) to test the significance of entering the j^{th} predictor under the null hypothesis that the current model contains all non-zero coefficients:

$$T_k = \left(\left\langle \boldsymbol{y}, X\hat{\boldsymbol{\beta}}(\lambda_{k+1}) \right\rangle - \left\langle \boldsymbol{y}, X_A \tilde{\boldsymbol{\beta}}_{\boldsymbol{A}}(\lambda_{k+1}) \right\rangle \right) / \sigma^2 \xrightarrow{d} \text{Exp}(1), \tag{3.3}$$

with $\hat{\boldsymbol{\beta}}(\lambda_{k+1})$ the estimated regression coefficient from Equation 3.2 with λ_{k+1} the location at which the $(j+1)^{th}$ predictor enters the set of non-zero regression coefficients; X_A and $\tilde{\boldsymbol{\beta}}_{\boldsymbol{A}}$ represent the reduced covariate matrix and the reduced estimated regression coefficients respectively, including only elements in the set A which includes all non-zero regression coefficients included before the j^{th} coefficient along the penalization path. The expression is a difference of inner products which are similar to an uncentered covariance matrix.

This type of testing procedure might be extended to PGEE with LASSO, EN or SCAD$_{L2}$ penalties. It would circumvent the tuning parameter selection problem, clarify the selection process and provide a significance level along the penalization path. Given that the asymptotic Exp(1) has been shown to hold for the EN and the SCAD penalty as well [12, 5], and by the same reasoning we conjecture it holds also for SCAD$_{L2}$, it remains to be generalized to the PGEE context. This would require

investigating the properties of solution paths within PGEE and the influence of within subject correlation (possibly incorrectly) specified by the working correlation matrix, which might be a non-trivial matter. Nevertheless these results might eventually throw light on all selection procedures including stepwise selection which is current practice in GEE model selection.

3.2 Alternative methods

3.2.1 Penalized Linear Mixed Models

In recent years several attempts have been made to use penalization methods to select both random and fixed effects in the linear mixed effect model [13]:

$$y_{it} = \boldsymbol{X}_{it}\boldsymbol{\beta} + \boldsymbol{Z}_{it}\boldsymbol{b}_i + \epsilon_{it}, \tag{3.4}$$

with y_{it} the response vector of subject i at time t; $\boldsymbol{X}_{it}$ the matrix of covariates belonging to the fixed effects, $\boldsymbol{\beta}$ the vector of regression coefficients (fixed effects), $\boldsymbol{Z}_{it}$ the matrix of covariates belonging to the random effect vector $\boldsymbol{b}_i \sim N(\boldsymbol{0}, G)$ and ϵ_{it} the random error with components independent and identically distributed as $N(0, \sigma^2)$ (following [6]).

Fixed effects selection and regularization can be performed by directly penalizing the marginalized likelihood. Since random effects represent draws of a distribution instead of taking a concrete value that can be shrunk, the manner as to how random effects are penalized (and asymptotic theory), differs strongly with penalizing fixed effects and between different random effect penalization methods. One line of taught is penalizing the elements of a Cholesky-decomposition of the marginal covariance matrix of the response vector in a grouped manner [2, 11]. Another is penalizing only the variances belonging to the random effects directly and in a second step ensuring the positive definiteness of covariance matrices [14]. Both approaches imply putting random effects to zero by shrinking their variances to zero (see [13] for a review).

Fan and Li [6] propose yet another approach. By using a profiled likelihood for the fixed effects and doing posterior mode estimation based on error contrasts for the random effects, they disentangle fixed and random effects estimation and formulate the mixed model estimation problem as two seemingly independent objective functions to be minimized (our notation):

$$Q_\beta(\boldsymbol{\beta}) = \frac{1}{2}(\boldsymbol{y} - \boldsymbol{X}\boldsymbol{\beta})^T \mathrm{W}_z (\boldsymbol{y} - \boldsymbol{X}\boldsymbol{\beta}),$$

for fixed effects estimation and

$$Q_b(\boldsymbol{b}) = \frac{1}{2}(\boldsymbol{y} - \boldsymbol{Z}\boldsymbol{b})^T \boldsymbol{M}(\boldsymbol{y} - \boldsymbol{Z}\boldsymbol{b}) + \frac{1}{2}\sigma^2 \boldsymbol{b}^T G^+ \boldsymbol{b},$$

for random effects estimation. With $\boldsymbol{y}$ a response vector for all subjects stacked after each other, $\boldsymbol{X}$ a stacked matrix of covariates, $\boldsymbol{\beta}$ a vector of fixed effects, $\boldsymbol{b}$ a stacked vector of random effects, $\boldsymbol{Z}$ a stacked matrix of subject specific covariance matrices (see 3.4). G^+ is the Moore-Penrose generalized inverse of the covariance matrix of the random effects G, $M = \boldsymbol{I} - \boldsymbol{X}(\boldsymbol{X}^T\boldsymbol{X})^{-1}\boldsymbol{X}^T$ from taking error contrasts and $\mathrm{W}_z = (\boldsymbol{I}+\sigma^{-2}\boldsymbol{Z}G\boldsymbol{Z}^T)$ implies the dependency between the two optimization problems. Now Fan and Li propose making the two optimization problems independent by plugging in a proxy matrix instead of the covariance matrix of the random effects G, i.e. treating the covariance matrix as a nuisance, an idea similar to GEE.

Now given these two objective functions, we can add a penalty:

$$Q_\beta^P(\boldsymbol{\beta}) = Q_\beta^P(\boldsymbol{\beta}) + P_\beta(\boldsymbol{\beta}),$$

$$Q_b^P(\boldsymbol{b}) = Q_b^P(\boldsymbol{b}) + P_b(\boldsymbol{b.k}),$$

with $P_\beta(\boldsymbol{\beta})$ a penalty function on the fixed effects and $P_b(\boldsymbol{b.k})$, with $\boldsymbol{b.k} = \left(\sum_{i=1}^N \beta_{ik}^2\right)^{1/2}$ a penalty on a group of random effects to insure the possibility of shrinking all random effects of a type to zero. Fan and Li [6] employ the SCAD-penalty or LASSO-penalty functions. Notice that for the random effect case there is already a ridge type penalty included as a special case of $\boldsymbol{b}^T G\boldsymbol{b}$. For practical use, the authors recommend starting with fixed effects selection using the penalized least squares by ignoring all random effects to lower the fixed effects dimension to below sample size and than to iterate between random and fixed effects selection, one time or several times. In summary this approach is very closely related to our proposed PGEE-estimator, whereby the working covariance matrix is informed by a random effects interpretation on which also selection and regularization can be applied. Naturally also penalty functions possessing the grouping effect could be incorporated for fixed effects estimation and since in the Gaussian case the optimization problem is equivalent, the same properties hold. For penalizing the random effects, there is already a ridge component included and adding an additional ridge component does not seem useful. In future research the random effects could be penalized as to incorporate mixture models and penalizing random and fixed effects together might be considered as well.

3.2.2 Non-parametric methods

Regression trees are a collection of popular non-parametric regression methods consisting of consecutively partitioning the covariate set by binary splits using some splitting criterion [4]. This generates a growing tree structure, which continues growing until some stopping criteria is satisfied, resulting in the final split called terminal nodes. Prediction can then be performed by using the mean value of the response for all observations classified within these terminal nodes. Recently random effects-expectation maximization regression trees (RE-EM) have been proposed by Sela and Simonoff [16], Fu and Simonoff [8], who extended existing regression tree algorithms to longitudinal and clustered data by incorporating them into the linear mixed model framework.

The idea is fitting a non-linear mixed effects model:

$$y_{it} = Z_{it}\boldsymbol{b}_i + f(x_{it1}, \ldots, x_{itk}) + \epsilon_{it},$$

whereby the function $f(x_{it1}, \ldots, x_{itk})$ is estimated by a regression tree algorithm, grown on $y_{it} - Z_{it}\boldsymbol{b}_i$, the response minus the subject specific effects (see Equation 3.4). Since the random effects $\boldsymbol{b}_i$ are unknown Sela and Simonoff [16] proposed initializing the random effects as zero, growing a regression tree on $y_{it} - Z_{it}\hat{\boldsymbol{b}}_i$. Next re-estimating the random effects by fitting a linear mixed model: $y_{it} = Z_{it}\boldsymbol{b}_i + \sum_p I(\boldsymbol{X_{it}} \in g_p)\mu_p + \epsilon_{it}$, with the same mean structure as the regression tree, represented by a set of indicator functions $I(\boldsymbol{X}_{it} \in g_p)$; with g_p ranging over all terminal nodes of the tree; μ_p are the fixed effects to be estimated by the linear mixed effects model. Iteration between random effects estimation and mean structure estimating by growing a regression tree is performed until convergence.

According to Fu and Simonoff [8] this approach can deal with time dependent covariates since splitting might occur on each covariate time point. So the regression tree method can be considered an alternative to penalization methods for determining the most important predictors in longitudinal data analysis with time dependent covariates. Although regression tree methods require little assumptions, are intuitive, easily interpretable and can deal with with non-linearities, the resulting estimator has problems recovering additive structures, has a non-smooth regression surface, and has a high variance and is in general unstable (for discussion see [9]). This instability problem will be aggravated by multicollinearity and adding several measurements of time dependent covariates will cause multicollinearity in the covariate set. Giving more specific advice on which method to use to determine the most important predictors in longitudinal data analysis requires comparative simulation studies.

3.3 Conclusion

Asymptotic results and simulation studies revealed the effectiveness of PGEE to simultaneously select and estimate the most important variables in longitudinal data analysis. The additional grouping effect possessed by the EN and SCAD$_{L2}$ penalty functions supports estimation and selection under multicollinearity. Using the independence working correlation for selection of time-dependent covariates and estimating their cross-sectional effects is shown in simulation studies and a data example to be a convenient method for determinant selection. However caution is needed, when the research interest is not related to cross-sectional associations and the number of observations per subject are greater. In that context, lag selection is recommended and PGEE with group penalization might be an option to be explore in future research in conjunction with exploring the impact of using the non-independence working correlation matrix. However, this might require representing the time dependent variable by a spline function and the development of new penalty functions.

To better deal with multicollinearity issues, alternative penalty functions possessing the exact grouping effect could be incorporated in either the PGEE or PLMM framework, this would have the additional advantage of recovering the grouping structure but might be computational intensive. For the PLMM framework new work could consider penalizing random and fixed effects jointly.

From a theoretical point of view the discovery of significance tests for the LASSO and related penalty methods could shed light on the influence of variable selection by penalization on significance testing. Generalization of that discovery to the longitudinal context merits further investigation.

The development of alternative methods to PGEE such as PLMM and more flexible methods such as RE-EM regression trees greatly extend the toolbox of statisticians working in variable selection in a longitudinal data setting. Choosing between various methods should primarily be driven by the research aims. Nevertheless there is a general lack of comparative studies across methods. Continuing development of more flexible longitudinal analysis methods merits future research because it opens a vast and interesting field of applications.

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Part III

Antibiotic consumption

Chapter 4

Antibiotic use and resistance

4.1 History of antibiotics and resistance

The discovery that bacteria could not proliferate in the vicinity of certain types of fungus by Alexander Fleming in 1928 revolutionised the treatment of bacterial infections. He discovered that specific fungi produced an organic chemical, *penicillin* that inhibited bacterial growth. This substance was the first antibiotic used to treat bacterial infection 12 years later and strongly reduced the bacterial disease burden from then on, knowing that before antibiotics there was essentially no treatment [6]. With the increased use of antibiotics some bacterial species developed resistance mechanisms eroding the antibiotics treatment effectiveness. To counter this, new antibiotics were developed. An evolutionary arms race took off between the human side developing new antibiotic compounds and the bacterial side developing resistance mechanisms.

Recent evidence suggests antibiotic resistance to predate antibiotic treatment. The origins of genetic features leading to resistance might have had another function in the past such as allowing bacterial growth in reactionary chemical environments such as in the presence of some types of metals [3]. Even for the first treatment with penicillin, some bacteria could produce an enzyme penicillinase neutralising its effect. [1].

Regardless of these recent discoveries, there is a general scientific consensus that historic antibiotic use has led to the current high resistance levels [7]. If this trend persists we risk to enter a post-antibiotic era where the human population is without cure for bacterial infections (for more information see [6]). To avoid or at least postpone this dismal scenario, one should be careful with the current arsenal of antibiotics. Especially since the development of new antibiotics has stalled in the last decade [6]). In this thesis part we study the determinants of antibiotic consumption and resistance. In the subsequent paragraphs, basic concepts of antibiotic use and resistance are explained, the Belgian and European antibiotic consumption scene is set and our main research into determinants of antibiotic dispensing is outlined.

4.2 Concepts

- *Bacteria* are microorganisms consisting of only one procariotic cell. They are the smallest living entities in the biosphere. Meaning that they can reproduce by themselves, unlike a virus which needs an external cell e.g. animal or plant cell to replicate its genetic material. Different bacterial species inhabit a vast number of different ecological niches such as the the soil, the earth's crust, the surface of the human skin and inside the human body. Usually bacterial presence within

the human body is benign, useful and even necessary. For example humans rely strongly on the bacterial flora in their intestine to aid in digestion. Despite the usefulness of bacteria for humans, they can cause disease potentially leading to death. Examples are infected wounds caused by Streptococcus pyogenes; diarrhea caused by a salmonella infection in the digestive system and pneumonia caused by the Streptococcus pneumoniae.

- *Antibiotics* are a class of organic molecules that inhibit microbial growth by specific interactions with bacterial targets, without any consideration of the source of the particular compound or class [6]. Penicillins are the first class of antibiotics used to treat disease. There is a great variety in antibiotics in terms of chemical constitution, functionality and spectrum of usage. So are small-spectrum antibiotics, active against a limited number of bacterial species, whereas broad-spectrum antibiotics inhibit the growth of a larger number of bacterial types.

- Due to the selective pressure of antibiotic use, increasing numbers of bacteria exhibit partial or full *antibiotic resistance*, meaning bacterial growth is less or not inhibited by the presence of a specific antibiotic. Mechanistically this resistance, for example against Macrolides, can by realized by very different means such as by actively pumping out the antibiotic substance (efflux); modifying the cell membrane (target-site modification) or neutralising the antibiotic by excretion of neutralising chemicals [8]. The development of antibiotic resistance is a textbook example of evolution by natural selection. Because the increased prevalence of antibiotic compounds in the bacterial environment, phenotypic mutants, which can resist a slightly higher dosage of antibiotics, have an edge in competing for resources. Phenotypic mutants can appear due to random mutation or by taking up genetic resistance coding from surrounding bacterial types (horizontal gene transfer), which is more likely. Given a continuous gradient of antibiotic exhibition or concentration, resistance features might accumulate over time, leading ultimately to full resistance and to further proliferation of genetic resistance elements to increasing proportions of antibiotic resistance within the bacterial species and even to other species by horizontal gene transfer.

- The *European Antimicrobial Resistance Surveillance System* (EARSS; `http://www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/index.aspx`) is an ECDC sponsored on-line database of antibiotic resistance levels informed by national surveillance systems for public health

research.

- The *European Surveillance of Antimicrobial Consumption* (ESAC-Net: `http://www.ecdc.europa.eu/en/activities/surveillance/esac-net/pages/index.aspx`) is a Europe-wide network of national surveillance systems, providing European reference data on antimicrobial consumption. ESAC-Net collects and analyses data on antimicrobial consumption from the European Union (EU), the European Environment Agency (EEA) and the European Free Trade Association (EFTA) countries, both in the community and in the hospital sector.

- The *ATC/DDD-methodology* is a standard of medication and dosage developed by the World Health Organisation (WHO) for drug utilization research (see `http://www.whocc.no/atc_ddd_methodology/`). In this methodology, medications are classified by their *Anatomical Therapeutic Chemical* (ATC) according to the organ or system on which they act and their therapeutic, pharmacological and chemical properties. To compare the quantity of use, a general unit is used: The *Daily Defined Dosage* (DDD), which is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults [9]. Although this general unit is useful for cross-country comparison, recently a Belgium study discovered that this measure should be used with caution and compared to other measures such as treated individuals, packages and prescriptions because DDD definitions might change over time [5]. Also the number of DDDs might not be the best correlate of antibiotic resistance.

- *Belgian Antibiotic Policy Coordination* (BAPCOP; `http://www.bapcoc.be`) is an organisation aimed at informing the general public about antibiotic use (e.g. `http://www.health.belgium.be/Antibiotiques`) and promoting the prudent use of antibiotics by media campaigns to the general public and focused campaigns to medical professionals.

4.3 Antibiotic use in Belgium and Europe

The ESAC studies brought large differences in both quality and quantity of prescribing across European countries to the surface. The number of DDDs per thousand inhabitants per day (DID) varied by as much as a factor 4.3 in 2009 (see Figure 4.1). Furthermore, despite awareness of the antibiotic resistance peril the antibiotic dispensing volume in DIDs increased for most European countries between 1997 and

2009, accompanied by a trend towards an increasing share of broad-spectrum antibiotics such as amoxicillin/clavulanic acid, macrolides and quinolones. Observed correlations between the seasonality of dispensing and the yearly amount of use suggest that a part of this difference can be explained by antibiotic usage for viral infections [2].

As you can see in Figure 4.1, there seems to be a north-south divide within Europe, with the southern countries such as Greece, Italy and Cyprus displaying much higher consumption figures than the northern countries such as Scandinavia, Switzerland and the Netherlands. The difference between Luxembourg, France and Belgium (high use) on the one hand and the Netherlands (low use) on the other hand is striking.

Throughout Europe antibiotic awareness campaigns try to influence trends in antibiotic prescribing by promoting more prudent antibiotic usage [4]. Hopefully those campaigns can invert the rising antibiotic trends. The effects of these campaigns remain difficult to distinguish from secular trends, but for Belgium, at least the number of antibiotic prescriptions per capita has decreased in recent years [5].

4.4 Determinants of antibiotics consumption

Although historic selective pressure distinct from antibiotic treatment might have primed the bacterial genomes for developing antibiotic resistance elements, antibiotic use is the current main driver of the high levels of antibiotic resistance we see today. Since antibiotic use is a human cause, policy might influence how antibiotic resistance figures, and associated bacterial disease burden may evolve over time. Unfortunately the relation between antibiotic consumption policy and resistance is too complex a problem to predict the impact of different antibiotic policy measures. For instance antibiotic consumption (and thence potential antibiotic policy) might exert an influence on antibiotic resistance at different levels: the individual patient, the hospital setting and population level. Various fundamental questions such as the influence of antibiotic dosing on resistance development are not well understood. Nevertheless, science should aim to inform smart antibiotic policy, be it with caution. A first step towards a better understanding of the problem of antibiotic resistance is well documenting its evolution together with its driving cause: antibiotic consumption. The ESAC project is for Europe a valuable foundation for the first step. A second step, the subject of this thesis part, is looking for associations between antibiotic prescribing, resistance and potential determinants. A third step is to move from mere associations to establishing plausible causal links and developing predictive mathematical models.

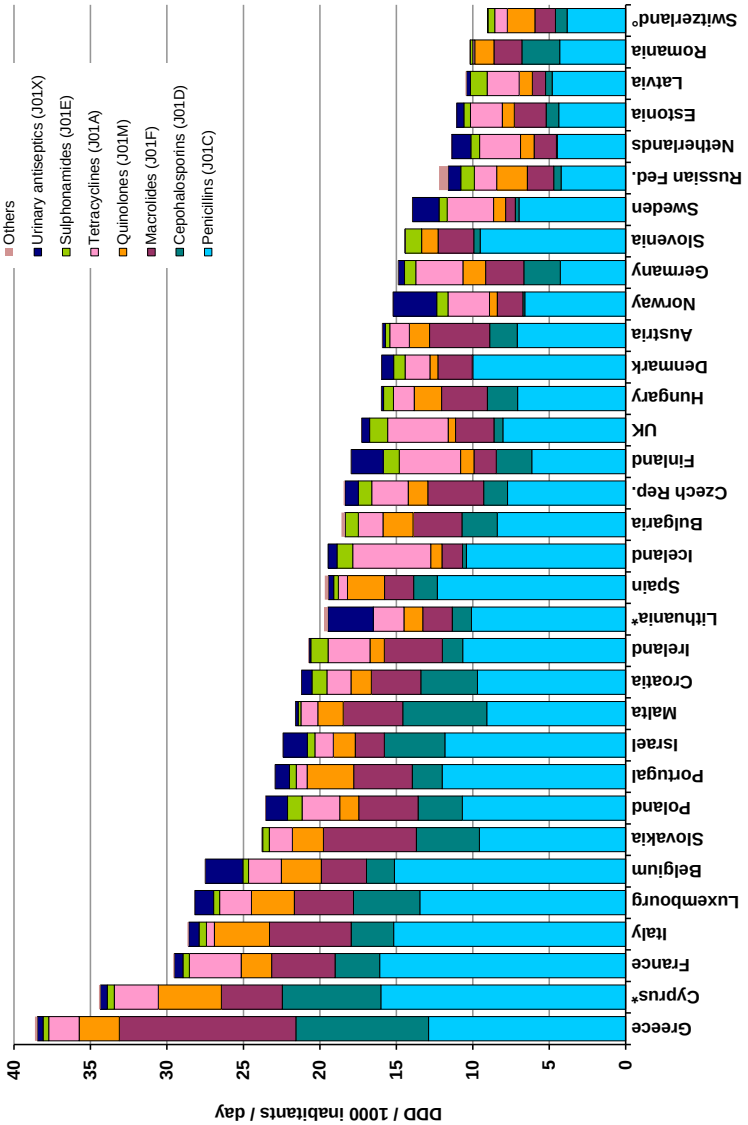

Figure 4.1: Comparison of total outpatient antibiotic use in 33 European countries in 2009 in DID (2004 data for Switzerland). For Cyprus and Lithuania, total care data are used. The category Cephalosporins includes carbapenems and monobactams; Macrolides includes lincosamides and streptogramins; Sulphonamides includes trimethoprim; Urinary antiseptics includes glycopeptide antibacterials, polymyxins, fusidic acid, imidazole derivatives, nitrofuran derivatives and other antibacterials; and Others includes J01B, J01G and J01R. Taken from [2] with permission.

We chose to focus on outpatient antibiotic use, which takes up the bulk of prescriptions. The hospital setting is also important to study specific disease burdens, but it requires an entirely different methodology outside the scope of this thesis.

4.4.1 Patient-prescriber level

Bacterial resistance to antibiotics, driven by antibiotic consumption, imposes a major threat to the effective treatment of bacterial infections. In addition to reducing the amount of antibiotics prescribed, avoiding broad-spectrum antibiotics could extend the lifetime of the current arsenal of antibiotic substances. Therefore in Chapter 5, we documented prescriber and patient characteristics associated with the choice between amoxicillin and broader spectrum alternatives (co-amoxiclav or moxifloxacin) in recent years in Belgium. To this aim complete reimbursement claims data (2002-09) for antibiotic prescriptions in outpatient care, including patient and prescriber characteristics, were collected for both young children (1-5 years) and the adult population (30-60 years). A backwards selection procedure within GEE retained the most relevant determinants. We found the age, gender and social category of the patient to be predictive of the extent to which amoxicillin was prescribed instead of the broader-spectrum alternatives, with female patients generally taking a higher proportion of amoxicillin than male patients. The age category of 40-44-year-old prescribers exhibited a preference for broad-spectrum antibiotics compared with both younger and older age groups. Significant interactions between the region and the prescribers qualification (general practitioner or paediatrician) on the choice of antibiotic for children were found. In conclusion patient (age, gender and social category) and prescriber characteristics (age, gender, region and qualification) had an influence on whether amoxicillin or the alternative broad-spectrum antibiotics were prescribed. These findings should help policymakers to better target future campaigns to promote prudent prescribing of antibiotics.

4.4.2 Country level

Supplementary to investigating determinants of outpatient use at the smallest level of the individual prescription, we zoomed out to the country level in Chapter 6. This is the scale on which health care policy differs due to political choices and socioeconomic differences. Concretely we aimed to identify key determinants explaining countryyear variations in antibiotic use and resistance. Ambulatory antibiotic use data [in defined daily doses per 1,000 inhabitants per day (DIDs)] for 19 European countries from 1999 to 2007 were collected, along with 181 variables describing countries in terms of their

agriculture, culture, demography, disease burden, education, health care organisation and socioeconomics. After assessing data availability, overlap and relevance, multiple imputation GEE was applied with a stepwise selection procedure to select significant determinants of global antibiotic use (expressed in DIDs), relative use of subgroups (amoxicillin and co-amoxiclav) and resistance of Escherichia coli and Streptococcus pneumoniae. Relative humidity, health care expenditure proportional to gross domestic product, feelings of distrust, proportion of population aged over 65 years and availability of treatment guidelines were observed to be associated with higher total antibiotic use expressed in DIDs. Restrictions on marketing activities towards prescribers, population density, number of antibiotics, educational attainment and degree of atheism were found associated with a lower number of total DIDs used. Relative prescribing of amoxicillin and co-amoxiclav was mainly determined by health care system choices [e.g. general practitioner (GP) registration and restricted marketing]. Specific antibiotic use was found to be a significant determinant of resistance for some but not all drug/organism combinations. Incentives to stimulate the GP gate keeper function were associated with lower levels of resistance, and life expectancy at age 65+ and atheism were associated with more resistance. So myriad factors influence antibiotic use and resistance at the country level and an important part of these can be modified by policy choices.

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Chapter 5

Patient-physician level determinants

5.1 Introduction

Rising antibiotic resistance presents a major public health threat, jeopardizing the future effective treatment of bacterial infections. The within-patient causal link between antibiotic consumption and the development of bacterial resistance to antibiotics has been shown conclusively by a double-blind placebo-controlled trial [18]. In addition to this experimental evidence, observational studies consistently confirmed the increased risk of infection with a resistant strain after antibiotic consumption in the individual patient [8].

This development of resistance in the individual patient, along with population-level selection mechanisms [16] gives rise to a population-wide antibiotic resistance problem, as shown by using mathematical models [21] and observational studies. Goossens et al. [10] for instance, found significant associations between the volume of use in a geographical area and the population-level resistance in that area.

Besides prescription or package volumes, other quality indicators of antibiotic prescribing practices are of importance, such as defined daily dose (DDD), efficiency in treating the illness, duration of treatment and spectrum [12]. Since narrow-spectrum antibiotics exert a less extensive ecological pressure than broad-spectrum antibiotics, they leave bacterial populations more susceptible to future antibiotic treatments. Mathematical models suggest that the decline of resistance after cessation of the use of a specific antibiotic in the community is typically slower than the increase due to current consumption [3]. Thus, a rapid reduction in resistance due to lowering consumption seems doubtful. Therefore, prudently prescribing the antibiotic of choice is highly important in sustaining the effectiveness of our current range of antibiotics.

In view of the expected impact of antibiotic consumption on the public health threat of resistance, the European Surveillance of Antimicrobial Consumption (ESAC) network strived to correctly document total systemic antibiotic use, its evolution and composition [1]. In addition to this increased surveillance of antibiotic use, several countries have implemented awareness and control campaigns in order to educate the public and influence physicians' prescribing habits [13]. By targeting healthcare professionals and the general public, such interventions aim to reduce the quantity and improve the quality of antibiotic prescribing in the short run, and reduce the burden of antibiotic resistance in the longer run. Some empirical evidence indicates the effectiveness of such campaigns, [6, 9], but to date such evidence remains relatively rare [14] because the specific contribution of campaigns to changes in antibiotic use over time is difficult to distinguish from other influences.

A comparison of the quality of antibiotic use between European countries in 2004

and 2009 listed Belgium with Luxembourg, Italy, France and Spain at the lower end of the quality ranking based on dispensed volume of both broad-spectrum and all antibiotics [2]. This comparison especially revealed large differences with the Nordic countries as well as with the Netherlands, a neighbouring country of Belgium, where consumption in DDDs per 1,000 inhabitants is less than half that of Belgium, and adherence to guideline-recommended antibiotics is higher. This fact illustrates there is still ample room for improvement through interventions.
Therefore, in this study we set out to identify groups of patients and prescribers who deviate from the average in terms of their preference for either amoxicillin, recommended as first-choice antibiotic for most respiratory infections in Belgium [5], or broader spectrum antibiotics such as co-amoxiclav and moxifloxacin. This information can serve to better target future intervention campaigns.

5.2 Methods

5.2.1 Reimbursement claims data

We base our analysis on all reimbursement claims data (2002–09) from Belgium. For the purpose of the analyses we divided its 10.6 million inhabitants between three main regions: the Flemish region (58%), the Walloon region (32%) and the Brussels Capital region (10%). Belgium has an accessible healthcare system with a generous basic basket of healthcare available to the entire population through compulsory social health insurance [23]. The impact of supplementary private insurance on healthcare consumption is mainly limited to billing practices in hospitals and dental care [24]. Although some socio-economic differences exist between the regions, we assume no major differences in infectious disease burden, which is a plausible assumption, given the size of the country, and the near-equivalence of the preventive public health programs. Socio-economic differences have been controlled for at the patient level rather than at the regional level.
Prescription-level data on antibiotic use was sourced from the national database of the Intermutualistic Agency (IMA), for the period 2002-09. The IMA database covers the entire insured population of Belgium and contains reimbursement claims data of seven sickness funds that manage compulsory health insurance in Belgium [23]. The extraction included, for each prescription, information on the prescriber (encoded), the insured individual (encoded) and the package. Self-employed individuals (10% of the currently insured population) were excluded from the analysis since their reimbursement status changed during the study period. We extracted information related

to 59,876,848 prescriptions.
Permission to study these detailed data was granted by the Sector Committee of Social Security and Health of the Commission for the Protection of Privacy (CPP), better known as the Belgian Privacy Commission (SCSZ/10/098 and SCSZ/10/103).

5.2.2 Data selection: time period, age groups and antibiotic classes

Since we were mainly interested in elucidating determinants of the choice of the antibiotic substance and not particularly in the time evolution of antibiotic consumption, we focused on the period from July 2008 to June 2009 (7,301,321 prescriptions). In this manner we avoided confounding with time effects and still covered a complete influenza season. The period July 2002 to June 2003 was additionally extracted for comparison.
The choice of the antibiotic as well as the amount used (in number of packages and DDDs) were stable in the age group between 30 and 60 years, but outside this age range we found the choice of the antibiotic to vary strongly with the patient's age (see Figure 5.1). Therefore, we focused the analysis in the current paper on two age groups: adults between 30 and 60 years and children between 1 and 5 years. For the adults, all prescriptions by general practitioners (GPs: licensed GPs with National Institute for Health and Disability Insurance number 003-004, GPs in training and other GPs), who were responsible for the vast majority of antibiotic prescriptions (76% between July 2008 and June 2009), were selected. Including specialist physicians would distort the focus of determinants in the choice of antibiotic prescribed since they encounter specific and distinct underlying pathologies, requiring specific antibiotic classes.
The age group of young children is important because of their substantial share (11% of all prescriptions) in total antibiotic use and because they form a key group for the transmission of infectious diseases. For this group we selected prescriptions of both GPs and paediatricians,who jointly accounted for 92% of all antibiotic prescriptions to children in the study period.
The definition of the antibiotic group was based on the Anatomical Therapeutic Chemical (ATC) classification system [26]. From the ATC subgroup J01, antibacterials for systemic use, we selected three commonly used antibiotic substances, which are used to treat respiratory tract infections, especially in Belgium: (i) amoxicillin (ATC J01CA04), (ii) co-amoxiclav (ATC J01CR02), and (iii) moxifloxacin (ATC J01MA14). These antibiotics differ in their antibacterial spectrum. Indeed, co-amoxiclav is a com-

bination of amoxicillin and clavulanic acid, a β-lactamase inhibitor, making this type of antibiotic still effective in combating β-lactamase-producing bacteria. Moxifloxacin has a broader spectrum as well, and is not recommended as the first-choice antibiotic in most, if not all, European countries [2] and should not be prescribed to children.

5.2.3 Study design

In order to identify specific prescriber and patient groups associated with more or less amoxicillin use, we regressed the odds of amoxicillin use as opposed to co-amoxiclav use against potential determinants. In the adult group under study, we also studied the odds of amoxicillin versus co-amoxiclav and moxifloxacin. In order to identify relevant factors for the choice for or against amoxicillin, the odds of amoxicillin versus relevant alternatives seemed a more direct and sensitive outcome measure than the proportion of amoxicillin to all antibiotics for systemic use.
Table 5.1 gives an overview of the variables (potential determinants) and categories included in the analyses. These variables represent a categorization of large patient and prescriber groups according to basic characteristics such as gender, age, region and social status. This list is limited but fully uses the information in the insurance claims database, which has the extra advantage of being unambiguous. Medically or socially relevant two-way interactions were considered. For the analysis of prescriptions to adults, interactions between the prescriber's gender, age category, qualification and the patient's gender, age, social category and diabetes indicator were included. Additionally, interactions between diabetes and age and gender of the patient were included, as well as interactions between the patient's low-income indicator and the patient's age and gender.
For the analysis of antibiotic prescriptions to young children, only the following interactions were considered: the interaction between gender of the prescriber and gender of the patient and the interaction between qualification and region of the prescriber. No interactions with the diabetes indicator of the patient were included because of the low number of diabetes patients in these age categories.

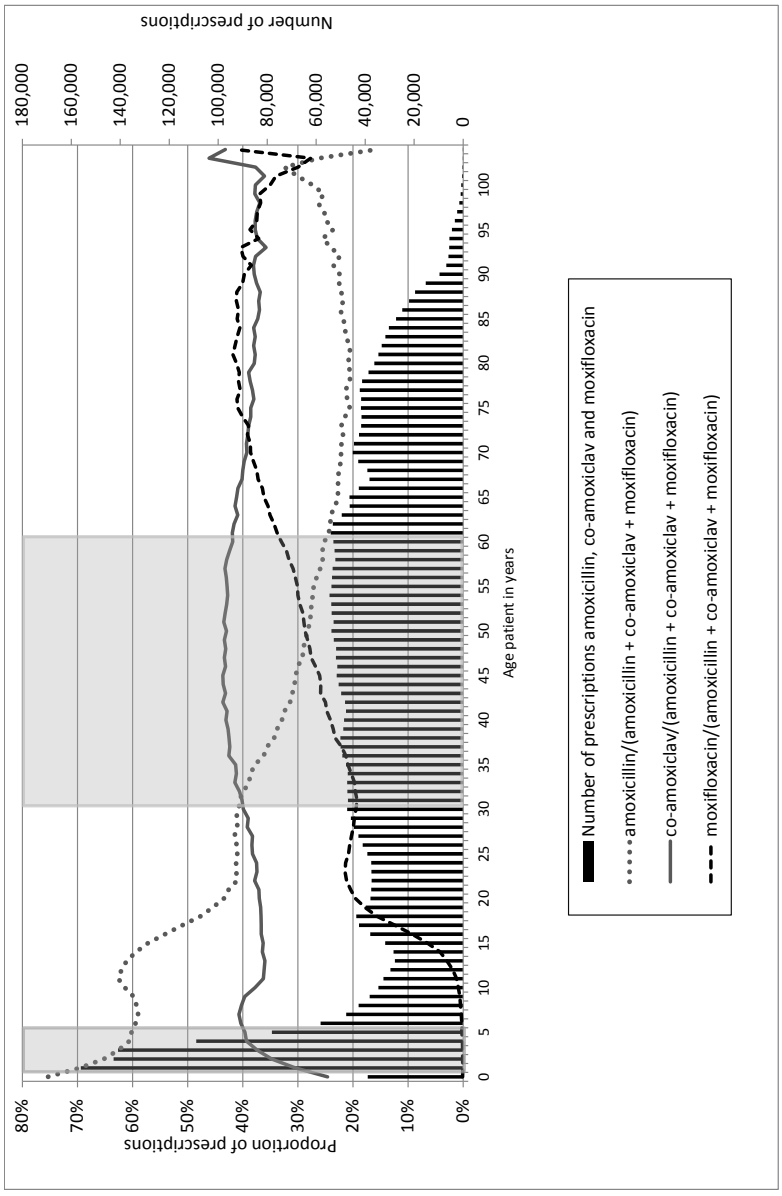

Figure 5.1: Total prescriptions for amoxicillin, co-amoxiclav and moxifloxacin with their respective proportions by age of the patient. The selected age groups (1-5 and 30-60 years) are marked by shaded rectangles.

Table 5.1: Determinants used in the analysis

Variable	Levels analysis adults	Reference category adults	Levels analysis children	Reference category children
Prescriber characteristics				
qualification	licensed GPs with NIHDI number 003-004, GPs in training, other GPs[a]	GP	GP; paediatrician	GP
gender	male; female	male	male; female	male
region	Flemish region; Walloon region; Brussels Capital region	Flemish region	Flemish region; Walloon region; Brussels Capital region	Walloon region[b]
active[c]	active; non-active	non-active	active; non-active	non-active
age	20-29; 30-34; 35-39; 40-44; 45-49; 50-54; 55-59; 60-64; 65-69; 70+	40-44	20-29; 30-34; 35-39; 40-44; 45-49; 50-54; 55-59; 60-64; 65-69; 70+	40-44
Patient characteristics				
age	age patient in years dived by 30		not included	
gender	male; female	male	male; female	male
reimbursement	higher reimbursement; no higher reimbursement	no higher reimbursement	higher reimbursement; no higher reimbursement	no higher reimbursement
diabetes	diabetes;no diabetes	no diabetes	diabetes;no diabetes	no diabetes
social category	active; unemployed; PWDO; other	active	not included	
low income[d]	indication of low income, no indication of low income	no indication of low income	not included	

Categorical variables were coded as indicators as opposed to a reference category. Differences in variables included and reference categories used between analyses for adults and children are indicated.

[a]GPs with National Institute for Health and Disability Insurance (NIHDI) number 001-002 (GPs with granted rights) or 007-008 (licensed GPs, rehabilitation specialists).

[b]A different reference category was purposely taken for children versus adults to enable illustration of the largest regional differences. The model fit was not dependent on the choice of this reference category and parameter estimates for the other variables were not influenced by this choice.

[c]An active prescriber was defined as a GP with at least 200 assigned patients, or a specialist physician with at least 200 patient contacts a year.

[d]A low-income patient was identified by being entitled to income guarantee for the elderly, subsistence level or a higher reimbursement of medical costs [Omnio status due to his or her difficult financial family situation (www.riziv.fgov.be/citizen/nl/medical-cost/general/omnio/faq.htm)].

5.2.4 Statistical methodology

Associations between antibiotic choice and both patient and prescriber characteristics were modelled using GEE (See Chapter 1 and [15, 27]), based on the binomial distribution with a logistic link function. This method yields consistent estimates of the population-averaged effects, treating the correlation between observations as a nuisance.
Since the prescriptions were nested within both the prescriber and the patient, whereby a patient is not limited to a unique prescriber, the GEE method must account for this. Therefore, we employed the adaptation to GEE for non-nested clustering implemented in SAS by Miglioretti and Heagerty [20], based on the working independence assumption. This approach achieves valid estimates and standard errors by combining two separate GEE fits: one with the prescriber and the other with the patient as cluster indicator.
All main effects presented in Table 5.1 were included in the final models. The decision of which interactions to include was based on a backward search based on the quasi-likelihood under the independence model criterion (QIC; [22]). We present the results as ORs with 95% CIs. Note that an interaction effect represents a ratio of ORs, and should be interpreted as a main effects modifier. If, for instance, we find an interaction effect between the gender and region of the prescriber, the interaction effect is to be interpreted as the OR of gender, given a region divided by the OR of gender for the reference region.

5.3 Results

Figure 5.1 shows the numbers and proportions of prescriptions for the selected antibiotics by patient's age. There is a generally decreasing trend with increasing age for amoxicillin and an increasing trend for moxifloxacin, both of which level off for the elderly. Furthermore, one can see a relatively stable proportion of prescriptions for co-amoxiclav over the lifespan. In the next sections,we discuss the results of subgroup analyses on two broad age groups of interest with a high volume of prescriptions, as shown by the bars and shaded areas in Figure 5.1.

5.3.1 Prescriptions to adults between 30 and 60 years old by GPs

Table 5.2 summarizes the results of the final selected models explaining variations in the odds of prescribing amoxicillin compared with co-amoxiclav only as well as co-amoxiclav and moxifloxacin combined. Prescriber–patient or within-prescriber interactions were selected but did not reach significance in explaining the choice for amoxicillin instead of these broader-spectrum alternatives. We found, however, a significant influence of the main effects of gender, region and qualification of the physician on the odds of prescribing amoxicillin. Physicians from the Walloon region had a lower preference for prescribing amoxicillin instead of either co-amoxiclav or moxifloxacin than physicians from the Flemish region. No significant differences between the Flemish region and Brussels region prescribers were observed. Female prescribers had a higher preference for amoxicillin than males compared with co-amoxiclav or moxifloxacin as well as with co-amoxiclav alone. Active prescribers had a lower preference for amoxicillin compared with co-amoxiclav and moxifloxacin as well as compared with co-amoxiclav alone. In the latter case, however, the effect did not reach significance.

The age of the prescriber was found to have a remarkable effect. The reference age category of 40-44 years old was less likely to prescribe amoxicillin than broader-spectrum antibiotics (co-amoxiclav or moxifloxacin) compared with younger aswell as with most older prescriber categories ($\geq$55 years). The youngest age category (20-30 years old) had a substantially higher preference for amoxicillin than all older prescribers. Compared with these observed age differences, the qualification of the prescriber was less influential. GPs in training showed a lower preference for amoxicillin than for broader-spectrum antibiotics compared with GPs of the same age category and gender who were not in training.

Patient characteristics may also contribute to the choice between amoxicillin and broader-spectrum alternatives. We found female patients at greater odds than males of having amoxicillin prescribed to them (versus co-amoxiclav alone, or versus co-amoxiclav and moxifloxacin). The difference between female and male patients was bigger when the patients came from a less favourable social category [i.e. unemployed or 'pensioners, widows, persons with disabilities and orphans' (PWDO)]. The PWDO category and the unemployed had, regardless of gender, lower odds of having amoxicillin prescribed instead of the two broader-spectrum antibiotics.

When studying the choice between amoxicillin and co-amoxiclav only, we found a significant effect of the patient's income and a significant interaction with the patient's

gender, which was absent in the comparison with co-amoxiclav and moxifloxacin combined. Having a lower income increased the odds of having amoxicillin prescribed instead of co-amoxiclav primarily for male patients. Patients with diabetes had lower odds of receiving amoxicillin instead of broader-spectrum antibiotics (co-amoxiclav). The patient's age influenced the type of antibiotic prescribed. Older patients in the group 30–60 years were less likely to receive amoxicillin. Table A.1 and A.2 in appendix, provide the amount of prescriptions and relative importance of prescriber and patient categories respectively, in antibiotic prescribing to adults between 30 and 60 years old in Belgium.

In order to assess whether our results would also apply to older age groups (i.e. >60 years), we refitted the identified models to older age groups per 10 year age class. Prescriber determinants (age, region, active or not, and qualification) were found to exert a similar influence as in the younger age group. The prescriber's gender was, however, no longer significant in predicting the choice of amoxicillin versus broad-spectrum alternatives. Differences in the age of the prescriber had the same sign but were less pronounced. The data also suggest a regional difference, not found for younger patients, with slightly higher rates of moxifloxacin prescribing to elderly patients (>60 years) in Brussels compared with Flanders. Patient characteristics were less relevant in predicting the choice for or against amoxicillin in elderly patients. Social category, income and diabetes were not found to be significant. The female gender of the patient was found to be a significant predictor of higher amoxicillin use compared with co-amoxiclav, but not when compared with co-amoxiclav and moxifloxacin.

5.3.2 Prescriptions to children between 1 and 5 years old by licensed GPs and paediatricians

Table 5.3 summarizes the selected models by age of the child to which the antibiotic was prescribed. Here we only modelled the odds of prescribing amoxicillin versus co-amoxiclav. Different prescriber and patient characteristics had a significant effect on this choice. A clear interaction between the region and the qualification of the prescriber was present over all patient ages. This indicates the difference in prescribing habits was strongly region dependent. Taking the size of the interaction into account, this implies that paediatricians of the Brussels Capital region prescribed a higher proportion of amoxicillin in comparison with GPs of that region. This contrasted with the reference region (Walloon region), where GPs prescribed a larger proportion of amoxicillin than paediatricians of that region. The Flemish region did not differ significantly from the reference Wallonia in this respect.

Table 5.2: Determinants of the odds of an amoxicillin prescription versus a co-amoxiclav prescription and of an amoxicillin prescription versus a co-amoxiclav or moxifloxacin prescription for patients aged between 30 and 60 years by licensed GPs and other GPs

Variable	Category 1	Category 2 (when interaction)	Amoxicillin vs. co-amoxiclav	Amoxicillin vs. co-amoxiclav or moxi-floxacin
Prescriber characteristics				
qualification	other		0.568(0.299-1.076)	0.556(0.290-1.066)
	GP in training		0.685(0.501-0.936)*	0.734(0.540-0.998)*
gender	female		1.070(1.018-1.124)**	1.098(1.045-1.153)***
region	Brussels		0.930(0.852-1.015)	0.989(0.908-1.078)
	Walloon		0.846(0.809-0.884)***	0.889(0.851-0.930)***
active	active		0.949(0.887-1.016)	0.880(0.822-0.942)***
age	20-29		1.642(1.455-1.852)***	1.580(1.402-1.780)***
	30-34		1.211(1.111-1.320)***	1.213(1.112-1.323)***
	35-39		1.134(1.047-1.227)**	1.130(1.043-1.224)**
	45-49		1.040(0.962-1.124)	1.061(0.981-1.147)
	50-54		1.020(0.943-1.102)	1.028(0.951-1.111)
	55-59		1.180(1.089-1.279)***	1.196(1.104-1.297)***
	60-64		1.201(1.091-1.321)***	1.195(1.086-1.315)***
	65-69		1.189(1.027-1.378)*	1.194(1.034-1.379)*
	70+		1.316(1.130-1.533)***	1.314(1.123-1.537)***
qualification*gender	other	female	1.039(0.664-1.624)	1.037(0.666-1.615)
	GP in training	female	1.206(0.992-1.467)	1.159(0.959-1.401)
Patient characteristics				
age			0.103(0.086-0.125)***	0.097(0.081-0.116)***
age^2			1.817(1.707-1.934)***	1.794(1.688-1.908)***
gender	female		1.258(1.243-1.274)***	1.210(1.196-1.225)***
reimbursement	yes		1.014(0.987-1.042)	1.030(1.007-1.054)*
diabetes	diabetes		0.874(0.847-0.902)***	0.815(0.714-0.931)**
social category	other		0.958(0.879-1.044)	0.999(0.919-1.086)
	PWDO		0.783(0.759-0.807)***	0.772(0.749-0.795)***
	unemployed		0.915(0.894-0.936)***	0.924(0.904-0.946)***
low income	low		1.089(1.008-1.177)*	0.975(0.950-1.002)
gender*diabetes	female	diabetes	0.983(0.941-1.027)	-
gender*social category	female	other	0.979(0.899-1.067)	0.939(0.867-1.017)
	female	PWDO	1.063(1.030-1.097)***	1.050(1.019-1.081)
	female	unemployed	1.029(1.002-1.058)*	1.017(0.990-1.044)
gender*low income	low	female	0.932(0.893-0.974)**	-
age*diabetes		diabetes	-	1.042(0.963-1.127)**

Multivariate population-based ORs (95% CIs). ORs of the current category (category 1 and category 2) versus the reference category in Table 5.1. The significance level is indicated as follows: *5%; **1%; ***0.1%. Age^2 is the quadratic age effect.

As in the analysis of prescriptions to adult patients, we found a significant effect of

Table 5.2: Determinants of the odds of an amoxicillin prescription versus a co-amoxiclav prescription and of an amoxicillin prescription versus a co-amoxiclav or moxifloxacin prescription for patients aged between 30 and 60 years by licensed GPs and other GPs, continued

Variable	Category 1	Category 2 (when interaction)	Amoxicillin vs. co-amoxiclav	Amoxicillin vs. co-amoxiclav or moxi-floxacin
Interaction patient prescriber characteristics				
gender prescriber*reimbursement patient	female	reimbursement	1.036(0.988-1.086)	-
gender prescriber*social category patient	female	other	1.035(0.939-1.141)	1.062(0.959-1.176)
	female	PWDO	0.982(0.945-1.020)	1.000(0.963-1.038)
	female	unemployed	0.995(0.962-1.030)	0.996(0.962-1.031)

Multivariate population-based ORs (95% CIs). ORs of the current category (category 1 and category 2) versus the reference category in Table 5.1. The significance level is indicated as follows: *5%; **1%; ***0.1%. Age^2 is the quadratic age effect.

the age of the prescriber on the odds of prescribing amoxicillin. The age group 40–49 years prescribed a smaller proportion of amoxicillin in favour of co-amoxiclav than both younger and older age categories. Overall, the largest difference was observed between the reference category of 40–44 years and older physicians of 60–64 years. We observed again active physicians prescribing a lower proportion of amoxicillin instead of co-amoxiclav. The effect of gender of the prescriber reached significance for children >3 years of age, for whom female prescribers were more likely to prescribe amoxicillin.

Patient characteristics were also predictive of the choice between amoxicillin and amoxiclav. For patients aged 1 or 2 years, who were under a higher reimbursement regimen, we observed higher odds of having amoxicillin prescribed versus co-amoxiclav. Remarkable as well was the effect of the patient's gender. Girls aged 1–5 years received a greater proportion of amoxicillin versus the broader-spectrum alternative co-amoxiclav than boys of the same age. For the prescriptions to patients aged 2 years, we found a significant interaction effect between patient gender and prescriber gender. Female physicians' preference for narrow-spectrum antibiotics (amoxicillin) over broad-spectrum antibiotics (co-amoxiclav)was primarily due to their more frequent amoxicillin prescribing to male patients compared with male physicians.

Table 5.3: Determinants of the odds of an amoxicillin prescription instead of a co-amoxiclav prescription for patients aged between 1 and 5 years by licensed GPs or paediatricians; separate model for each age group

Variable	Category 1	Category 2 (when interaction)	1 year old	2 years old	3 years old	4 years old	5 years old
Prescriber characteristics							
qualification	paediatricians		0.835(0.683-1.020)	0.852(0.688-1.056)	0.758(0.619-0.927)**	0.721(0.578-0.901)**	0.690(0.543-0.876)**
gender	female		1.078(0.970-1.198)	1.100(0.997-1.214)	1.102(1.013-1.199) *	1.126(1.036-1.224)**	1.146(1.053-1.247)**
region	Brussels		0.987(0.801-1.217)	1.047(0.854-1.283)	1.163(0.964-1.404)	1.156(0.973-1.373)	1.143(0.969-1.348)
	Flemish		0.973(0.905-1.045)	1.014(0.947-1.086)	1.028(0.962-1.098)	1.055(0.985-1.129)	1.024(0.953-1.100)
active	active		0.682(0.600-0.776)***	0.636(0.558-0.724) ***	0.594(0.525-0.672)***	0.673(0.596-0.760)***	0.654(0.575-0.745)***
age	20-29		1.416(1.105-1.814)**	1.646(1.304-2.077) ***	1.770(1.407-2.227)***	2.098(1.664-2.646)***	2.046(1.625-2.576)***
	30-34		1.329(1.149-1.537)***	1.456(1.263-1.679) ***	1.415(1.234-1.622)***	1.425(1.242-1.635)***	1.422(1.232-1.642) ***
	35-39		1.234(1.089-1.399)***	1.338(1.189-1.505) ***	1.270(1.131-1.425)***	1.293(1.148-1.455)***	1.272(1.124-1.439)***
	45-49		0.966(0.830-1.124)	0.989(0.867-1.128)	0.985(0.869-1.117)	1.021(0.905-1.152)	1.032(0.912-1.168)
	50-54		1.167(1.022-1.333)*	1.164(1.031-1.314) *	1.079(0.962-1.211)	1.109(0.987-1.245)	1.068(0.951-1.200)
	55-59		1.235(1.063-1.435)**	1.259(1.105-1.435)***	1.263(1.115-1.430)***	1.258(1.111-1.425)***	1.181(1.040-1.340)*
	60-64		1.776(1.318-2.393)***	1.697(1.312-2.195)***	1.616(1.295-2.018)***	1.649(1.343-2.026)***	1.537(1.246-1.896)***
	65-69		1.567(1.156-2.126)**	1.653(1.273-2.145)***	1.707(1.325-2.198)***	1.781(1.414-2.241)***	1.855(1.473-2.336)***
	70+		1.254(0.830-1.894)	1.452(1.029-2.050)*	1.562(1.189-2.051)**	1.627(1.192-2.220)**	1.654(1.240-2.207)***
region*qualification	paediatricians	Brussels	2.577(1.712-3.877)***	2.382(1.592-3.564)***	2.479(1.631-3.769)***	2.425(1.603-3.669)***	2.401(1.545-3.732)***
	paediatricians	Flemish	1.187(0.917-1.535)	1.116(0.843-1.477)	1.206(0.913-1.593)	1.170(0.867-1.579)	1.085(0.779-1.509)
Patient characteristics							
gender	female		1.121(1.091-1.152) ***	1.118(1.082-1.155)***	1.085(1.057-1.114)***	1.082(1.049-1.115)***	1.073(1.036-1.112) ***
reimbursement	higher		1.079(1.010-1.154) *	1.064(1.003-1.129) *	1.028(0.975-1.084)	1.026(0.965-1.091)	1.040(0.975-1.110)
diabetes			0.674(0.302-1.506)	0.665(0.378-1.169)	1.271(0.804-2.008)	1.499(0.927-2.422)	0.936(0.507-1.727)
Interaction patient prescriber characteristics							
gender prescriber*gender patient	female	female	-	0.943(0.893-0.996)*	-	-	-

Multivariate population-based ORs with 95% CIs. ORs of the current category (category 1 and category 2) versus the reference category in Table 5.1. The significance level is indicated as follows: *5%; **1%; ***0.1%.

5.3.3 Age, time and cohort effects

The age of the prescriber had a distinct influence on the choice between amoxicillin and broader-spectrum antibiotics, for both adult and child patients. In order to investigate whether this observation was an age effect or rather a cohort effect, we compared prescribing practices over time. A pure cohort effect would imply that differential prescribing remained constant as the cohort aged. A pure age effect, in contrast would imply that the same age groups, and not the cohorts, would stand out at different timepoints.

In order to distinguish these two effects, we compared the proportion of amoxicillin relative to a larger group (amoxicillin and co-amoxiclav or amoxicillin, co-amoxiclav and moxifloxacin) between the two most distant July–June periods available in our dataset: namely the periods 2002–03 and 2008–09. In this part of the analysis, the age cohort of the prescriber was defined based on the age at first prescription in the period from July 2002 to June 2003 only. No additional prescribers were included for the comparison with the second period.

There was a cohort effect of the preference for amoxicillin; differential prescribing remained more or less constant over time, though small age effects were possible (Figure 5.2). In addition, there was a strong time effect observed. The proportion of amoxicillin prescribed shifted almost in parallel upwards across the different age cohorts. This indicates that physicians partly maintained their prescribing habits of the past as they aged.

5.4 Discussion

In this study, we used complete antibiotic prescription-level data for the Belgian population from the period 2002–09.We selected the data for the period from July 2008 to June 2009 to identify the main patient and prescriber characteristics associated with the choice between narrow-spectrum antibiotics (amoxicillin) and broader-spectrum (co-amoxiclav, moxifloxacin) antibiotics.

5.4.1 Main results

We found significant effects of prescriber characteristics on the choice of antibiotic in multivariate analyses, while controlling for relevant patient features. Female and non-active prescribers, for instance, prescribed more amoxicillin for both children and adults. Region and qualification of the prescriber interacted significantly, but in different ways depending on patient age. For both young children and adults, physicians

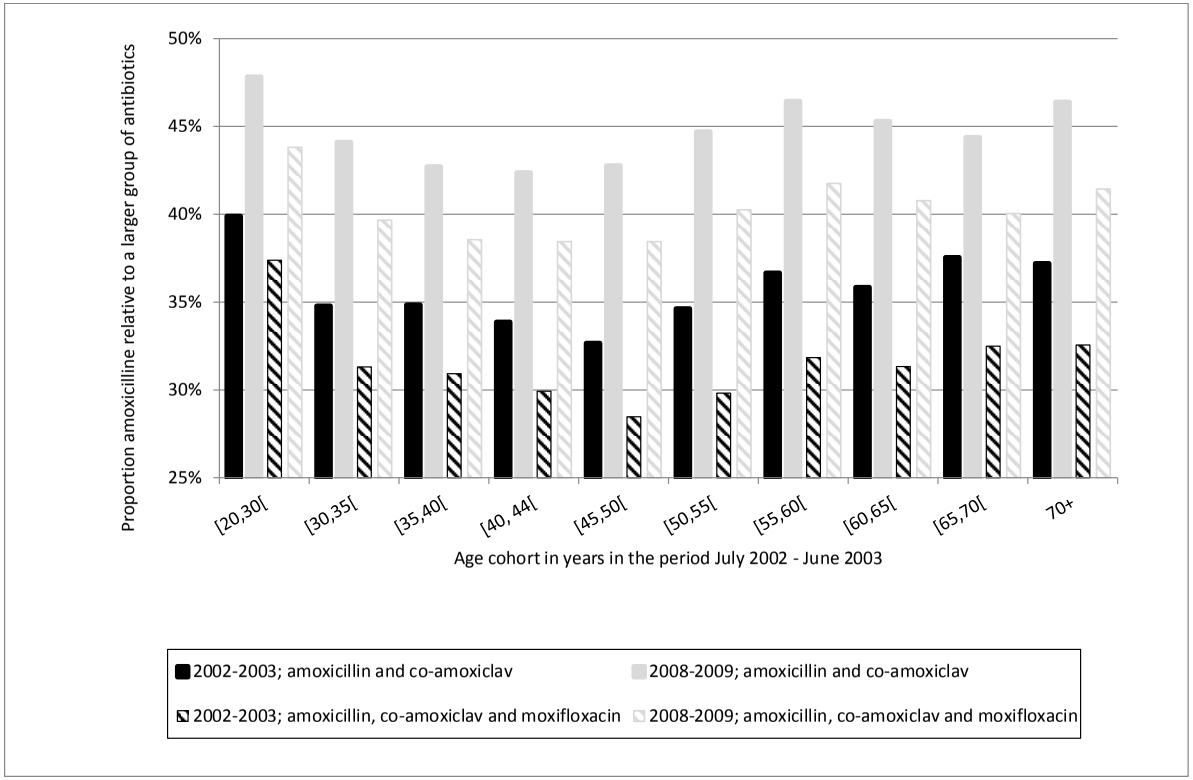

Figure 5.2: Proportion of amoxicillin relative to a larger group of antibiotics by age cohort of the prescriber: a comparison between the periods from July 2008 to June 2009 and from July 2002 to June 2003. Prescriptions to patients between 30 and 60 years old by licensed GPs and other GPs.

of the age category 40–44 years prescribed a smaller proportion of amoxicillin than both older (>54 years) and younger (20–40 years) physicians. A comparison with the period from July 2002 to June 2003 revealed that the differences associated with prescribers' ages were mainly due to a cohort effect, meaning prescribers tended to stick with their prescribing habits. The 40–44-year-old prescribers belonged to the high number of well-educated children of children from the baby boom generation. A possible explanation for the particular prescribing behaviour of these physicians could be the higher competition perceived, which might have driven the use of newer antibiotics. Another explanation might have been the intense marketing of co-amoxiclav, patented in 1984, i.e. close to the time when this generation graduated. The youngest generations of physicians, on the other hand, had been educated in the context of growing antimicrobial resistance and prudent antibiotic use, supported by the development, dissemination and implementation of guidelines for the appropriate use of antibiotics in ambulatory care. Across different age cohorts, however, the preference for amoxicillin increased in the period 2002–09. A possible explanation for this effect is the impact of public awareness campaigns and individual prescriber's feedback during the study period [6]

Patient characteristics such as gender, social category and reimbursement rights affected the choice of the antibiotic prescribed. Adults from a less favourable social category were prescribed less amoxicillin. This effect differed by their gender. A remarkable finding was that female patients, even as children, were more likely than male patients to be prescribed amoxicillin. A possible explanation might be that, as for other medical treatments, physicians treat females less intensively , which in the case of amoxicillin versus amoxiclav is producing better-quality prescribing, whereas in, e.g. the treatment of cardiovascular disease it might be harmful [4, 19]. Nevertheless, we believe this finding deserves further investigation to better understand this relationship and possibly identify opportunities to improve antibiotic prescribing in male patients.

5.4.2 Strengths and limitations

In this analysis, both patient and prescriber characteristics were included at the level of the prescription and appropriate statistical methodology was used to take into account both within-patient and within-prescriber clustering. The data are complete; each reimbursed antibiotic prescription in the period from July 2008 to June 2009 is included for the whole country. Therefore, this analysis had substantially more power to elucidate small differences in prescribing behaviour than more selective surveys.

Notice that these moderate differences in prescribing preferences are important because they represent a vast number of antibiotic prescriptions. To our knowledge, this is the first time that such an analysis has been performed. Although the prescribing differences we observed might not apply to other countries with a different prescribing and reimbursement model, the methodology can in principle be applied to similar datasets from other countries.

A drawback of the use of reimbursement claims data is the absence of information on the underlying pathology for which a prescription is issued or of information on additional comorbidities, such as HIV or cancer. Possibly some of the effects related to patient characteristics could be attributed to differences in underlying pathologies or comorbidities between patient groups. However, we controlled for important covariates, such as patient age, gender, social category, diabetes and low income class, whenever relevant. In this manner, differences in prescriber categories were partially controlled for the patient mix. An additional limitation of working with prescription data is the impossibility of verifying whether an issued prescription has led to usage of the antibiotic by the patient, and if so, how well the patient has adhered to the prescribed regimen. These aspects, related to the development of resistance at the population level, remain to be investigated through quantitative analyses, and merit further attention in future survey-based work.

In addition to the quality of prescribing, the methodology could also be applied to the search for prescriber groups with a deviating quantity of antibiotic prescriptions. For this task, a physician-specific denominator is needed, which is lacking in our current dataset.

In the analysis presented, we treated the correlation between prescriptions as a nuisance parameter, although dependencies between consecutive prescriptions might also be relevant to the evaluation of prescribing practices as such. We therefore compared the first and second prescriptions within 1 month of the first for the substances amoxicillin, co-amoxiclav and moxifloxacin in 2008–09. A clear difference between amoxicillin and co-amoxiclav as first prescription was observed. When the first prescription was for amoxicillin, 55% of second prescriptions were again for amoxicillin, 37% for co-amoxicillin and 8% for moxifloxacin. On the other hand, if the first was a co-amoxiclav prescription, 10% of the second prescriptions were for amoxicillin, 77% for co-amoxiclav and 13% for moxifloxacin. Factors influencing the transition from one prescription regimen to another falls outside the scope of this work, but merit future research.

5.4.3 Comparison with existing literature

Few studies have evaluated the impact of prescriber and patient characteristics on the antibiotic of choice. Steinman et al. [25] for instance, studied the choice between broad-spectrum and narrow-spectrum antibiotic prescribing for acute respiratory tract infections in adult primary care based on survey data. Although different factors were identified, the conclusion that non-clinical factors, e.g. physician specialty and region, influence prescribing behaviour is also found in data from the USA. It is to be expected that contributing factors differ between countries. The method of identifying deviating groups can, however, be generally applied.
Patient and prescriber predispositions, such as the patient's belief with regard to the appropriateness of the use of antibiotics [11], parental expectations in the case of prescribing to children [7] and the physician's fear of complications in the patient [17], have been singled out in the literature as the main underlying factors explaining self-medication with antibiotics, paediatricians' antibiotic prescribing, GPs' antibiotic prescribing and misprescribing of antibiotics, respectively. These factors cannot be investigated by reimbursement claims data, but might be an underlying explanation of some of the found associations between patient characteristics and the choice of the antibiotic substance, to be investigated in future studies.
In conclusion, we identified large prescriber groups with deviating prescribing habits, while controlling for relevant patient characteristics. Interventions can be designed and targeted taking the main characteristics of these deviating groups into account, along with information on the quantity of their prescriptions. Future analysis may aim to identify physician groups with deviating quantity as well as quality of prescribing. This may facilitate actions targeted at the group level, additional to a personalized approach, through which individual physicians are confronted with their deviating prescribing versus that of their colleagues.

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Chapter 6

Country level determinants

6.1 Introduction

It is well established that the use of antibiotics (usually expressed as the number of packages or number of defined daily doses sold or expended) and the prevalence of resistance against various groups of antibiotics vary substantially between countries and over time [1, 2]. Although many factors are presumed to account for these observed differences, formal data analysis to establish contributing factors has been scarce. In the rare analyses that have been published to date [23, 22, 17, 16, 12, 13, 11, 10, 6], the focus has been on a small number of potential determinants based on medical and economic theory. We, in contrast, attempted to identify determinants of total outpatient antibiotic use, relative use of antibiotic subgroups and antibiotic resistance from as naive a starting point and for as many European countries as feasible. Determinants were selected based on statistical significance, rather than a preconceived judgment of the relative importance of variables in explaining the observed variations in antibiotic use and resistance.
In the next section, we introduce the data sources, describe the data and outline the methodologies used for addressing the different research questions. The subsequent sections present the results of our analyses and discuss our approach and results in the wider context of antibiotic use and of previous studies.

6.2 Methods

6.2.1 Data sources

A list of more than 100 potential determinants of antibiotic use in primary care, produced at an international workshop during the European Conference on Antibiotic Use in Europe (Brussels, 15-17 November 2001), was used as a basis for discussing and developing an updated list of variables of potential influence on antibiotic use and resistance during two consecutive international meetings of the European Surveillance of Antimicrobial Consumption (ESAC) network (see the Acknowledgements section for participant lists).
On the basis of the list of potential variables, we constructed a dataset by searching the following international databases: Eurostat [9], the WHO Health for All database [35], the WHO European mortality database [33], the 2009 Organisation for Economic Co-operation and Development (OECD) database [28], the Hofstede indices [18], the Food and Agriculture Organisation statistical database (FAOSTAT; [14]), the World values survey [36], the World Bank [29], the EARS-Net database on mi-

crobial resistance [8], Transparency International's Corruption Perceptions Index [30] and Mathematica's Weather Data [32]. Eurostat was used as primary source when other sources were identified for the same variable. The database was complemented with a survey amongst the lead national representatives (LNRs) in the ESAC project to obtain information on general characteristics of the healthcare system in each country. The questions put forward about the respective countries were broad in nature and asked about the organisation of prescribing antibiotics to patients by different types of prescribers. Yearly data were retrieved from 1999 until 2007 for 32 European countries (see Table B.1 in appendix). A complete list, describing the 181 potential determinants and the sources from which they were obtained can be found in Table B.2 in appendix. Based on medical plausibility, overlap and availability, the list of potential determinants was reduced to a short list of 57. We numbered this short list of variables (Table B.2 in appendix) and repeated the complete variable description in the results tables (Table 6.2 and 6.3) for clarity. In the results section, we now refer to the determinant number. Table B.1 in appendix describes the countries for which data were gathered, as well as data availability after imputation of missing values. The imputation methodology is described in the subsection on statistical methodology and in more detail in Section B.1 in appendix. Antibiotic consumption data was sourced from the ESAC database [27]. The WHO Anatomical Therapeutic Chemical (ATC) classification system [34] was used to define antibiotic substances. In this manner, total antibiotic use was defined as the total number of defined daily-doses per 1,000 inhabitants per day (DID), for every country-year combination in the ATC class J01 (antibiotics for systemic use).

Besides total antibiotic use, we also identified determinants of the use of subgroups of antibiotics relative to a larger class of antibiotic substances. Amoxicillin (ATC J01CA04) and co-amoxiclav (ATC J01CR02) consumption were expressed relative to both all antibiotics (ATC J01) and penicillins (ATC J01C). These expressions can be seen as rough quality indicators, using the interpretation that proportionately more amoxicillin and less co-amoxiclav is to be preferred.

A similar dataset was obtained from IMS Health, with the aim to check the consistency of the findings in relation to the outcome measure of consumption.

Resistance data was extracted in the form of count data. The number of isolates with intermediate or full resistance and the total number of isolates taken were sourced from the EARS-Net database on microbial resistance [8] for five resistance types from 2 bacterial groups. For Escherichia coli (E. coli), we obtained data on resistance against aminopenicillins (AMINOPEN), 3rd generation cephalosporins (CEPH) and fluoroquinolones (FLUORO). For the Streptococcus pneumoniae (S. pneumoniae) we ex-

tracted data on resistance against penicillins (PNSP) and the joint resistance against penicillins and macrolides (PNSP).

Table 6.1: Specific consumption data used for analyses of antibiotic resistance

		Pathogen				
		E. coli			*S. pneumoniae*	
		resistance to aminopenicillins (AMINOPEN)	resistance to third-generation cephalosporines (CEPH)	resistance to fluoroquinolones (FLUORO)	resistance to penicillins (PNSP)	Combined resistance to penicillins and macrolides (PNSP)
ATC	description					
J01CA	penicillins with extended spectrum	X	X		X	X
J01CE	β-lactamase-sensitive penicillins	X	X		X	X
J01CR	combinations of penicillins, including β-lactamase inhibitors	X	X		X	X
J01DB	first-generation cephalosporins	X	X		X	
J01DC	second-generation cephalosporins	X	X		X	
J01DD	third-generation cephalosporins		X	X		
J01F	macrolides Lincosamides, streptogramins					X

6.2.2 Statistical methodology

We encountered several statistical challenges: missing covariate data, within-country correlations, time dependent covariates and a large number of potential covariates. Although methods have been described and used to deal with each of these challenges, when they arise jointly a generally agreed methodology is not readily available. Therefore, we used a practical but valid selection and modelling approach summarized below; details can be found in the Section B.1 in appendix. The limitations of this and potential alternative methods are raised in the discussion section. We augmented the data availability using multiple imputation [26] wherever possible to avoid losing incomplete records. We created five imputed datasets to account for the uncertainty related to the imputation process. Remaining missingness in the covariate data was eliminated by selecting a complete subset suggested by biclustering [19] performed on the data availability matrix. Table B.1 illustrates the impact of multiple imputation on data availability and of biclustering on the number of observations selected for each country. We conducted a stepwise search using Generalized Estimating Equations (GEEs; [37, 20] and Chapter 1) to identify relevant predictors for each imputed dataset separately. We subsequently combined all identified variables in a final multiple imputation GEE (MI-GEE; [26]) model and employed a backward selection step to obtain the final estimates with valid P-values. A working independence matrix was used for the GEE and MI-GEE models to preserve the unbiasedness and consistency properties of GEE estimation in the presence of time dependent variables [3, 5].
MI-GEE based on the log-normal distribution, as an alternative to the overdispersed Poisson, was used to find determinants of total antibiotic use. Subgroups of antibiotic consumption were modelled using MI-GEE based on the Poisson distribution with logarithmic link function and using the larger group as the offset. To model resistance rates, the Poisson distribution was used with the number of resistance counts as response and the total count of bacterial samples per country-year were taken as an offset. The Poisson-GEE model includes a parameter accounting for overdispersion. In this part of the analyses, we were mainly interested in assessing cross-sectional associations between the rate of resistance and antibiotic use in specific subclasses, expressed in DID as summarized in Table 6.1.

6.3 Results

In this section, we summarized and explained the identified determinants of variations in total antibiotic use, use of subgroups and antibiotic resistance. Indicated associa-

tions should be interpreted as cross-sectional, since we did not consider associations at different time points. For clarity, we indicate the variable number brackets to indicate which determinants of the list of 57 determinants (See Table B.2 in appendix) were selected by the stepwise search. The terms *positive* and *negative* are used throughout the text to indicate the sign of the association, not to describe the potential desirability of the effect. A positive association means that an increase in a determinant will cause an increase in the dependent variable (i.e. antibiotic use), whereas a negative association means that an increase in the determinant will cause a decrease in the dependent variable. Categorical variables [e.g., restrictions on pharmaceutical companies: yes/no (D10)] are represented as an indicator of whether the statement is true (yes). Thus, a positive association means that the presence of the indicator is associated with more antibiotic use. When more than two levels were present multiple indicator variables were used. We refer to all levels in brackets when one or several indicators were selected, since the interpretation of selected determinants depends on which indicator variables are included or excluded.

6.3.1 Determinants of total antibiotic use

The final MI-GEE model retained 14 factors explaining variations in antibiotic use between countries as measured in DIDs (see Table 6.2).

The extent to which feelings of religiousness (D45) and trust (D46) are present tends to vary between countries, but was stable over the time horizon of our analyses. Both of these worldview aspects were found to be significantly associated with total antibiotic consumption. The larger the proportion of the population describing themselves as religious instead of atheistic, the more antibiotics were used. Additionally, antibiotic consumption was larger in countries where a larger percentage of inhabitants indicated that they distrust other people.

The organisation of the healthcare system was also found to be predictive of the amount of antibiotics used in outpatient care. The presence of restrictions on the conduct of pharmaceutical companies towards physicians (D10), for instance, was associated with less antibiotic use. Perhaps surprisingly, countries in which guidelines have been implemented to treat respiratory tract infections (D12) use relatively more antibiotics measured in DIDs. Guidelines may suggest the prescription of higher dosages, which might explain this effect. The general practitioner (GP)-patient relationship was also identified as a significant factor. If patients are obliged to register with the GP they consult and it is not easy for them to consult another GP (D6-9), the country's observed antibiotic consumption was lower than in countries where this

was not the case. Furthermore, the existence of a financial incentive to register with and consult a single GP, in the absence of an obligation to do so (D6-9), did not have a significant impact on ambulatory antibiotic use. Additionally, the number of antibiotic products available in a country (D4) was found to be negatively associated with antibiotic use. However, the significance of this negative association was conditional on the other variables included in the model. By contrast, the percentage of gross domestic product (GDP) spent on healthcare (D23) was positively associated with antibiotic use.
Several other factors related to climate, burden of disease, demography and socio-economics were found to contribute significantly to differences in antibiotic use. Relative humidity, expressed as the year average dew point (D41), was positively associated with total antibiotic use. There was also a positive association between the resistance rate of the *E. coli* to third-generation cephalosporins (D51) and total antibiotic use. Furthermore, the proportion of elderly persons in the population (D36) was positively associated with antibiotic use. Higher educational attainment (D25) and higher unemployment rates (D2) were negatively associated with antibiotic use.

6.3.2 Determinants of relative amoxicillin and co-amoxiclav use

When focusing on subgroups of antibiotics (amoxicillin, co-amoxiclav) relative to either total antibiotic consumption (ATC J01) or the consumption of β-lactam antibacterials and penicillins (ATC J01C), somewhat different sets of significant determinants were identified. Table 6.2 lists these results, ordered by the number of times they were selected as a significant determinant.
A number of variables were significantly associated with the relative prescribing rate of both amoxicillin and co-amoxiclav. Regulations concerning the position of the GP within the healthcare system were important in explaining which of these antibiotics were prescribed and to what extent. For instance, mandatory patient registration with a single GP (D6-9) independently reduces the relative rate of co-amoxiclav and amoxicillin prescribing (relative to all antibiotics and relative to penicillins only), especially if it is difficult to change between GPs (D6-9). The existence of a financial incentive, when registration with a GP is not mandatory (D6-9), was associated with higher relative amoxicillin use. The existence of restrictions on the conduct of pharmaceutical companies (D10) towards physicians was associated with a decreased rate of amoxicillin consumption and an increased rate of co-amoxiclav use (relative to penicillins only). The use of guidelines for treating respiratory tract infections (D12),

in contrast, was associated with lower co-amoxiclav prescribing and with a higher rate of amoxicillin prescribing.
In addition to the influence of GP-related issues, other factors explained the remaining variation in relative prescribing rates of both amoxicillin and co-amoxiclav. Indeed, a higher percentage of the private households' share in total health expenditure (D15) was associated with a lower rate of amoxicillin prescribing (relative to both total antibiotics use and penicillin use only) and with a lower rate of co-amoxiclav prescribing (relative to penicillin use only). A larger population density (D35) was associated with a higher relative use of both co-amoxiclav (relative to both total antibiotics use and penicillin use) and amoxicillin (relative to penicillins). A higher population density was also negatively associated with total antibiotic consumption. Furthermore, the percentage of infants vaccinated against mumps (D21) was associated with relatively more co-amoxiclav (relative to both total use and penicillins) and less amoxicillin prescribing (relative to penicillins).
Some remaining factors were significantly associated with co-amoxiclav, but not with amoxicillin. A larger average household size (D22) was strongly associated with a higher rate of co-amoxiclav consumption relative to other penicillins. The size of this effect was smaller when we modelled the rate of co-amoxiclav use relative to all antibiotics. The percentage of *E. coli* intermediately and fully resistant to fluoroquinolones (D52) was positively associated with a higher relative rate of co-amoxiclav use (relative to all antibiotics and to a lesser extent to penicillins).

Some other remaining factors were mainly associated with the extent to which amoxicillin was prescribed. A mandatory visit to a GP before seeing a gynecologist, pulmonologist or paediatrician (D13) was associated with a higher relative rate of amoxicillin prescribing versus other penicillins. Providing feedback to GPs, gynaecologist, paediatricians or pulmonologists on how they prescribed antibiotics relative to their peers (D11) was found to be associated with a higher rate of amoxicillin prescribing relative to total antibiotic use.
We also found that the percentage of people who knew that antibiotics do not kill viruses (D26) was associated with a lower rate of amoxicillin prescribing relative to all antibiotics. Finally, a higher poverty rate (D1) was associated with a higher rate of amoxicillin prescribing relative to total antibiotic use.

6.3.3 Determinants of resistance

Table 6.3 summarizes the determinants significantly associated with antibiotic resistance. Antibiotic class-specific consumption was included in the selection procedure

as a potential covariate (see Table 6.1). Since the resistance data were not imputed as an outcome measure, the analysis on determinants of resistance was conducted on a subset of the observations used in the consumption analysis. With specific antibiotic consumption expressed in DIDs, a significant association was identified for *E. coli* resistance to CEPH and FLUORO, but not for resistance to aminopenicillins AMINOPEN. For the *S. pneumoniae* we found a significant association for resistance to PNSP, but not for combined resistance to PNSP .

Cross-country variations in resistance cannot fully be accounted for by the specific consumption expressed in DIDs. Alternative factors explain this better, and in the case of AMINOPEN and PNSP , specific consumption in DIDs was not even selected as an explanatory variable. We discuss the determinants in addition to consumption below. By comparing these determinants, we observed a clear difference between the factors found for AMINOPEN and other drug/organism combinations. A subgroup of variables exerted similar effects on the various combinations, with the possible exception of AMINOPEN. We discuss factors found to be significant over different drug/organism combinations, in order not to over-interpret the results. All identified factors can, however, be found in Table 6.3.

As for antibiotic consumption, the gatekeeper role of GPs was found to be important in explaining the observed differences in resistance levels. Most notably, the presence of any incentive for consulting a GP first before seeing a pulmonologist, paediatrician or gynaecologist (D14) was negatively associated with the resistance rate for all resistance classes, except for AMINOPEN. For this latter class, a positive association was observed. A larger average household size was positively associated with increased resistance over all classes investigated except for AMINOPEN, where it was not selected. The extent to which people describe themselves as atheistic rather than religious (D45) correlated with higher resistance for: CEPH, PNSP, PNSP but was not retained in the final model for AMINOPEN or FLUORO. A higher life expectancy at 65 years (D31 and D49) of age was related to higher resistance levels for both males (PNSP, PNSP) and females (AMINOPEN, CEPH, FLUORO), albeit for different groups and pathogens. Total health expenditure as a percentage of GDP (D23), in contrast, correlated negatively with all resistance rates studied except for AMINOPEN, where this variable was not retained.

Other factors contributed to the explanation only of resistance rates of specific pathogens or even specific drug/organism combinations.

6.4 Discussion

6.4.1 Main determinants of consumption and resistance

We identified factors exerting a significant influence on either antibiotic use or resistance from a large determinants database by means of statistical significance testing within a multivariate MI-GEE model.
Several factors describing the organisation of the healthcare system were found to be associated with either higher (guidelines for treating respiratory tract infections) or lower (restrictions on the commercial conduct of pharmaceutical companies; number of antibiotics available) antibiotic use (measured in number of DIDs). In addition to the healthcare system, factors describing climate, burden of disease, demography and socio-economics each partially explained differences in antibiotic prescribing. Relative humidity and health expenditure as a percentage of GDP, feelings of distrust and the proportion of the population aged over 65 were positively associated with antibiotic use. Population density, the proportion of adults who completed upper secondary education and the extent to which people describe themselves as atheistic rather than religious were negatively associated with antibiotic use.
The existence of guidelines for treating respiratory infections counter-intuitively increases antibiotic use. This might be due to guidelines being developed under the auspices of pharmaceutical companies, or to 'better prescribing' leading to 'more prescribing' when it is measured in DIDs. We did not consider guidelines for non-respiratory infections as a potential determinant in our analysis. Therefore, if the existence of such guidelines was associated with those for respiratory infections, we might have captured part of the effect of the existence of guidelines for non-respiratory infections. The impact and effectiveness of different guidelines on the quantity and quality of antibiotic use remain to be studied in detail.
The (average) extent to which people in a country described themselves as being an atheist rather than religious was found to have a highly significant association with both total use and antibiotic resistance of specific groups (CEPH, PNSP, PNSP). That is, a higher proportion of people in a country who classified themselves as atheistic rather than religious, predicted lower antibiotic consumption and, counter-intuitively, higher antibiotic resistance. This variable might contain information on culture and perceptions of illness. Baquero et al. [3] suggested that religion plays a role in antibiotic consumption, in that antibiotic use is consistently lower in predominantly Protestant populations than in predominantly Catholic populations. In the dataset we used there were no separate indicators for Protestantism

and Catholicism, but secularisation (as indicated by feelings of no religiousness) has been documented to be more pronounced in historically protestant countries [5]. In this regard this finding is in line with that of Baquero et al. [3].

In our efforts to capture the defining characteristics of culture and community values for countries that could be relevant for antibiotic use, we used data from the World Values Survey (WVS). The WVS is a recurring survey of values (currently the sixth wave), and a commonly used resource in the social sciences. It adheres to a strict methodology for data collection to elicit community values and beliefs in many countries. Although one could argue that subjective valuations on feelings of religiousness and trust can be challenging to summarize at the population level, we believe that our multidisciplinary approach to determinant collection has enriched the analysis and the insights it provides.

The relative prescribing rate of amoxicillin and co-amoxiclav was found to be associated with the organisation of the healthcare system (GP registration, restrictions on pharmaceutical companies, treatment guidelines for respiratory tract infections) and two factors linked to the transmissibility of infections (humidity, population density). Remaining explicative factors for relative prescribing rates differed between the different analyses. The same methodology was applied to search for determinants of antibiotic resistance, whereby specific consumption in DIDs was added as a potential determinant. Specific consumption in DIDs was, however, only retained as a significant variable for CEPH, FLUORO and PNSP but not for AMINOPEN and PNSP . Previous studies [31, 4, 15] linking antibiotic use and resistance at the country level have found a significant association between specific ambulatory use and resistance for the same drug/organism combinations as we considered. These studies, however, did not include any other determinants in the analysis. Overall we discovered several factors to be highly associated with higher (average household size, life expectancy at 65 years old either for males or females, and non-religious feelings) or lower (incentives to visit a GP before consulting a specialist physician) resistance levels in a country for all drug/bug combinations except for AMINOPEN. For AMINOPEN the selected group of determinants differs from all other resistance types studied. In addition to these overall factors, a wide range of other determinants were only selected for specific resistance outcomes. The fact that so many different factors are selected in addition to, and in some cases instead of antibiotic consumption, illustrates that antibiotic resistance is a complex phenomenon, whereby specific antibiotic consumption expressed in DIDs is not sensitive enough a measure to fully predict antibiotic resistance. It has to be considered that antibiotic consumption is the main driver of antibiotic resistance. For resistance to occur, however, several

aspects interplay: (i) the amount of dispensed antibiotic, for which we modelled the total amount of DIDs, (ii) the quality of dispensing, which we assessed with relative prescribing rates of amoxicillin and co-amoxiclav, and (iii) appropriate use, for which we used a large set of determinants that might be related to resistance in addition to DID dispensing. The large set of determinants also determines the quantity and quality of antibiotic dispensing.

Significant determinants identified through our analyses might express differences in disease epidemiology, prescribing practices or compliance with treatment. Selective pressure exerted by antibiotic use as such might not coincide with DID measurements either. Relatively lower dosage consumption may eventually lead to more resistance than higher dose consumption [21]. An analysis based on packages per 1,000 inhabitants per day was not considered because this information was unavailable for too many countries. Furthermore, in our analyses we did not consider hospital antibiotic use as a potential determinant of resistance, as the resistance data do not allow a distinction between community associated and healthcare-associated strains. Because of this mismatch between response and determinant, we are probably underestimating the significance of the association between antibiotic consumption and resistance. The distinct influence of hospital and ambulatory antibiotic use on resistance development is a topic for future research. This requires country-representative antibiotic use and resistance data from hospitals, as well as being able to distinguish community from healthcare associated bacterial isolates. Both of these are currently lacking.

6.4.2 Methodological strengths, weaknesses and alternatives

To our knowledge, this is the first study using multi-country longitudinal data to investigate the potential impact of a large number of potential covariates on both antibiotic use and resistance by a combination of expert screening and analysis of statistical significance. This naive starting point results in the discovery of distinct determinants for antibiotic consumption and resistance which would otherwise remain undiscovered. Previous attempts to find determinants of antibiotic use of aminopenicillins [23, 22, 17, 16, 12, 13, 11, 10, 6] correlated a limited set of a *priori*-defined determinants with consumption data. Masiero et al. [23], for instance, explained causes of variation in antibiotic consumption in Europe using some of the same data we used. The approach taken in the current work is, however, very different. Masiero et al. [23] started by proposing an a priori econometric model containing only a limited number of covariates, such as GDP per capita, and subsequently fitted this model to data to test the theory-based hypothesis. Conversely, we took an empirical approach

and identified potential determinants based on the significance of their association with the response, with as few a *priori* assumptions as methodologically feasible. The discovery of factors associated with antibiotic consumption and resistance, in turn, enables scientific hypotheses to be proposed for a causal structure in an area where scientific evidence and relevant theory are sparse. In future research, these identified factors can be used to enrich theoretical models such as the mixed model approach used by Masiero et al. [23], provided correct lag times are investigated.

We did not used any causal discovery algorithms as did Rettenmaier and Wang [25] when they searched for determinants of health. Note that the approach taken by Rettenmaier and Wang [25] makes use of an underlying multivariate normal distribution, which is not satisfied here due to the use of various categorical variables. Furthermore, the causal discovery algorithms they used are cross-sectional, and extension to longitudinal data with fixed country effect removed is not backed by relevant statistical theory or simulation studies. This might be an interesting route for future studies on determinants of country-level differences in health outcomes provided appropriate statistical methodology is available. An additional strength of our analysis is that it uses proper statistical methodology to incorporate relevant information, both between countries and over time. By using multiple imputation, we avoid losing too many sparsely available country-variable combinations. It should be noted that the statistical methodology used here is different from that used by Masiero et al.[23]. Firstly, we took a marginal (GEE) approach versus a country-specific approach (mixed model). Secondly, we did not include geographical indicators because we did not want to obfuscate the underlying determinants of geographical differences. Lastly, we dealt with time-dependent variables such as antibiotic resistance differently. Masiero et al.[23] explored two options for this problem: using instrumental variables and including lagged covariates. The instrumental variable approach assumes a cause-effect relationship between instrument and covariate, which we tried to avoid. Taking lagged covariates in turn relies on the strict condition required for unbiasedness. That is, that all information (past and future) of all time-dependent variables with respect to the response should be included [24, 7], even when using the mixed model approach. We believe this is not satisfied by taking one fixed time lag. Therefore, we used GEE based on the working independence correlation matrix, which always provides unbiased cross-sectional associations when time dependent variables are present.

In order to test the stability of the results, we repeated the analysis using IMS Health antibiotic consumption data for a selection of 117 country-year combinations instead of the 153 country-year combinations available in the ESAC-based consump-

tion analysis. The overall determinants of antibiotic consumption, such as education, regulation concerning GPs, the proportion of people aged 65+ in the population and the influence of religion, still clearly emerge as determinants of total IMS Health-based antibiotic use. We found that the selection of significant determinants became smaller and slightly different. The differences were mainly due to lower data availability using IMS Health, which implies that some variables no longer reach significance and are therefore not retained in the final model. This is especially the case for the resistance analysis based on IMS Health data. Another reason for the differences is the instability of the stepwise variable selection procedure under multicollinearity. Multicollinearity implies that overlapping information is present in the variables, and different subsets of determinants can explain the same variation in the response. For example, female and male life expectancy are highly correlated and could be equally predictive of antibiotic resistance. Therefore, the causal interpretation of the identified determinants has to be treated with caution. Recently new statistical methodology has been proposed to perform determinant selection for multicollinearity and time dependence; however, its performance with multiple imputation has not been investigated, but might provide more stable selection (see Chapter 2) Furthermore, in this study only cross-sectional associations were investigated, whereas antibiotic resistance evolves dynamically, with current resistance levels being determined by selection pressure over time. Identifying the dynamics of resistance development would require longer and more precise data of both antibiotic consumption and resistance measurements.

6.5 Conclusions

Our study showed that, apart from societal aspects over which policy has no control in the short run (such as population density, religiousness, and trust), there are a number of aspects that can be modified by policy makers and that might have a significant impact on antibiotic use and resistance in the short run. Such policies include strengthening the gatekeeping function of GPs and the authority of physicians over their patients. This can be done, for instance, by restricting the freedom of patients to consult many different GPs or to consult specialists directly. However, it should be accompanied by placing restrictions on direct marketing activities by pharmaceutical companies aimed at prescribing physicians, as this would also have a significant impact on consumption of antibiotics. Furthermore, it would seem prudent to provide feedback to physicians on their prescribing habits versus those of their

peers. Clearly, such measures would have consequences far beyond the prescription of antibiotics. Therefore, they should be considered in their country-specific context, balancing aspects of access, quality, affordability, equity and cost-effectiveness of care.

Table 6.2: Determinants of total antibiotic consumption and relative consumption of subgroups

			Amoxicillin		Co-amoxiclav	
Number	Determinant, relative to ATC class (offset in the Poisson-based MI-GEE model)	Total	J01[a]	J01C[a]	J01[a]	J01C[a]
8	patients have to be registered with a GP and it is not easy to change between GPs (1 = true, 0 = false)	-22.49% (-27.49%;-17.15%)***	-54.25% (-60.40%;-47.14%)***	-24.58% (-33.66%;-14.26%)***	-94.43% (-97.62%;-86.98%)***	-91.38% (-95.85%;-82.07%)***
10	are there any restrictions on pharmaceutical companies regarding providing dinners, conferences, breakaways or presents to physicians? (1=yes; 0=no)	-6.44% (-12.19%; -0.31%)*	-52.43% (-59.76%; -43.75%)***	-63.73% (-66.98%; -60.15%)***	61.54% (35.97%; 91.93%)***	-
12	do pulmonologists, GPs or paediatricians have guidelines for treating respiratory tract infections? (1 = yes; 0 = no)	55.42% (46.02%; 65.42%)***	-	28.30% (14.11%; 44.25%)***	-56.65% (-62.07%; -50.45%) ***	-37.62% (-48.84%; -23.94%)***
35	average population density per km^2	-0.13% (-0.15%; -0.11%)***	-	0.07% (0.06%; 0.08%)***	0.35% (0.23%; 0.47%)***	0.37% (0.29%; 0.45%) ***
6	patients do not have to be registered at a GP, but there is a financial benefit for being registered at a GP (1 = true, 0 = false)	44.54% (33.55%; 56.43%)***	59.88% (36.42%; 87.37%)***	44.05% (28.56%; 61.39%)***	-	-
41	year average dew point (in °C) as measure of relative humidity of the air	2.57% (1.60%; 3.55%)***	4.99% (3.44%; 6.56%)***	-	-	-3.32% (-6.47%; -0.07%)*
45	extent to which persons describe themselves as atheistic versus religious[b]	-41.72% (-49.00%; -33.42%)***	-	-	-66.56% (-78.40%; -48.23%)***	-50.99% (-66.15%; -29.03%)***
46	percentage of people who feel one should be careful in trusting others	25.64% (0.30%; 57.38%)*	-	-	763.80% (335.63%; 1612.81%) ***	663.83% (297.66%; 1367.18%) ***

Table 6.2: Determinants of total antibiotic consumption and relative consumption of subgroups, continued

			Amoxicillin		Co-amoxiclav	
Number	Determinant, relative to ATC class (offset in the Poisson-based MI-GEE model)	Total	J01[a]	J01C[a]	J01[a]	J01C[a]
25	percentage of adult population (25-64 years old) that has completed upper secondary education	-1.00% (-1.17%; -0.84%)***	-	-0.49% (-0.78%; -0.20%)**	-	-1.20% (-1.90%; -0.50%)***
4	number of different antibiotic products for sale in the pharmacy	-0.75% (-0.92%; -0.59%)***	-	0.69% (0.36%; 1.01%)***	-	-
23	total health expenditure as percentage of GDP	7.24% (5.02%; 9.50%)***	-	-9.32% (-13.05%; -5.43%)***	-	-
51	E. coli percentage intermediate and fully resistant to third-generation cephalosporins	126.95% (19.77%; 330.02%)*	-	-	-	-
36	percentage of population aged ≥65 years	3.83% (2.91%; 4.77%)***	-	-	-	-
2	unemployment rate of active population (154 years)	-0.92% (-1.62%; -0.21%)*	-	-	-	-
15	private householdsout-of-pocket expenditure on health as a percentage of total health expenditure	-	-2.08% (-2.65%; -1.51%)***	-3.48% (-4.07%; -2.89%)***	- -1.73% (-3.07%; -0.37%)*	
21	percentage of infants vaccinated against mumps	-	-	-1.55% (-1.91%; -1.19%)***	1.99% (1.21%; 2.78%)***	2.13% (1.08%; 3.20%)***
28	average household size	-	-22.48% (-37.26%; -4.20%)*	- 157.06% (84.77%; 257.61%)***	327.26% (169.03%; 578.56%)***	

Table 6.2: Determinants of total antibiotic consumption and relative consumption of subgroups continued

			Amoxicillin		Co-amoxiclav	
Number	Determinant, relative to ATC class (offset in the Poisson-based MI-GEE model)	Total	J01[a]	J01C[a]	J01[a]	J01C[a]
52	percentage of *E. coli* intermediate and fully resistant to fluoroquinolones	-	-	-	191.15% (54.21%; 449.68%)***	119.60% (14.97%; 319.46%)*
14	is there any incentive for seeing a GP before seeing a pulmonologist, paediatrician or gynaecologist? (1 = yes; 0 = no)	-	-	-	-77.32% (-83.90%; -68.07%)***	-82.67% (-88.66%; -73.50%)***
7	patients have to be registered with a GP and it is easy to change between GPs (1 = true, 0 = false)	-	-	-	-69.72% (-83.33%; -44.98%)***	-68.84% (-81.68%; -47.00%)***
13	do patients have to consult a GP first before seeing a gynaecologist, pulmonologist or paediatrician? (1 = yes; 0 = no)	-	-	29.60% (21.36%; 38.40%)***	-	-
57	age-standardized death rate per 100,000 due to pneumonia	-	-	-	-1.49% (-2.69%; -0.28%)*	-
39	percentage of people living in an urban environment	-	-	-	-1.08% (-1.88%; -0.28%)**	-
44	extent to which people consider greater respect for authority undesirable	- -48.92% (-59.72%; -35.22%)***	-28.16% (-40.10%; -13.85%)**	-52.02% (-60.35%; -41.93%)***	-	
5	number of hospital beds per 100,000 inhabitants	-	-0.16% (-0.21%; -0.12%)***	-	-0.27% (-0.42%; -0.11%)***	-
34	male life expectancy at birth in years	-	-7.78% (-9.36%; -6.18%)***	-	-23.62% (-32.02%; -14.19%)***	-

Table 6.2: Determinants of total antibiotic consumption and relative consumption of subgroups, continued

			Amoxicillin		Co-amoxiclav	
Number	Determinant, relative to ATC class Total (offset in the Poisson-based MI-GEE model)		J01[a]	J01C[a]	J01[a]	J01C[a]
38	percentage of population aged between 0 and 14 years	-	-	-3.32% (-5.64%; -0.95%)*	-	-7.41% (-12.90%; -1.56%)*
27	number of women per 100 men	-	-	8.13% (6.62%; 9.66%)***	-	14.82% (9.64%; 20.25%)***
26	percentage of people who know antibiotics do not kill viruses	-	-0.60% (-0.90%; -0.30%)***	-	-	-
1	poverty rate: percentage of people earning < 60% of the median income (made equivalent after social transfers)	-	2.69% (1.13%; 4.28%)***	-	-	-
11	do gynaecologists, pulmonologists, GPs or paediatricians receive any feedback on their antibiotic prescriptions? (1 = yes; 0 = no)	-	23.02% (10.80%; 36.59%)***	-	-	-
42	standard deviation over a year of the daily dew point in 8°Cas a measure of variability of relative humidity of the air	-	-	-5.68% (-8.92%; -2.31%)**	-	-
16	total health expenditure in purchasing power parity per capita, WHO estimates	-	-	-0.01% (-0.01%; 0.00%)*	-	-
29	female life expectancy at birth in years	-	-	-	26.24% (12.57%; 41.56%)***	-

Selected determinants of total antibiotic use and relative rate ofamoxicillin and co-amoxiclavconsumption are displayed as exponentiated regression coefficients (with95%Wald CI) of an MI-GEE model based on the normal distribution with log link for total antibiotic consumption and based on the Poisson distribution with log link for subgroup consumption.

[a]For subgroup consumption, amoxicillin or co-amoxiclav consumption was used as the response, with the larger group, indicated by the ATC class (J01 or J01C), as the offset. The effects have a multiplicative interpretation. One unit increase in the determinant leads to a multiplication of the specific effect. For instance, if the year average dew point increases by 18° C , the expected total antibiotic consumption is 1.02570 times higher. The significance level is indicated as *5% level, **1% level and ***0.1% level. Selection was based on a 5% significance threshold.

[b]In this case the average of a religiousness score is used, where people who declared themselves to be atheist were assigned the value 1 and those who declared themselves religious were assigned the value -1. Thus, this variable indicates the balance between self-declared atheists and self-declared religious people.

Table 6.3: Determinants of antibiotic resistance

		E.coli[a]			S.pneumoniae[a]	
Number	Determinant	AMINOPEN[a]	CEPH[a]	FLUORO[a]	PNSP[a]	PNSP [a]
	specific antibiotic consumption in DIDs	–	7.07 (2.58; 11.76)**	47.31 (24.51;74.28)***	5.37 (3.16;7.63)***	–
14	is there any incentive for consulting a GP before seeing a pulmonologist, paediatrician or gynaecologist?(1=yes;0=no)	45.91 (25.99;68.99)***	-92.88 (-96.41;-85.88)***	-42.52 (-56.95;-23.24)***	-84.75 (-88.34;-80.05)***	-91.71 (-95.42;-84.98)***
28	average household size	–	289.88 (121.39;586.62)***	129.67 (67.23;215.43)***	311.62 (174.89;516.33)***	394.63 (138.36;926.40)***
25	percentage of adult population(25–64 years old) that has completed upper secondary education	–	6.72 (5.35;8.11)***	1.91 (1.11;2.73)***	-1.20 (-1.79;-0.61)***	-1.65 (-2.69;-0.60)**
35	average population density per km^2	–	0.18 (0.13;0.24)***	–	-0.23 (-0.29; -0.18)***	-0.38 (-0.46;-0.30)***
45	extent to which persons describe themselves as atheistic versus religious[b]	–	510.70 (205.53; 1120.69) ***	–	231.85 (106.19;434.10)***	237.35 (0.58;1031.56)*
23	total health expenditure as percentage of GDP	–	-42.24 (-52.42;-29.88)***	-11.15 (-18.23;-3.46)**	–	-25.97 (-33.07;-18.11)***
8	patients have to be registered with a GP and it is not easy to change between GPs(1=yes;0=no)	-12.58 (-17.20;-7.71)***	293.60 (185.46;442.72)***	–	-44.03 (-58.81;-23.94)***	–
12	do pulmonologists, GPs or paedriaticians have guidelines for treating respiratory trac infections?(1=yes;0=no)	20.76 (15.62;26.13)***	-72.78 (-81.15;-60.67)***	-33.88 (-45.77;-19.39)***	–	–
31	male life expectancy at 65 years of age in years	9.63 (5.15;14.31)***	38.11 (22.13;56.19)***	69.23 (26.27;126.79)***	-	–
11	do gynaecologists, pulmonologists, GPs or paedriaticians receive any feedback on their antibiotic prescriptions? (1=yes;0=no)	-17.17 (-22.91;-11.01)***	-73.08 (-79.91;-63.94)***	–	94.71 (61.15;135.27)***	–
7	patients have to be registered with a GP and it is easy to change between GPs(1=true;0=false)	-	-37.42 (-51.56;-19.14)***	–	-33.55 (-42.29;-23.48)***	–

Table 6.3: Determinants of antibiotic resistance, continued

		E.coli[a]			S.pneumoniae[a]	
Number	Determinant	AMINOPEN[a]	CEPH[a]	FLUORO[a]	PNSP[a]	PNSP [a]
36	percentage of population aged≥ 65 years	–	51.08 (36.83;66.80)***	–	–	25.67 (20.32;31.25)***
49	age-standardized death rate per 100000 due to other acute respiratory infections	–	19.00 (3.64;36.63)*	–	–	21.74 (0.68;47.21)*
30	female life expectancy at 65 years of age in years	–		–	28.35 (11.56;47.65)***	22.35 (6.27;40.85) **
41	year average dew point (in °C) as measure of relative humidity of the air	–		11.30 (7.82;14.89)***	13.24 (7.22;19.60)***	
21	percentage of infants vaccinated against mumps	–		–	1.36 (0.05;2.68)*	2.89 (0.86; 4.96)**
1	poverty rate: percentage of people earning < 60% of the median income(made equivalent after social transfers)	-1.59 (-2.35;-0.83)***	9.02 (4.05;14.23)***	–	–	–
4	number of different antibiotic products for sale in the pharmacy	–	2.92 (1.38;4.48)***	–	–	–
29	female life expectancy at birth in years	–	–	-24.29 (-37.87;-7.76)**	–	–
38	percentage of population aged between 0 and 14 years	–	–	-11.46 (-14.72;-8.06)***	–	–
44	extent to which people consider greater respect for authority undesirable	–	–	-39.55 (-54.56;-19.57)***	–	–
34	male life expectancy at birth in years	–	–	–	-19.83 (-25.65;-13.56)***	–
6	patients do not have to be registered with a GP, but there is a financial benefit for being registered with a GP(1=true;0=false)	–	–	–	–	109.00 (53.69;184.21)***

Table 6.3: Determinants of antibiotic resistance, continued

		E.coli[a]			S.pneumoniae[a]	
Number	Determinant	AMINOPEN[a]	CEPH[a]	FLUORO[a]	PNSP[a]	PNSP [a]
5	number of hospital beds per 100,000 inhabitants	–	–	–	–	0.36 (0.26;0.47)***
22	number of GPs per 100000 inhabitants	-0.09 (-0.15;-0.02)*	–	–	–	–
3	United Nations Development Programme (UNDP) Human Development Index (HDI)	-79.24 (-94.13;-26.56)*	–	–	–	–
15	private households' out-of-pocket expenditure on health as a percentage of total health expenditure	1.83 (1.45;2.21)***	–	–	–	–
18	public sector expenditure on health as a percentage of total government expenditure, WHO estimates	4.71 (3.37;6.06)***	–	–	–	–
43	percentage of regular daily smokers in the population aged > 15 years	-1.06 (-2.00;-0.11)*	–	–	–	–
10	are there any restrictions on pharmaceutical companies regarding providing dinners or conferences or breakaways or presents to physicians?(1=yes;0=no)	41.85 (30.03;54.74)***	–	–	–	–

Determinats of resistance rates, displayed as exponentiated regression coefficients(with95%Wald CI),in an MI–GEE model based on the Poisson distribution with log link.Numbers of intermediate and fully resistance counts were used as the response and the total number of tests was used as the offset.The effects have a multiplicative interpretation. One unit increase in the determinants leads to a multiplication of the specific effect. For instance, if specific consumption increases by 1 DID, the expected proportion of resistance counts is 1.47305 times higher.

[a]For E.coli we studied resistance to aminopenicillins(AMINOPEN), third–generation cephalosporins(CEPH) and fluoroquinolones(FLUORO). For S.pneumoniae we studied resistance to penicillins (PNSP) and joint resistance to penicillind and macrolides(PNSP). The significance level is indicated as *5% level, **1% level and ***0.1% level.

Significance level:*5%,**1%,***0.1% level. Selection was based on a 5% significance threshold.

[b]In this case the average is based on a religiousness score where people who declared themselves atheist were assigned the value 1 and those who declared themselves religious were assigned the value -1. Thus, this variable indicates the balance between self-declared atheists and self-declared religious people.

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Part IV

Cost-effectiveness analysis

Chapter 7

Economics of respiratory disease prevention

In this thesis part we shift focus from the empirical study of the treatment of infectious diseases with antibiotics using statistical models to the assessment of the cost-effectiveness of prevention of prevalent respiratory infectious diseases by vaccination using simulation models. Concretely we study seasonal influenza and pneumoccocal disease, which have a large impact and for which Belgian health care authorities are considering reimbursement [4]. In this introductory chapter we first provide the general biomedical background for these two illnesses, explain the concepts of cost-effectiveness analysis and outline the cost-effectiveness analyses of the next chapters.

7.1 Respiratory diseases

7.1.1 Influenza

Influenza disease is an acute viral respiratory infection caused by a strain of the influenza virus (A, B or less frequent by C) and occurs seasonally in the winter months in the northern hemisphere [18]. The virus' genetic information is coded by small RNA segments contained in the cell's nucleus which is covered by a cell membrane (envelop) containing surface proteins which help the virus invade a cell and on which the host's immune system responds (B-cell response). Because the virus can modify these surface proteins by frequent mutations in specific RNA fragments causing the substitution of amino acids in the surface protein while maintaining its function (antigenic drift) or by resorting its genome by exchanging RNA fragments with another influenza virus when two viruses invade the same cell (antigenic shift), the virus can evade an immune response of the host and reappear every season [14].

Transmission of the virus from one person to the next occurs by infected droplets which get into the air when an infected individual coughs or sneezes and which can be breathed in by unaffected individuals, leading in absence of a sufficient immune response of the newly infected, to the typical influenza symptoms: fever, cough, headache and muscle pain [18].

Estimation of the influenza specific disease burden is not straightforward since different viral and bacterial pathogens can cause the above symptoms called influenza like illness (ILI; [10]). Regression methods combining incidence and laboratory data have been proposed to estimate pathogen specific incidences [7]. The WHO assesses that globally about 5% to 10% of adults and 20% to 30% of children are affected. Usually this causes symptoms below 2 weeks in healthy adults but in high risk groups such as the young, elderly or chronically ill, hospitalisations and fatalities are likely to occur [18]. Even though chances of severe disease consequences are low for healthy

adults, the number of affected individuals at working age can have severe societal consequences due to productivity losses. For the UK a simulation study has estimated that under severe pandemic situations (more than 1% of the population dying) might reduce GDP up to 4.5% [13].

Due to the large influenza burden there is a large potential health impact for preventive measures such as vaccination and hygiene measures such as promotion of washing hands more frequently [18]. Vaccination can exert a strong influence on the influenza disease burden both directly by reducing the probability of acquiring disease by those vaccinated and indirectly by reducing disease transmission leading also to less cases in the non-vaccinated population (herd-immunity effects) [4].

In Belgium two vaccines might be considered to be used [4]:

- Life Attenuated Influenza Vaccine (LAIV) given as a nasal spray and approved for use to the age category 2-17 years by the European Medicines Agency
- Trivalent Inactivated Influenza Vaccine (TIV) given by injection and indicated for all ages above 6 months

Both vaccines are effective to prevent influenza disease and transmission, yet both share two important drawbacks. First since the influenza virus is constantly changing a prediction on which strains to include has to be made, which might be imprecise in some years. Second, since the technology to produce these vaccines is still based on eggs, the production is difficult to increase quickly leading to potential vaccine shortages [4].

7.1.2 Pneumococcal disease

Streptococcus pneumoniae or *pneumococcus* is a bacterial pathogen that can cause invasive and non-invasive disease which affects children and adults worldwide. The outer surface of this bacteria is covered by specific polysacharides protecting the bacteria from phagocytosis and distinguishing over more then 100 serotypes having a different polysacharide surface buildup, on which by the host's immune system responds to distinctively, although some cross-protection might exist between serotypes [6]. Figure 7.1 displays the colonisation and infection process of the pneumococcus. Like the influenza virus, the pneumococcal bacteria can be contained in small droplets in the air, which when breathed in might compete for colonisation of the nose and throat area (nasopharix) with other bacteria and other pneumococcal serotypes. Colonization is usually asymptomatic, but is of importance because it is the main driver of transmission [6]. In a very small percentage of cases this pneumococcal carriage can

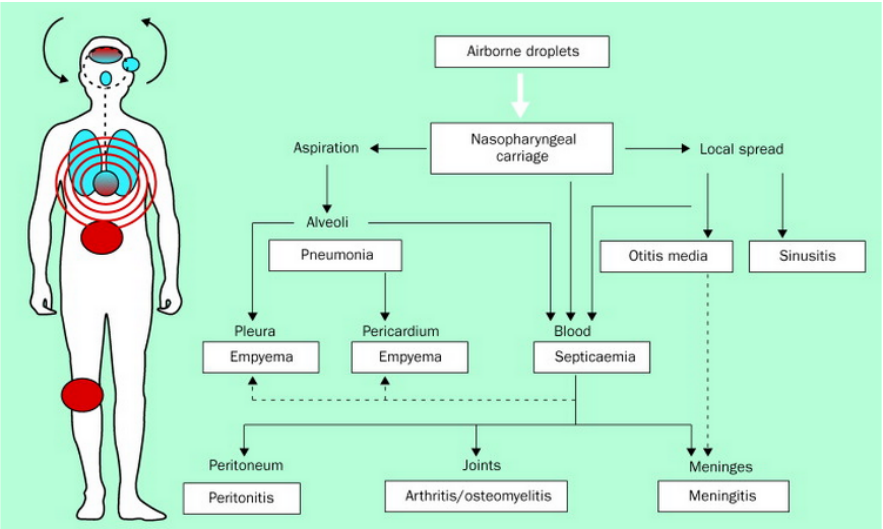

Figure 7.1: Pathogenic route for pneumococcal infection. Organs infected through the airborne and haematogenic routes are depicted in blue and red, respectively. Figure taken from [6] who redrew it from [16].

result in an infection of the ear (otitis media), sinuses (sinusitis) or lung (pneumonia), which eventually can give rise to the bacteria invading the bloodstream (bacteremia) which can result in an inflammatory response (sepsis), infection of the nerve cells in the spine and brain (meningitis, also following otitis media or sinusitis) or infection in other areas of the body [16]. We will make the distinction between non-invasive pneumoccoccal disease (non-IPD: sinusitis, otitis media and non-bacteremic pneumonia) where no bacteria enter an otherwise sterile site and invasive-pneumococcal disease (IPD: bacteremic pneumonia, meningitis and sepsis) where they do. Otitis media and sinusitis are most prevalent in children while pneumonia and its consequences affect both young children and the elderly [3]. Disease consequences can be severe especially in small children and the elderly population. A recent Belgian study showed that one third of elderly IPD patients required admission to an intensive care unit and 16% of patients died during hospitalisation and an additional 21% within one month after discharge [17]. In Belgium the yearly attributable disease burden over all ages of the pneumococcus before vaccination (2005) was estimated at 1,403 IPD cases of which 96 cases of meningitis and 500 of bacteremia predomently in young children and the elderly [3]. The reasons for which some pneumococcal colonisations result in disease are not completely understood, but the influenza virus is an important factor because

it can alter the lungs in a way that predisposes to adherence, invasion, and induction of disease by the pneumococcus [15].

The disease burden of the pneumococcus is alleviated by antibiotic treatment and prevention by vaccination. However, the antibiotics currently used to treat pneumococcal infections are losing their effectiveness because of the worldwide dissemination of penicillin-resistant and multiple antibiotic-resistant pneumococcal clones [8], making vaccination of increased importance. Two main types of pneumococcal vaccines exist: (1) *Polyvalent polysaccharide* vaccines contain a collection of polysaccharides found in the serotype specific pneumococcal capsule and in that way induce an immunity response (B-cell response); (2) In *Conjugated vaccines* the polysaccharides are conjugated to a carrier protein therefore inducing also T-cell-dependent immune response [6]. The additional T-cell immune response of the conjugated vaccine has the advantage of being long lasting even in young children whereas the polysacharide vaccines are not immunogenic in children and have only a limited duration of immune respose in adults [11]. A drawback of both type of vaccines is that they contain only a limited proportion of all serotypes, and when herd immunity effects occur, other serotypes might fill the gap eroding future vaccine effectiveness. Further details on pneumococcal vaccination in Belgium are provided in Section **??**.

7.2 Cost-effectiveness analysis

For both influenza and pneumococcal disease there exist various ways to reduce the disease burden. A society has to decide upon which measures to take. It could for instance take initiative and install a global vaccination program or decide to leave it up to the individual to choose to pay for vaccination and be vaccinated or not. On which basis could a society make this decision? Obviously health care choices have both health and financial implications. Setting up a vaccination program implies financing both vaccine and vaccine administration costs. On the other hand, vaccination will prevent some influenza cases, hospitalisations and fatalities which also have a value to society but are hard to express in monetary terms. Health economics is the framework studying such trade-offs between the monetary value (or other scarce resources) and health benefits.

The neoclassical view of economics claim that under some conditions, free markets, minimal government intervention will lead to Pareto optimal results. In the context of vaccination decisions, this would imply that letting everyone to decide for themselves to pay for vaccination or not will lead to an equilibrium were nobody can be

made better off without making at least one individual worse off (Pareto optimum). Alas markets fail to provide such an optimum in health care markets in general and vaccination markets in particular because of: (1) *Uncertainty*; patients are uncertain whether a vaccine will increase their health; (2) *Asymmetry of information*: a vaccine manufacturer or a physician knows more about disease risks then a patient; (3) *External effects*: the decision of one individual to be vaccinated will effect others [2]. The last issue is of particular importance because of possible herd effects of vaccination. A decision from a societies' point of view will be clearly more in favor of vaccination than a decision from an individual point of view, if vaccination creates health benefits beyond the individuals vaccinated.

Instead of relying on markets to make health care decisions, we will use cost-effectiveness analysis as a tool to rank different government health care interventions according to a comparison of the incremental cost and incremental effects of such interventions by representing them as a measure of population *health* per unit of monetary value. A society can then make an informed decision according to its willingness to pay for a quantity of *health* gained together with other values such as the fairness of the distribution of health gains of the intervention amongst inhabitants. Cost-effectiveness analysis entails calculating the incremental cost and incremental effects of an health care intervention usually relying on *models* which are simplifications of reality representing the causal pathway from the intervention to its costs and effects. Normally all relevant caused cost and effects should be taken into account, constrained by the viewpoint of the analysis: e.g. a health care payer's perspective takes only medical cost into consideration whereas a societal perspective also takes productivity losses into account. An overview of cost-categories to include can be found in [2].

To assess the cost-effectiveness of a vaccination program one can simulate the impact of increased vaccine uptake by running a model specifying the influence of vaccine coverage through vaccine protection to a number of disease cases leading to final outputs both in monetary value (cost of the vaccine, savings in other medical expenditure, ...) and effects (number of disease cases prevented the number of life years gained, ...) which are *discounted* to the present year. The key point is then to aggregate all effects into one health-measure. The aggregated Quality-Adjusted Life Years (QALY) gained is a population health measure which captures both reduced morbidity (quality gains) and reduced mortality (quantity gains) by taking the sum of quality weighted differences between life span under the intervention and non-intervention scenarios [9]. The weighing factor is an assessment of the quality of life which is measured on a scale from 0 for death to 1 for perfect health. The underlying

assumption is that the QALY represents a preference ordering in health states of a society, meaning more QALY is always preferred to less. A discussion on the relation between QALYs and utilities, different instruments to measure a QALY and alternative population health measures can be found in [9] and [12] and fall outside the scope of this introduction. Having calculated both total incremental costs (€) and incremental effects (QALYs) the ratio called the *Incremental Cost-Effectiveness Ratio* (ICER) is taken to order health care interventions by their cost-effectiveness. In *Probabilistic Sensitivity Analysis* (PSA) uncertainty of input parameters in a model is taken into account by drawing uncertain input values from the joint distribution function of the uncertain parameters and running a cost-effectiveness model multiple times yielding an empiric distribution function of incremental costs, effects and ICERs. In addition to PSA, uncertain values of which no distribution is available can be varied as fixed values in deterministic sensitivity analysis [5].

7.3 What we studied

We studied the cost-effectiveness of implementing vaccination programs to prevent respiratory diseases (influenza or pneumococcal disease) in adult risk groups focusing on prioritised adult risk groups in the case of influenza and on the comparison between alternative vaccines in the case of pneumococcal disease. Both studies rely on static models because herd effects are less important in the specific risk groups studied. Other risk groups require dynamic models, which for influenza are studied elsewhere [4]. For pneumococcal disease informing a dynamic model would require pneumococcal carriage data which is currently lacking for Belgium.

7.3.1 Prioritising influenza target groups

Risk groups with increased vulnerability for influenza complications such as pregnant women, persons with underlying illnesses as well as persons who come into contact with them, such as health care workers, are currently given priority (along with other classic target groups) to receive seasonal influenza vaccination in Belgium. In Chapter 8 we evaluate this policy from a health care payer's perspective by cost-effectiveness analysis in the three specific target groups above, while accounting for effects beyond the target group. Increasing the coverage of influenza vaccination is likely to be cost-effective for pregnant women (median €6,589 per quality-adjusted life-year (QALY) gained [€4,073-€10,249]) and health care workers (median €24,096/QALY gained [€16,442-€36,342]), if this can be achieved without incurring additional administra-

tion costs. Assuming an additional physician's consult is charged to administer each additional vaccine dose, the cost-effectiveness of vaccinating pregnant women depends strongly on the extent of its impact on the neonate's health. For health care workers, the assumed number of preventable secondary infections has a strong influence on the cost-effectiveness. Vaccinating people with underlying illnesses is likely highly cost-effective above 50 years of age and borderline cost-effective for younger persons, depending on relative life expectancy and vaccine efficacy in this risk group compared to the general population. The case-fatality ratios of the target group, of the secondary affected groups and vaccine efficacy are key sources of uncertainty.

7.3.2 Choice of pneumococcal vaccine

A recent trial demonstrated the 13 valent conjugate pneumococcal vaccine (PCV13) to be effective against invasive and non-invasive pneumococcal disease in the adult population. PCV13 might therefore be considered as an alternative to the currently used 23 valent polysaccharide vaccine (PPV23) in adults for which the effectiveness of preventing non-bacteremic pneumonia has not been demonstrated [1]. In Chapter 9 we explore influential factors for the cost-effectiveness of vaccinating adults over 50, with either PCV13 or PPV23 alone, or with a combined strategy using both PCV13 and PPV23. To this aim a static multi-cohort model was developed simulating the consequences of pneumococcal vaccination in adults over 50 from a health care payer's perspective, for different scenarios of duration of vaccine protection and serotype evolution. At currently expected prices, PCV13 vaccination is unlikely to be cost-effective either compared with no vaccination or in combination with PPV23 versus PPV23 only. Further research is needed on vaccine efficacy of the combination strategy, and the duration of protection for all options.

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Chapter 8

Seasonal influenza vaccination in adult risk groups

8.1 Introduction

Seasonal influenza causes a substantial number of symptomatic infections, hospitalisations and fatalities, especially in young children, the elderly and people with underlying illnesses [20]. The Superior Health Council of Belgium recommends giving priority to immunizing people at increased risk of influenza complications, namely people living in institutions, people with underlying illnesses and the elderly (>65 years). Furthermore, health care workers (HCWs), pregnant women in the 2nd and 3rd trimester of pregnancy, the general population between 50 and 64, and poultry and pig farmers and their household members, have priority over the general population [13]. Prioritisation is important, because the demand for influenza vaccines has surpassed supply in recent years [5]. Although these recommendations were based on the medical literature, their potential cost-effectiveness was largely unknown. Also, doubts have been expressed about the usefulness of influenza vaccination in view of uncertainties related to season-specific effectiveness in at-risk groups [22]. Therefore, up to date information on the cost-effectiveness of vaccinating these risk groups, may improve the prioritisation and acceptability of seasonal influenza vaccines. In this paper, we evaluate the cost-effectiveness of increasing seasonal influenza vaccine uptake in (1) pregnant women in their 2nd and 3rd trimester, (2) HCWs and (3) people with underlying illnesses. Currently these groups have relatively low vaccine uptake ($\leq$35% in 2008 [20]), despite the above recommendations. Cost-effectiveness analyses of influenza vaccination of the elderly are presented elsewhere [5]. We did not consider here the specific risk group of poultry and pig farmers, because the rationale for their vaccination (recombination of viruses in their work environment with potential risk to the general population) requires a different modelling approach.

The cost-effectiveness of vaccinating pregnant women [3, 23, 27], HCWs [19, 16, 12, 10] and people with underlying illnesses [2, 26, 28, 34, 36] has been evaluated before in other countries, but the results depended strongly on assumed vaccine efficacy. In this study, we use the most up to date estimates [30], and consider the potential impact of influenza vaccination beyond the target group. Vaccination during pregnancy has the potential to reduce foetal death through avoided maternal mortality, and confers vaccine-induced immunity to the neonate [40]. In previous cost-effectiveness analyses, these potential effects were not [3, 27] or only partially [23] accounted for. Vaccinating HCWs was also shown to have an effect on the patients they contact [9, 31]. This could be of particular importance for institutionalised or hospitalised patients and the elderly in general, and is therefore also considered in our analyses.

8.2 Material and methods

8.2.1 Decision analytic model

Since the groups of pregnant women, HCWs and people with underlying illness are relatively small in Belgium and are not core transmitter groups for the influenza virus, the cost-effectiveness of their vaccination can be analysed using a static model [4, 37]. For each risk group, a decision tree model was developed in the R software (R development Core Team, 2012, http://www.R-project.org). The general structure is displayed in Figure 8.1 and model parameters are listed in Table 8.1. The model assumes that susceptible individuals (unvaccinated or vaccinated without being protected) experience an age dependent rate of acquiring a symptomatic influenza infection for which they seek medical care. This rate is based on estimates from a dynamic model for influenza like illness (ILI) fitted to ILI surveillance data [5], combined with laboratory confirmed influenza proportions on these ILI data. We obtained the total number of symptomatic cases and thence the age-specific number of cases who do and do not seek medical care (i.e. do not consult a physician). Thus we obtained the number of cases not receiving medical care, ambulatory cases, hospitalisations and fatalities.

Direct medical costs and QALY losses associated with these outcome categories were included in order to compare the costs and QALYs of current with increased vaccine uptake scenarios (up to 50%; 40% for persons with underlying illnesses [20]). In accordance with Belgian guidelines [11], a health care payer's perspective was used under which morbidity and mortality-associated productivity losses to society were excluded. We did not make an exception for the target group of HCWs despite the fact that reductions in HCWs' productivity due to illness or death represent specific opportunity costs to the health care sector. However, we show in scenario analysis the potential impact of including such costs under a health care payer's perspective. Costs and non-fatal health outcomes were not discounted because of the short analytical time horizon (one year). Future life-years lost due to influenza-attributable mortality were discounted at an annual rate of 1.5%, in accordance with Belgian guidelines [11]. We assumed the vaccine is offered to pregnant women, on average in calendar week 47 (i.e. mid-November). We assumed also a 4-week delay before vaccinees benefit from vaccine protection. Hence, costs and QALY losses were included for infections occurring between calendar week 51 and 25 (assumed end of the influenza season), by using a partial attack rate in the model (84% of the yearly ILI cases occurs in that time window). According to the Belgian guidelines, pregnant women should receive

an influenza vaccine during the second or third trimester of their pregnancy, implying the average delivery date of pregnant vaccine recipients is in calendar week 7 (assuming uniformly distributed deliveries over the year and vaccination in calendar week 47). It is assumed that when the pregnant mother dies due to influenza, so does the foetus. Therefore, to account for fatalities in the period leading up to calendar week 7, the discounted expected life years lost of both the mother and her unborn child are summed to calculate the associated cost-effectiveness ratios. From calendar week 7 until week 25, infants can be assumed to be exposed to an autonomous risk of acquiring an influenza infection (one third of the annual attack rate in the infant (<1 year) age category). Within that period we foresee potential transferred vaccine-induced immunity from mother to child. Since the extent to which an immune response may translate into clinical protection is not yet demonstrated for our setting [32], we vary the factor by which vaccine efficacy is transferred from mother to child from 0% over 50% to 100% in sensitivity analysis. We ignore any separate health or cost consequences for the infants due to influenza-related deaths in mothers in the period after birth. Finally the occurrence of multiple pregnancies has not been accounted for, since they only make up a small part of the total number of pregnancies.
The health outcomes for secondary symptomatic influenza infections amongst elderly in contact with health care workers are calculated in the same manner as those for primary infections.

8.2.2 Data sources and input parameters

Table 8.1 contains all input parameters by risk group. In this subsection, we provide some background and clarification for these parameters.
The choice of age groups of people with underlying illnesses and elderly in contact with HCWs is based on the available input data and on plausible options for vaccination. The elderly population in contact with HCWs are conservatively assumed to have the same characteristics (hospitalisation costs, hospitalisation and death rates, etc.) as the general population of the same age class. We limited the analysis to above 50 year olds.
The number of yearly influenza-related hospitalisations and fatalities were estimated by applying an attributable fraction for influenza to reported influenza and pneumonia hospitalisations and fatalities. This attributable fraction was obtained by regressing weekly counts of influenza and pneumonia admissions and deaths on the weekly numbers of laboratory confirmed cases of respiratory pathogens that may cause influenza-like-illness or pneumonia (influenza (A and B), S. pneumoniae, aden-

ovirus, respiratory syncytial virus, M. pneumoniae, parainfluenza, and haemophilus), population size, holiday and school term indicators. Details of this regression analysis are described elsewhere [5].
Cost-effectiveness was only assessed for increased uptake of the trivalent inactivated influenza vaccine (TIV), up to 2013 the only influenza vaccine type available in Belgium, and reimbursed for pregnant women, HCWs and people with underlying illnesses (amongst other risk groups). TIV provides moderate protection against outpatient virologically confirmed influenza with a pooled vaccine efficacy of 59% [95% CI 51%-67%] [30]. This estimate was used irrespective of age or risk class, because there is currently no evidence suggesting differences according to such characteristics [20, 5, 30]. More recent evidence from case-control studies confirms this assumption [17, 21, 25, 33].

8.2.3 Uncertainty, variable importance and sensitivity analysis

Where appropriate, uncertainty around the input variables was specified as probability distributions (Table 8.1, [7]). For the hospitalisation and case-fatality ratios, the number of successes and the number of failures from the beta distribution are based on the predictions obtained from different selected 'best' regression models (see above). Model uncertainty was taken into account by randomizing with equal probability between selected regression models for the different outcome measures. To assess the uncertainty of the cost-effectiveness results, we conducted Monte-Carlo sampling with 10,000 draws taken from the joint input distribution, assuming independence of the uncertain input variables (i.e. probabilistic sensitivity analysis).
The relative influence of each of the uncertain variable was investigated by fitting multiple linear regression models with as covariates all standardized uncertain input variables and as response the incremental costs, the incremental QALYs gained and the net benefits. The net benefit was calculated by subtracting the incremental costs from the QALYs gained valued at €35,000 per QALY, corresponding to the criterion of 'very cost effective' strategy by the World Health Organization (WHO; [38]). The larger the absolute value of the regression coefficients, the more important the sampled input variable is in determining the response (incremental costs, QALYs and net benefits).
Probabilistic sensitivity analysis was repeated for different key model assumptions regarding clinical protection against influenza transferred from mother to child, the number of influenza cases caused in the elderly through contacts with HCWs, vaccine

efficacy and life expectancy of people with underlying illnesses relative to that of the general population. An important question regarding implementation is whether we can assume zero marginal administration costs for vaccinating pregnant women or HCWs, or whether an additional GP visit will be charged for these acts. Since this was unknown to the Belgian program managers, both these options were evaluated.

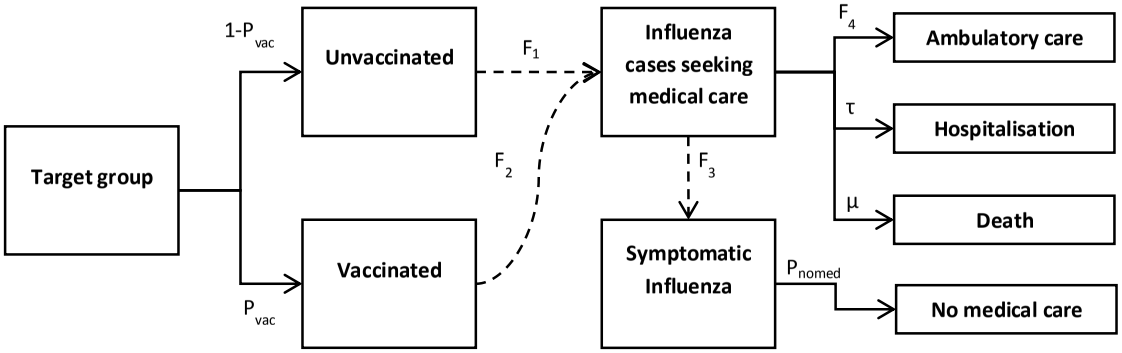

Figure 8.1: Basic structure of the static influenza model. Full arrows indicate the causal structure of the model. Dashed arrows indicate how the group sizes were calculated, when it is different from the causal structure, and how the sizes of the different groups were calculated using the input data available in Table 8.1. $F_1 = \lambda_{ILI} * P_{influ}$; $F_2 = F_1 * (1 - \epsilon)$; $F_3 = 1/(1 - P_{nomed})$; $F_4 = 1 - \mu - \tau$; P_{vac} is the vaccination coverage of the target group; λ_{ILI} is the yearly attack rate of influenza like illness (ILI) for which medical care is sought; P_{influ} is the proportion of influenza relative to the ILI cases seeking medical care; ϵ is the vaccine efficacy against influenza; τ is the influenza hospitalisation rate, μ the influenza death rate and P_{nomed} is the proportion of symptomatic influenza cases not seeking medical care (see also Table 8.1).

Table 8.1: Input parameter values and distributions used for pregnant women, health care workers and people with underlying illnesses

Parameter	Pregnant women[a]	Health Care Workers (HCWs)[a]	People with underlying illnesses	Source
Vaccination program and vaccine characteristics				
Size target group	121,363 (total birth cohort as a proxy for number of pregnant women per year)	239,740 (number of active registered HCWs in 2009 based on reimbursement data)	117,473 (0-14 years of age) 407,613 (15-15-49 years of age) 320,672 (50-64 years of age) 559,788 (over 65 years of age)(based on self-reported proportion of underlying illness applied to the population size per age group in 2010)	Table 1 and section 8.3 page 64 in [20]:
Vaccine uptake (P_{vac})	0 Assumed current vaccine coverage 0.50 Targeted vaccine coverage by the Belgian Health care knowledge centre (KCE) as a rough estimate of the proportion of yearly pregnant women eligible for vaccination due to relative timing of influenza season and pregnancy	0.35 Estimated current vaccine coverage 0.50 Targeted vaccine coverage by the KCE	0.20 Estimated current vaccine coverage 0.40 Targeted vaccine coverage by the KCE	Table 1 and page 65 in [20], estimates from 2008
Fixed marginal cost vaccination programme	€0			

[a]Pregnant women's age based on range 15 to 49 years (youngest and oldest mother in Belgium 2011), the health care workers' age is based on the entire age range of HCWs in Belgium (20-65 years), but narrower age categories (20-30; 30-50 and 50-65 years of age) are used in sensitivity analyses.

[b]Based on self-reported proportion of underlying illness applied to the population size per age group in 2010.

HCW: Health care workers

Table 8.1: Input parameter values and distributions used for pregnant women, health care workers and people with underlying illnesses, continued

Parameter	Pregnant women[a]	Health Care Workers (HCWs)[a]	People with underlying illnesses	Source
Variable vaccination costs: TIV per dose	€11.81			[1]
Variable administration cost per dose (GP visit in Belgium)	€0 or €23.32	€0 or €23.32	€23.32	[1]
Vaccine efficacy of the TIV vaccine (ϵ)	Gaussian (mean=0.59; sd=0.04)			[30]
Epidemiological parameters				
Yearly attack rate of influenza like illness (ILI) seeking medical care (λ_{ILI})	Weighted average over the age distribution			The yearly attack rate for patients with ILI seeking medical care was obtained by dividing the predicted number of ILI infections, under current vaccination coverage, from a dynamic transmission model (Section 5.1.1 in [5]) by the population size in that age cohort.
The proportion of influenza within the ILI cases seeking medical care (P_{influ})	Beta(2,070; 2,075)[b] for pregnant women Beta(132; 2,075) for neonates	Beta(2,070; 2,075)	Beta(751; 593) (0-14 years of age) Beta(751; 593) (0-14 years of age) Beta(2,070; 2,075) (15-49 years of age) Beta(2,070; 2,075) (50-64 years of age) Beta(142; 202) (over 65 years of age)	Laboratory test results in GP sentinel surveillance by the scientific Institute of Public Health Table 2 in [20]

[a]Pregnant women's age based on range 15 to 49 years (youngest and oldest mother in Belgium 2011), the health care workers' age is based on the entire age range of HCWs in Belgium (20-65 years), but narrower age categories (20-30; 30-50 and 50-65 years of age) are used in sensitivity analyses.

[b]Based on self-reported proportion of underlying illness applied to the population size per age group in 2010.

ILI: Influenza like illness

TIV: Trivalent Inactivated Influenza Vaccine

HCW: health care workers

Table 8.1: Input parameter values and distributions used for pregnant women, health care workers and people with underlying illnesses, continued

Parameter	Pregnant women[a]	Health Care Workers (HCWs)[a]	People with underlying illnesses	Source
The proportion of symptomatic influenza cases who do not seek medical care: no GP visit, not hospitalised. (P_{nomed})	Beta(1,107; 1,143)			Belgium ILI survey Section 4.2.1 in [5]
The hospitalisation rate of influenza cases seeking medical care (τ)	We randomize with equal probability between 3 scenarios: • Beta(7, DENOM[c]-7) • Beta(11, DENOM[c] -11) • Beta(15, DENOM[c] -15)	We randomize with equal probability between 2 scenarios: • Beta(18, DENOM[c] -18) • Beta(55, DENOM[c]-1.3)	• Beta(76, DENOM[c] -76) (0-14 years of age) • Beta(127, DENOM[c] -127) (15-49 years of age) • Beta(160, DENOM[c] -160) (50-64 years of age) For the age group over 65 years, we randomize with equal probability from the hospitalisation rates of the general population of that age (see reference)	Section 4.1.2 in [5]
The case fatality ratio of influenza cases seeking medical care (μ)	For pregnant women we randomize between 2 scenarios: Beta(0.1, DENOM[c]-0.1) Beta(0.2, DENOM[c] -0.2)	For HCW, we randomize between 2 scenarios: • Beta(0.6, DENOM[c] -0.6) • Beta(1.3, DENOM[c] -1.3)	• Beta(2, DENOM[c] -2) (0-14 years of age) • Beta(8, DENOM[c] -8) (15-49 years of age) • Beta(30, DENOM[c] -30)	Section 4.1.2 in [5]

[a]Pregnant women's age based on range 15 to 49 years (youngest and oldest mother in Belgium 2011), the health care workers' age is based on the entire age range of HCWs in Belgium (20-65 years), but narrower age categories (20-30; 30-50 and 50-65 years of age) are used in sensitivity analyses.

[c] DENOM refers to the denominator of the case fatality ratio and hospital rate, and has the meaning of the number of Influenza cases seeking medical care sampled from a run of the static model (see Figure 8.1) with the current uptake scenario vaccination coverage. Working with model based versus observed denominators had an ignorable impact on the cost-effectiveness.

ILI: Influenza like illness

Table 8.1: Input parameter values and distributions used for pregnant women, health care workers and people with underlying illnesses, continued

Parameter	Pregnant women[a]	Health Care Workers (HCWs)[a]	People with underlying illnesses	Source
	For neonates we randomize between model predictions of the general (hospitalised) population between 0-5 years of age[d]	We randomize between models for the elderly (hospitalised) population[d]	(50-64 years of age)	
			For the age group over 65 years we randomize from the case fatality ratios of the general (hospitalised) population of that age[c]	
Outcomes: quality of life and life expectancy				
QALY loss for an ambulatory patient	0.0071[e]			[29] , [5]
Duration of symptoms for an ambulatory patient	Gaussian(mean=6.43;sd=0.14)			[6]

[a]Pregnant women's age based on range 15 to 49 years (youngest and oldest mother in Belgium 2011), the health care workers' age is based on the entire age range of HCWs in Belgium (20-65 years), but narrower age categories (20-30; 30-50 and 50-65 years of age) are used in sensitivity analyses.

[c] DENOM refers to the denominator of the case fatality ratio and hospital rate, and has the meaning of the number of Influenza cases seeking medical care sampled from a run of the static model (see Figure 8.1) with the current uptake scenario vaccination coverage. Working with model based versus observed denominators had an ignorable impact on the cost-effectiveness.

[d] Hospitalisation rates and case fatality ratios of an age class of the general population were calculated by applying the attributable fraction of influenza derived from regression models to the observed number of influenza and pneumonia per observed influenza cases in the target group.

[e] This estimate is obtained based on the data presented in [29] This study provided the average VAS score per day for 7 days (+ standard error of the average), and the average number of days with symptoms (+ 95% confidence interval). To account for uncertainty, to each of these 8 data points (VAS scores for 7 days and number of days with symptoms), a normal distribution was assigned with standard deviation based on the standard error of the mean (VAS) or confidence interval (number of days). In the probabilistic sensitivity analysis, these 8 distributions were sampled independently to obtain the QALY loss for an ambulatory patient (=[sampled number of days with symptoms sum of the 7 sampled VAS scores]/365), and to propagate the uncertainty into the outcome of the cost-effectiveness analysis. This way of specifying uncertainty is not ideal (for example it assumes no correlation between number of days with symptoms and VAS scores per day), but represents in our opinion the best way, given the limitations of the data available. Also with this approach, the estimated average QALY loss for an ambulatory patient is similar as presented in O' Brien et al. [29] study (without confidence interval): 4.24 QALDs (cumulative utility score for 7 days [35]) = 6.8 - 4.24 QALDs lost = 0.0071 QALYs lost.

Table 8.1: Input parameter values and distributions used for pregnant women, health care workers and people with underlying illnesses, continued

Parameter	Pregnant women[a]	Health Care Workers (HCWs)[a]	People with underlying illnesses	Source
Duration of symptoms for a hospitalised patient	Gaussian(mean=8.5;sd=1.04)			[6]
Duration of symptoms for a person not seeking medical care	Gaussian(mean=5.51;sd=0.14)			[6]
QALY loss for a hospitalised patient	QALY loss ambulatory patient * ratio duration of symptoms hospitalised patient and duration of symptoms ambulatory patient			Assuming average QALY loss for a day with influenza does not differ between ambulatory patients, hospitalised patients and persons not seeking medical care
QALY loss for a person not seeking medical care	QALY loss ambulatory patient * ratio duration symptoms person not seeking medical care and duration of symptoms ambulatory patient			[29], Section 4.2.1 in [5]
Life expectancy	as a function of age	as a function of age	as a function of age multiplied with a factor 1 or 0.5 or 0.3 to investigate the influence of shorter life expectancy due to underlying illnesses	Eurostat data 2011 , http://epp.eurostat.ec.europa.eu/portal/page/portal/statistics/themes

[a]Pregnant women's age based on range 15 to 49 years (youngest and oldest mother in Belgium 2011), the health care workers' age is based on the entire age range of HCWs in Belgium (20-65 years), but narrower age categories (20-30; 30-50 and 50-65 years of age) are used in sensitivity analyses.

Age specific parameters such as the attack rate, hospitalisation costs and life expectancy were summarized by taking averages, weighted by the age distribution in the general population in 2011. For pregnant women, the weights were based on the frequency of live births by age of the mother.

Table 8.1: Input parameter values and distributions used for pregnant women, health care workers and people with underlying illnesses, continued

Parameter	Pregnant women[a]	Health Care Workers (HCWs)[a]	People with underlying illnesses	Source
Outcomes: Costs:				
We use a single randomization parameter for the following 3 cost categories, to randomize between the highest and lowest costs with equal probability				
Out-of-hospital costs for a hospitalised patient	lowest unit costs: Gaussian(mean=€119.65, sd=€17.69)			Section 4.2.1.5, Table 29 in [5]
	highest unit costs: Gaussian(mean=€139.94, sd=€20.19)			
Cost for an ambulatory patient (i.e. consulting GP)(no difference between ILI and influenza)	lowest unit costs: Gaussian(mean=€51.04, sd=€1.18)			Section 4.2.1.5, Table 27 in [5]
	highest unit costs: Gaussian(mean=€63.8, sd=€1.34)			
Cost for a person with ILI not seeking medical care	lowest unit costs: Gaussian (mean=€3.39, sd=€0.21)			Section 4.2.1.4, Table 23 in [5]
	highest unit costs: Gaussian (mean=€7.17, sd=€0.37)			

[a] Pregnant women's age based on range 15 to 49 years (youngest and oldest mother in Belgium 2011), the health care workers' age is based on the entire age range of HCWs in Belgium (20-65 years), but narrower age categories (20-30; 30-50 and 50-65 years of age) are used in sensitivity analyses.

ILI: Influenza like illness

Age specific parameters such as the attack rate, hospitalisation costs and life expectancy were summarized by taking averages, weighted by the age distribution in the general population in 2011. For pregnant women, the weights were based on the frequency of live births by age of the mother.

Table 8.1: Input parameter values and distributions used for pregnant women, health care workers and people with underlying illnesses, continued

Parameter	Pregnant women[a]	Health Care Workers (HCWs)[a]	People with underlying illnesses	Source
In-hospital cost for a hospitalised patient[f]	For pregnant women, we randomize between two options: • weighted average of primary influenza hospitalisation costs, for women with primary diagnosis influenza (€1,838.16) and • cost of women with primary diagnosis influenza and secondary diagnosis pregnancy complication (€1,481) For neonates we use the average hospitalisation cost of primary diagnosis influenza (€2,572)	Depending on the age group: • €2,513 (HCW, 20-65 years of age) • €1,653 (HCW, 20-29 years of age) • €2,300 (HCW, 30-49 years of age) • €3,660 (HCW, 50-65 years of age) • €3,660 (elderly, 50-64 years of age) • €4,825 (elderly 65-74 years of age) • €5,664 (elderly, over 75 years of age)	We calculate the cost per age of admission[g]: • €3,437 (0-14 years of age) • €4,576 (15-49 years of age) • €6,293 (50-64 years of age) • €7,507 (65+ years of age)	Supplement S1.1 of [5]

[a]Pregnant women's age based on range 15 to 49 years (youngest and oldest mother in Belgium 2011), the health care workers' age is based on the entire age range of HCWs in Belgium (20-65 years), but narrower age categories (20-30; 30-50 and 50-65 years of age) are used in sensitivity analyses.

[f]Direct costs for a deceased person are implicitly accounted for in the costs for medication, GP visit and hospitalisation, as the sum of these 3 relates to the total number of influenza cases (including those who die from influenza)

[g]People with underlying illnesses were identified by looking for following underlying ICD-9 diagnostic codes (http://icd9.chrisendres.com): asthma (493; V17.5), cardiovascular disease (989.1, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428, 413, 412, 410, 411, 414, 420, 422), chronic obstructive pulmonary disorder (490-492), diabetes (249, 250, V18.0, V77.1, 253.5, 588.1), HIV (042), hypertension (401-405, 997.91, 459.3) and stroke (430-438, 342).

Age specific parameters such as the attack rate, hospitalisation costs and life expectancy were summarized by taking averages, weighted by the age distribution in the general population in 2011. For pregnant women, the weights were based on the frequency of live births by age of the mother.

Table 8.1: Input parameter values and distributions used for pregnant women, health care workers and people with underlying illnesses continued

Parameter	Pregnant women[a]	Health Care Workers (HCWs)[a]	People with underlying illnesses	Source
Discount rates				
Discount rate for costs	0.03			[11]
Discount rate for health effects	0.015			[11]
Specific factors for the pregnancy model				
Proportion of attack rate (λ_{ILI}) exposure during pregnancy and during the period of vaccine protection for the cohort giving birth, on average, on 15th February. This period is defined as week 51-week 25	0.84	-	-	See attack rate (λ_{ILI})
In mothers who acquire influenza and die during pregnancy, the proportion of neonates who are not yet born. (Cases week 51-week 7 of the mother/ cases week 51-25 for women)	0.58	-	-	See attack rate (λ_{ILI})
Proportion of the attack rate (λ_{ILI}) applicable to neonates after they are born. (week 8-25)	0.33	-	-	See attack rate (λ_{ILI})

[a]Pregnant women's age based on range 15 to 49 years (youngest and oldest mother in Belgium 2011), the health care workers' age is based on the entire age range of HCWs in Belgium (20-65 years), but narrower age categories (20-30; 30-50 and 50-65 years of age) are used in sensitivity analyses.

ILI: Influenza like illness

Age specific parameters such as the attack rate, hospitalisation costs and life expectancy were summarized by taking averages, weighted by the age distribution in the general population in 2011. For pregnant women, the weights were based on the frequency of live births by age of the mother.

8.3 Results

8.3.1 Pregnant women

The cost-effectiveness of increasing vaccine uptake in 2nd or 3rd term pregnant women depends on the assumed vaccine administration cost and the degree of vaccine protection indirectly inferred to the new-born child. Increasing vaccine uptake is very likely to be cost-effective when there are no marginal administration costs. At marginal administration costs of 1 GP consult (€23.32), seasonal influenza vaccination of pregnant women would only be cost-effective, if indirectly transferred vaccine protection to the child is high (i.e. 100% in Figure 8.2). Figure 8.3 shows the variable importance, indicating that the case-fatality ratio of the mother, vaccine efficacy and QALY loss are all influential. Ignoring the life years lost due to the death of a foetus only has a minor impact on the cost-effectiveness (median ICER of €6,706 instead of €6,616 per QALY gained). With a per-season median of 26 versus 3 hospitalisations prevented, the incremental health gains of the program are larger for the neonates than for the pregnant women, respectively (see Table 8.2), due to the higher risks for neonates afflicted by ILI (mean proportion hospitalised 2.92%, based on the 0-4 year old age group).

8.3.2 Health care workers

Also for HCWs, vaccine administration costs have a large influence on the cost-effectiveness of influenza vaccination, as well as the extent of indirect protection conferred to the elderly population. That is, the assumed number of secondary symptomatic influenza infections among the elderly caused by an influenza case in the HCWs is influential. At zero marginal administration costs (i.e. vaccination during a routine medical visit or through occupational health doctor), increased influenza vaccination of active HCWs is likely to be cost-effective, even without accounting for secondary influenza cases (median ICER: €24,103 per QALY gained; 95% ICER range: €16,421-€36,355). If we assume at least one secondary symptomatic influenza infection in the elderly above 75 years of age per symptomatic infection in the HCWs the program becomes even cost-saving.

At marginal administration costs of one GP visit (€23.32), increased influenza vaccine uptake in HCWs can be considered cost-effective, only if at least one secondary symptomatic influenza infection in people older than 64 is assumed per 3 primary symptomatic infections in the HCWs. Alternatively, at least one secondary influenza case in persons aged 50-64 per primary case in HCWs can compensate for these marginal

Table 8.2: Incremental direct costs, Quality-Adjusted Life-years (QALYs) and cost-effectiveness ratio (ICER) of increased seasonal influenza vaccination uptake in different target groups. Results of 10,000 simulations, presented as median (mean) [95% range] (price level 2011)

	Pregnant women[a] (121,363 persons)	Health care workers[b] (239,740 persons)	People with underlying illnesses[c]		
			0-14 years of age	15-49 years of age	50-64 years of age
Program coverage	From 0% to 50%	From 35% to 50%	From 20% to 40%	From 20% to 40%	From 20% to 40%
Assumed marginal administration costs	€0	€0	€23.32	€23.32	€23.32
hospitalisations prevented - neonate	26 (26) [20-33]	-	-	-	-
hospitalisations prevented - target group	3 (3) [1-5]	3 (4) [1-8]	10 (10) [8-13]	17 (17) [13-21]	21 (21) [17-26]
Deaths prevented - neonate	0.07 (0.09) [0.04-0.33]	-	-	-	-
Deaths prevented - target group	0.00 (0.04) [0.00-0.33]	0.07 (0.10) [0.00-0.42]	0.23 (0.27) [0.03-0.77]	1.02 (1.06) [0.45-1.93]	3.96 (4.02) [2.63-5.77]
Incremental direct costs	€385,978 (€383,962) [€309,787-€450,365]	€709,703 (€709,133) [€673,983-€740,952]	€689,687 (€689,189) [€658,694-€716,877]	€2,476,027 (€2,473,748) [€2,388,545-€2,552,104]	€1,902,263 (€1,901,102) [€1,830,151-€1,967,352]
Incremental QALYs	58 (59) [40-85]	29 (30) [20-43]	31 (33) [20-56]	100 (101) [70-139]	132 (133) [97-176]
ICER	€6,616 (€6,763) [€4,097-€10,345]	€24,096 (€24,595) [€16,442-€36,342]	€22,008 (€22,596) [€12,180-€36,574]	€24,768 (€25,278) [€17,623-€35,725]	€14,378 (€14,610) [€10,627-€20,005]

[a] Assuming 100% vaccine efficacy transfer, leading to clinical protection, from mother to child trough maternal antibodies and zero marginal vaccine administration costs

[b] Assuming no secondary influenza infections in the patients they contact and zero marginal vaccine administration costs

[c] Assuming the same life expectancy as the general population of the same age and assuming the same vaccine efficacy estimate as the general population. Deviations from these assumptions are investigated in Figure 8.6. The group of over 65 year olds is not included because of lacking information on vaccine efficacy of that risk group

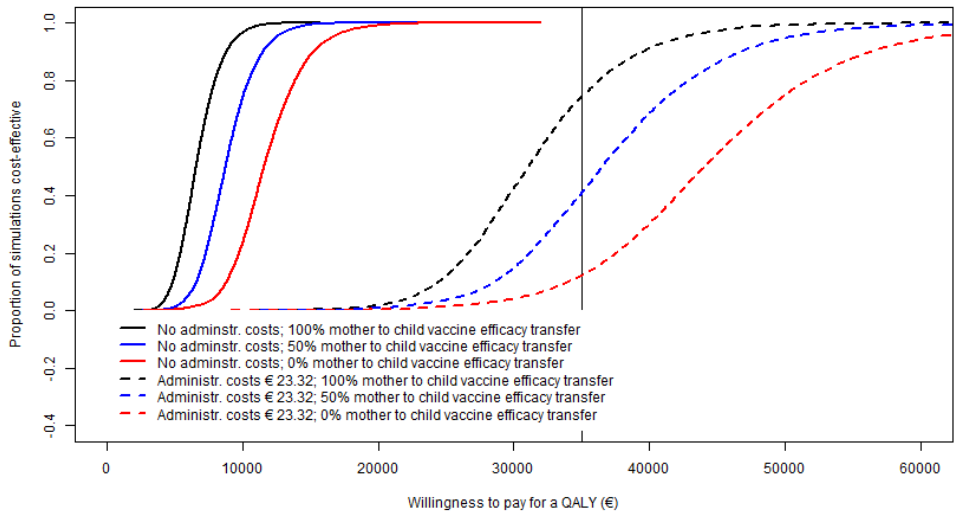

Figure 8.2: Cost-effectiveness acceptability curves for vaccinating 50% versus 0% of 2nd or 3rd term pregnant women while varying the administration cost from €0 to €23.32 and the percentage of transferred vaccine efficacy from mother to child after birth form 0% over 50% to 100%. The vertical bar indicates a willingness to pay for a Quality-Adjusted Life-Year (QALY) of €35,000.

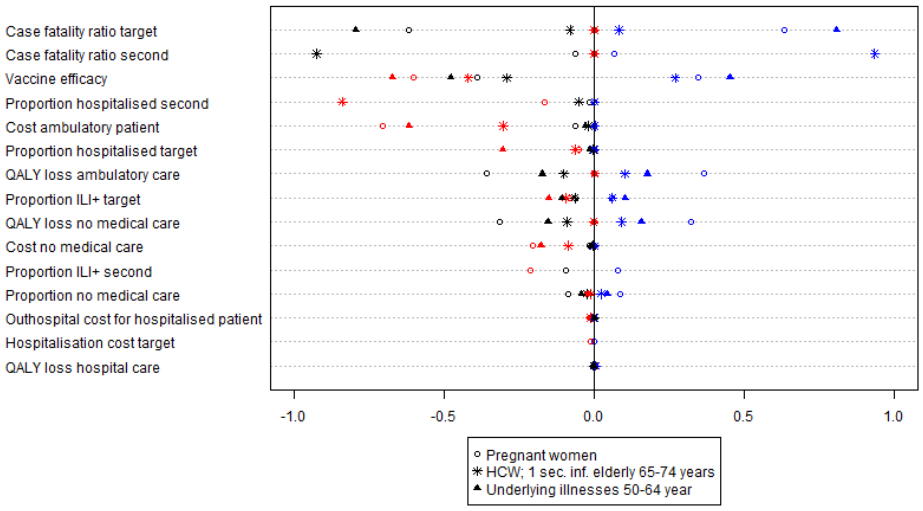

Figure 8.3: Variable importance by standardized coefficients in a linear regression model with as response incremental costs (red) of the program, incremental QALYs gained (blue), and net benefits[a] (black). The higher the absolute value of the standardized coefficient, the larger its relative influence.[b]

[a] To calculate the net benefit, 1 QALY gain was given an equivalent monetary value of 35,000. [b] Variables are ordered by the sum of squared regression coefficients of each variable over the different cost-effectiveness analysis and outcome measures (incremental costs, incremental QALYs gained and net benefits), so as to roughly order the variables from high importance to low importance. For clarity only one age class is presented for people with underlying illnesses and the elderly in contact with health care workers (HCW). Probabilistic sensitivity analysis of all age classes can be found below. Influence on a secondary group: neonates and the elderly for pregnant women and HCW respectively was taken into account. Variables related to the target group end with 'target', while variables related to the secondary group end with 'second', where relevant. ILI+ indicates lab confirmed influenza within symptomatic influenza like illness cases.

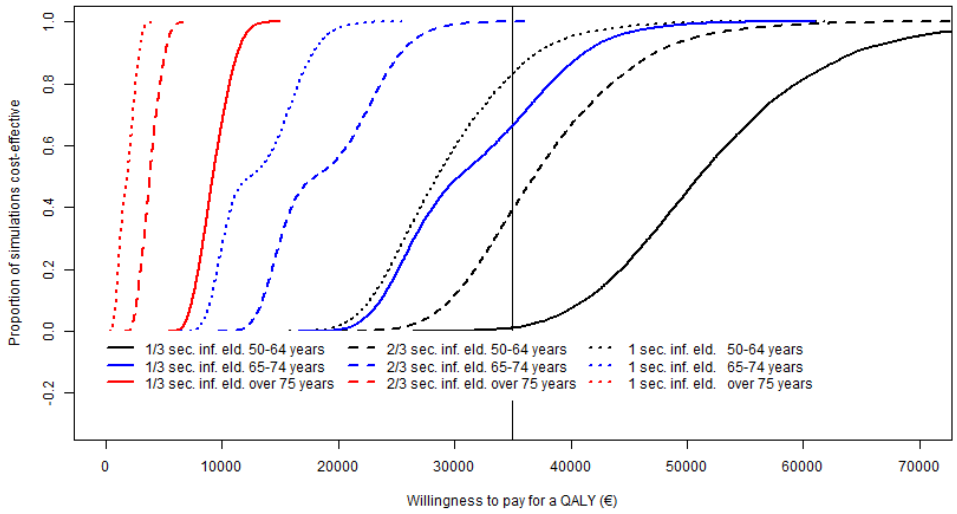

Figure 8.4: Cost-effectiveness acceptability curves for vaccinating 50% versus 35% of health care workers 20-65 years of age, with varying numbers of secondary infections in elderly patient groups of various ages ("sec. inf. eld." In graph legend), assuming marginal administration costs of €23.32. The vertical bar indicates a willingness to pay for a Quality-Adjusted Life-Year (QALY) of €35,000.

administration costs (see Figure 8.4). Including conservative (valued at nurse level of payment) morbidity associated productivity losses of HCW's would make vaccination significantly more attractive but not cost-effective to the health care system without assuming the prevention of secondary cases (see Figure 8.5). Without secondary cases prevented, the threshold productivity loss would need to be valued at €933 per day of illness in a HCW for the expected cost per QALY gained of vaccination to fall below the threshold of €35,000 and at €1,617 for cost savings to occur. Probabilistic sensitivity analysis, assuming one secondary symptomatic influenza infection per symptomatic infection in the target group, reveals that the uncertainties around the case-fatality ratio for secondary cases and the vaccine efficacy exert the highest relative influence on QALYs gained and consequently on the net benefits, irrespective of the age of secondary cases (see Figure 8.3). We additionally investigated splitting up the group of HCWs according to age. Observed changes in ICER values are minor, since differences in input variables between HCW age groups are small.

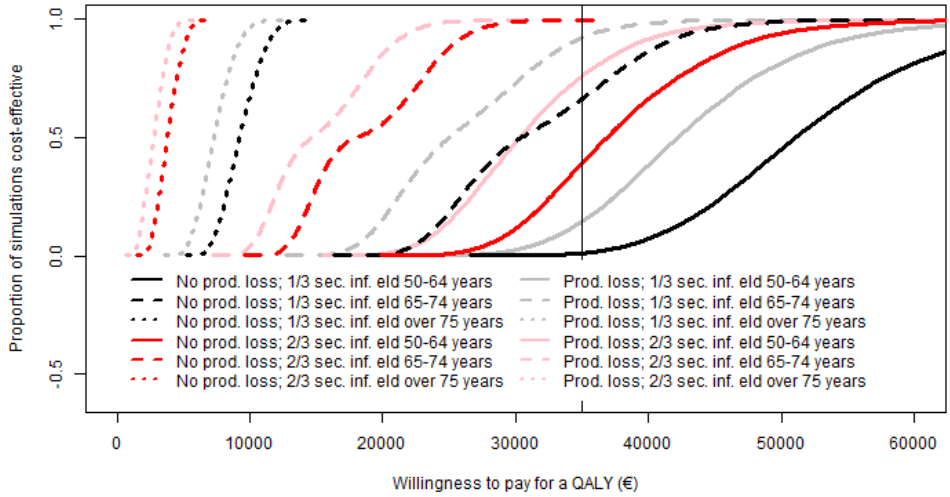

Figure 8.5: Cost-effectiveness acceptability curves for vaccinating 50% versus 35% of health care workers 20-65 years of age, with and without taking productivity loss[a] into account ("prod. Loss" In graph legend); for varying numbers of secondary infections in elderly patient groups of various ages ("sec. inf. eld." In graph legend), assuming marginal administration costs of €23.32. The vertical bar indicates a willingness to pay for a Quality-Adjusted Life-Year (QALY) of €35,000.

[a] Cost of productivity loss per day of symptoms in ambulatory or hospital care for health care workers was crudely estimated by the day cost of an ordinary nurse 274 (legal fixed monthly redistribution of full time equivalent health care worker by the Belgian health care system in 2011, divided by 20 days assuming full time employment in a 5 day per week schedule; http://www.riziv.fgov.be/care/nl/residential-care/pdf/residentialcare127.pdf) Differences in day cost between different categories of nurses had very minor effects on the cost-effectiveness results.

8.3.3 Persons with underlying illnesses

Increasing vaccine uptake in people with underlying illnesses is cost-effective for persons aged 50 and older, for all life expectancies considered (Figure 8.6 and Table 8.2). Also for younger persons, it is likely to be cost-effective for most combinations of uncertain parameters and life expectancies. The ICERs become less favourable when life expectancy of younger persons with underlying diseases is assumed to be only 30% of that of the general population of the same age group, and for small values of case-fatality ratios. Indeed, the uncertainty around the case-fatality ratio and to a lesser extent around vaccine efficacy are the most influential for all age groups, with the case fatality ratio being more influential in younger age groups. (Figure 8.3).
Joint deterministic sensitivity analysis of vaccine efficacy and life expectancy reveals that vaccinating older age groups (>65 years of age) is still likely to be cost-effective at substantially lower (e.g., <30%) vaccine efficacy values, provided the quality-adjusted life expectancy of the target group is at least 40% that of the same-aged general population (Figure 8.7.

8.4 Discussion

For pregnant women, we found increased influenza vaccine uptake to be particularly cost-effective (median ICER < €10,000 per QALY gained). This result is similar to that of Jit et al. [23], when assuming identical administration costs. Jit et al did not attribute life years lost to fetal death, but used a higher overall vaccine efficacy estimate.
Also for elderly with underlying illness (65+), increased vaccine uptake yielded generally acceptable cost-effectiveness. This contrasts with the few other studies for this target group (summarized in De Waure et al. [14]), mainly because we used a more favorable rapport between vaccine efficacy and occurrence of preventable disease.
Ours is one of the few studies to evaluate the cost-effectiveness of influenza vaccination in HCWs [24]. We demonstrated that the cost-effectiveness of vaccinating HCWs depends strongly on the assumed number of secondary symptomatic influenza infections prevented in elderly they contact, as well as these persons' ages and vulnerability to influenza. Up to now only Chicaiza-Becerra et al. [10] included such patient benefits. They found vaccination of Colombian HCWs who care for cancer patients, to be cost saving. Some of the studies not accounting for patient benefits, also reported favourable results [19, 12, 8]. Furthermore, there is empirical evidence to show that vaccination of HCWs might be more effective in preventing disease and

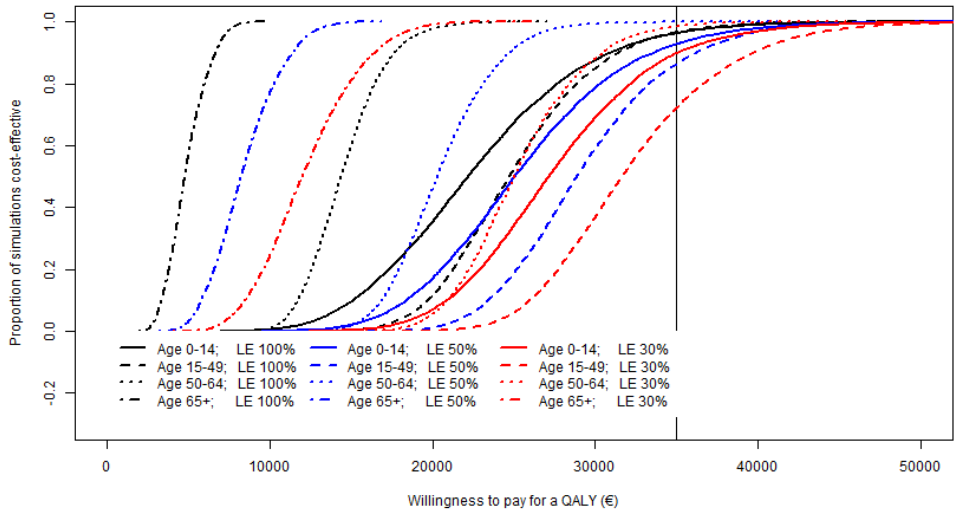

Figure 8.6: Cost-effectiveness acceptability curves for vaccinating 40% versus 20% of people with underlying illnesses, while varying their life expectancy (LE) from 100% over 50% to 30% of that of the general population of the same age. The vertical bar indicates a willingness to pay for a Quality-Adjusted Life-Year (QALY) of €35,000.

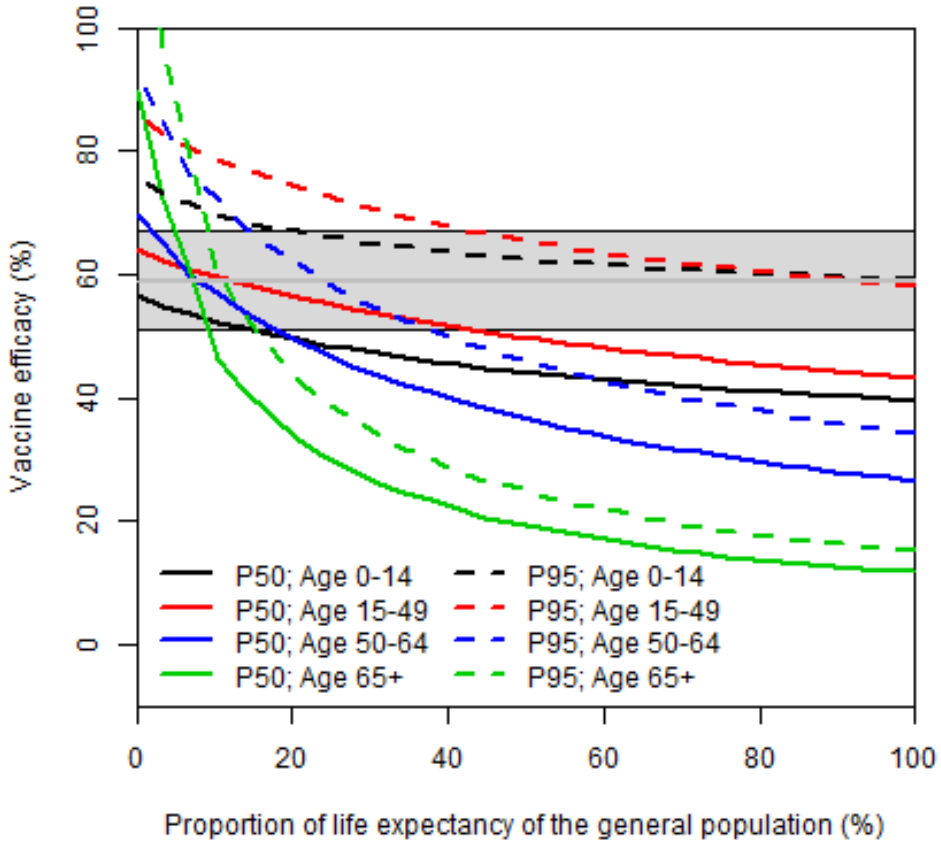

Figure 8.7: Combinations of vaccine efficacy (%) and the proportion of the target group's versus the general population's quality-adjusted life expectancy at the same age, which result in a median (P50) or 95th percentile (P95) incremental cost-effectiveness ratio of 35,000 per Quality-Adjusted Life-Year (QALY) gained. The shaded area represents the 95% confidence interval of the vaccine efficacy used in baseline analysis for healthy adults between 18 and 65 years of age. These values are calculated by varying the proportion of life expectancy over a grid (30 points equally spaced) and calculating the vaccine efficacy value which yields an incremental cost-effectiveness ratio equal to 35,000 per QALY gained. We simulated 10,000 draws from the joint distribution while changing vaccine efficacy and life expectancy values. Combinations of vaccine efficacy and life expectancy values above the 95th percentile curves (P95) are likely cost-effective at a maximum willingness to pay of 35,000 per QALY gained. P50 curves illustrate the associated parameter uncertainty in relation to the P95 curves.

death in the elderly in long-term care, than vaccinating these elderly patients directly [9, 31]. These results are likely to be generalizable to HCWs making contact with other vulnerable groups such as people living in institutions and persons with severe underlying illnesses. In investigating the cost-effectiveness of vaccinating HCWs in addition to such risk groups, secondary patient's effects are a key issue, requiring future empiric inquiry.

Our study has several limitations such as the above mentioned assumed secondary infections caused by HCWs and the use of one vaccine efficacy estimate irrespective of age, risk group and disease outcome. The vaccine efficacy was assumed constant over the different age and risk groups considered here since the most recent authoritative trial review found no age difference (in <65 years of age, [30]) and more recent observational studies found similar efficacy across risk groups [35, 32, 21, 18]. For vaccinating people with underlying illnesses above 65 years of age, reaching cost-effectiveness does not require that high a vaccine efficacy assumption (Figure 5). Setting up a clinical trial to determine the vaccine efficacy for this elderly population (>65 years) is recommended to fill this gap of knowledge as is investigating the possible differential influence of vaccination on the incidence of different disease outcomes. Better knowledge of vaccine efficacy would strongly reduce uncertainty in all presented cost-effectiveness results, because it remains a main source of uncertainty.

A further limitation arises from some conservative assumptions underlying the basic structure of our decision-analytic model. Firstly, for pregnant women and people with underlying illnesses, herd immunity effects were not accounted for. Indeed, for these target groups herd immunity is likely to be small, because they are not core transmitter groups in the general population or in specific settings. However, some mathematical models suggested that indirect protection could be conferred even in these risk groups [15, 39]. Possible indirect protection would make our results (somewhat) more cost-effective. Secondly, we assumed the vaccine would protect for only one season against the circulating strains. However, it seems plausible that some vaccine recipients would enjoy some residual protection into the next season. Thirdly, we opted for a mean approach for the relative timings of vaccination of pregnant women in relation to the onset of the influenza season and gestational age, based on previous seasons. However, previous studies found assumptions regarding these relative timings to be influential for the cost-effectiveness [23, 27]. Clearly, vaccination of second or third term pregnant women is more effective and cost-effective, if it can take place before or as early as possible in the flu season.

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Chapter 9

Adult pneumococcal vaccination

9.1 Introduction

Pneumococcal infection can cause severe invasive (IPD: meningitis and septicemia, pneumonia with bacteremia) and non-invasive diseases (non-IPD: otitis media, pneumonia without bacteremia). The invasive types have a high mortality in infants, the elderly and particular risk groups [15]. Currently two main vaccines are on the market to prevent the risk of severe pneumococcal disease in adults: (1) the 23-valent polysaccharide vaccine (marketed as Pneumovax23, henceforth called PPV23), protects against IPD caused by one of 23 prevalent serotypes taken up in the vaccine[12, 20]; (2) The 13-valent conjugate pneumococcal vaccine, marketed as Prevenar13 (henceforth called PCV13), provides protection against 13 serotypes [7, 8]. Recently, PCV13's efficacy in the elderly has been investigated in the CAPITA study, which showed the vaccine to be effective against both IPD -as PPV23- and non-bacteremic pneumonia [8] for which PPV23's protection is not demonstrated. Given the high incidence of pneumonia cases (bacteremic and non-bacteremic) in the elderly [22], this vaccine is being considered to replace PPV23 or to be given in addition to it. Previous conjugate vaccines have also been used in childhood containing fewer (PCV7 and PCV10) or the same number of serotypes (PCV13). Herd immunity effects of these childhood vaccination programs reduce - and in the long term may potentially lead to an overall elimination of - the vaccine type serotypes in the whole population, lowering the potential utility of pneumococcal vaccines in older age groups. Due to the new evidence on PCV13's efficacy in the elderly and the herd immunity effects of childhood vaccination programs, previous cost-effectiveness analyses on this subject require revision. In this paper we assess the cost-effectiveness of vaccination with either PCV13 or PPV23 for the healthy elderly population by age group (50-64, 64-75, 75-90) compared with no vaccination and the incremental cost-effectiveness of PCV13 and PPV23 versus PPV23 only. Given the large uncertainty on the evolution of vaccine serotype specific incidences and other input parameters, the results of this analysis should be seen as a preliminary fencing of the conditions (price, serotype coverage and duration of vaccine protection) under which vaccination strategies might be cost-effective. In the next section we explain the mathematical model, the data sources used and simulation scenarios considered.

9.2 Methodology

9.2.1 Model structure

We developed and applied an age-structured static multi-cohort model to simulate the costs and effects of adult pneumococcal conjugate vaccination strategies (See Figure C.1 in appendix). Single year age cohorts between 50 and 90 years of age are simultaneously followed from the moment of vaccination until death of the last survivor in the youngest cohort. The vaccines (PCV13, PPV23 or both), their timing and the applied scenario of duration and waning of vaccine-induced protection, determine each cohort's vaccine efficacy and together with serotype evolutions also the population at risk for every age in years post-vaccination, separate for IPD and non-IPD per serotype category (See Section C.1.1.1 in appendix). Age specific incidences are then applied to calculate IPD (pneumonia with bacteremia, meningitis and septicemia) and non-IPD (pneumonia without bacteremia) and their associated cost, deaths and quality-adjusted life years lost (QALYs). Long-term consequences of meningitis (hearing loss or neurological sequelae) are also taken into account. For details on the model structure see Section C.1.1 in appendix.

9.2.2 Model parameters

Table 9.1 and 9.2 contain the input parameters used in the model. In this subsection, we clarify main assumptions made.

Serotype-specific incidence (to calculate $Q_\tau(a, c)$ see Section C.1.1.1 in appendix) in adults is influenced by previous childhood (PCV13 and PCV7) vaccination. In the absence of Belgian studies on herd effects in adults, we used the same proportional yearly decay of circulating PCV7 serotypes as observed in 2-4 year olds over the period 2003-2008 (24% yearly decline [14]), and we show the impact of varying this percentage (from 0% over 12% to 24% proportional decline). The annual decline of 24% is almost identical to the PCV13 type specific incidence reduction recently reported for England and Wales (-64% over 4 years, [23]). The extent of serotype replacement, assumed equal for IPD and non-IPD, was varied between 0% and 100%. However, unless specified otherwise the middle of 50% was used to present results.

In the absence of empirical evidence and for ease of comparison we conservatively show results assuming PCV13 and PPV23 produce equal durations of vaccine protection of 5 years.

PPV23's protection against non-bacteremic pneumonia is assumed zero and the combination of PCV13 and PPV23 is assumed to have the per serotype best protection

over the two vaccines.

Where appropriate, uncertainty around input parameters estimates is specified in terms of probability distributions used for probabilistic sensitivity analysis, assuming independence between inputs.

In order to facilitate the interpretation of the results, we used a pragmatic cost per quality-adjusted life year gained (QALY) threshold of €35,000. This amount has been used before as a benchmark for Belgium [16, 5, 4, 6].

Table 9.1: Input parameters

Parameter	Description	Value (95% C.I.[a] or distribution)	Ref.
Vaccines and vaccination program characteristics			
Target vaccine uptake (P_{vac})	plausible scenario based on influenza vaccination in the elderly	75% versus no vaccination	[13]
PCV13 vaccine efficacy	against vaccine type non-invasive CAP	41.1% (12.7%; 60.7%)	[8]
	against vaccine type invasive pneumococcal disease	75.0% (41.4%; 90.8%)	[8]
PPV23 vaccine efficacy	against vaccine type invasive pneumococcal disease	55% (46%; 62%)	[20]
PPV23 duration of vaccine protection	against invasive and pneumococcal disease	5 years without waning, varied in sensitivity analysis	[24]
PCV13 duration of vaccine protection[b]	against invasive and non-invasive pneumococcal disease	5 years without waning, varied in sensitivity analysis	
Vaccine serotype coverage (A_τ)	before program implementation (2012-2014)	0% serotypes in PCV13 only; 54.81% in both vaccines; 34.68% PPV23 only, and 10.51 in no vaccine	National reference centre see Section C.2 in appendix
Vaccine administration cost per dose	List price conventional GP-visit	€23.32	[1]
Vaccine price PCV13	1 dose	€74.55; varied in sensitivity analysis	[1]
Vaccine price PPV23	1 dose	€28.46; varied in sensitivity analysis	[1]
Epidemiological parameters			
Proportion of outpatient pneumonia that is caused by the pneumococcus (P_{pncoc})	first term proportion identified by conventional techniques, second term proportion by urinary techniques	27.3% (23.9%; 31.1%) + 11.4% (9.6%; 13.6%); the total is varied over 0%-100% in sensitivity analysis	[21]

Table 9.1: Input parameters, continued

Parameter	Description	Value (95% C.I. or distribution)	Ref.
Proportion of hospitalised pneumococcal pneumonia that occurs with bacteremia (P_{bact})		24.8% (21.3%; 28.9%)	[21].
Probability severe bilateral hearing loss (e) after meningitis (d); ($\varphi_{IPD}(a, c, d, e)$)		16%	[19]
Probability of neurological sequelae (e) after meningitis (d); ($\varphi_{IPD}(a, c, d, e)$)		14%	[19]
Proportion of yearly PCV13 serotype decay	assumed proportional and equal for IPD and non-IPD	24% (varied 0%, 12% and 24% in sensitivity analysis)	[14]
Proportion serotype replacement	proportional accross non-PCV13 types	50% initially (0%and 100% in sensitivity analysis)	
Outcomes: (quality-adjusted) life years lost			
All cause death rate	as a function of age in years for 2012 (data last available year)		[2]
Life expectancy	quality-adjusted in total QALY calculation[c]		[2]
Population size at each age in years			[2]
Outcomes: costs			
Cost of hearing aids	per pair every 7 years	€1,000	[3]
Cost long term sequelae	per case	€35,000	[3]
Discounting and other cost-effectiveness settings			
Discount rate for costs		3%	[10]
Discount rate for health effects		1.5%	[10]

[a] These percentages were simulated as $exp(1 - lognorm(\mu, \sigma))$, with $lognorm$ representing a draw from the log-normal distribution with μ the log of the proportion estimate and $\sigma = \log(\frac{1-LL}{1-UL})$ caclulated from the lower and upper (UL) confidence limits(LL), following Briggs et al. [9]

[b] Duration of PCV13 vaccine protection is unknown, the CAPITA trial subjects were followed for 3.97 years on average [8], to allow direct comparison initially the duration of protection was taken the same as PPV23

[c] Age specific incremental QALY losses due to IPD and non-IPD for the adult population were calculated by multiplying the average disease-specific incremental QALY loss (Table 9.2) by the ratio of the average age specific health related quality of life in Belgium and the adult population's average health related quality of life in Belgium, assuming that the QALY loss due to IPD and non-IPD scales with the relative average health related quality of life measured in Belgium by the EQ5D instrument (unpublished data)

Table 9.2: Disease specific input parameters

Parameter	**Description**	**Value or distribution**			**Ref. Source**
		Pneumonia	**Meningitis**	**Septicemia**	
Hospitalisation rate (I_{hpn}[a] for pneumonia; $\gamma_{IPD}(a,c,d)$ other disease categories)	per disease category per 100,000 per year	17.4 (45-64 years)	0.9 (45-64 years)	1.9 (45-64 years)	[3]
		40.9 (65-74 years)	1.3 (65-74 years)	5.0 (65-74 years)	
		95.7 (over 75 years)	1.0 (over 75 years)	10.3 (over 75 years)	
Outpatient all cause pneumonia incidence (I_{opn}[b])	per 100,000 per year	361 (45-64 years); 650 (65-74 years); 1,053 (over 75 years)			[3]
Case fatality ratio ($\omega_{IPD}(a,c,d)$)	proportion of hospitalisations that are fatal	per ten year age group from 0.05 for 50-59 year olds to 0.35 for over 100 years olds[c]	10.3% (45-64years)	17.9% (45-64years)	[3]
			17.6% (65-74years)	15.9% (65-74years)	
			31.3% (over 75years)	27.1% (over 75years)	
Average QALY loss decrement	Age specific decrement calculated by multiplying this average with a Belgian age specific factor[d]	pneumonia 0.004 outpatients and 0.006 inpatients	0.460 QALY loss year one + 0.2 QALY loss every later year	Bacteremia 0.0079 per case	[18]

Table 9.2: Disease specific input parameters, continued

Parameter	**Description**	**Value or distribution**			**Ref.**
		Pneumonia[a]	**Meningitis[a]**	**Septicemia[a]**	**Source**
Hospitalisation costs (€)	Price level 2014; prediction mean (95% confidence interval)				[3]
	50 years of age	9,118 (7,075; 11,542)	9,415 (7,331; 11,897)	7,365 (4,880; 11,178)	
	65 years of age	11,476 (9,055; 14,450)	9,925 (7,954; 12,454)	10,961 (7,816; 14,722)	
	75 years of age	12,096 (9,385; 15,624)	10,254 (8,072; 13,057)	12,673 (9,017; 17,495)	
	90 years of age	14,267 (10,569; 18,595)	10,909 (7,791; 14,902)	14,940 (8,564; 25,152)	
Medical cost for out patient pneumonia		€1,032[e]			

[a] Following [3] hospitalised disease categories were identified using ICD-9 codes in the first diagnostic field of the Belgian government's hospitalisations database: Pneumococcal meningitis (320.1), pneumococcal septicaemia (038.2) and all cause pneumonia: (481 + 482.9 + 485 + 486).

[b] for d = outpatient pneumonia $\gamma_{nIPD}(a,c,d) = I_{opn} * P_{pncoc}$; for d = hospitalised non-bacteremic pneumonia $\gamma_{nIPD}(a,c,d) = (1 - P_{bact})\, I_{hpn}$; for d = hospitalised bacteremic pneumonia $\gamma_{IPD}(a,c,d) = P_{bact} * I_{hpn}$

[c] CAP mortality based on age specific Belgian data by gender, weighted average using population size to weigh (from Eurostat)

[d] See footnote [c] in Table 9.1

[e] Only 1 datapoint, varied in sensitivity analysis between zero and cost of hopitalised pneumonia, insignificant influence

9.2.3 PCV13 or PPV23 versus no vaccination

Since the duration of vaccine efficacy and the decline in PCV13 serotype specific incidence under the influence of the children's vaccination program are both highly uncertain, we studied these two factors in sensitivity analysis for the vaccination of 75% of each target group with either PCV13 or PPV23 compared to no vaccination. Given a limited follow up period of vaccine efficacy, we considered two distinct waning scenarios: In the first ("no waning scenario") we assumed no vaccine waning and a constant vaccine efficacy over the assumed duration of protection (varied between 4 and 15 years). In the second ("exponential waning scenario") we assumed 5 years of no waning (period of complete vaccine protection) followed by an exponential decay with its half-life value varied between 0 and 10 years. PCV13 serotype change was expressed as a simple proportional decline and was varied from 0 over 12 percent to 24 percent, the observed PCV7 decline. Compensation of this PCV13 incidence reduction, by serotype replacement, is assumed proportional to the current incidence of non-PCV13 serotypes and varied between none and complete PCV13 specific incidence compensation.

At each draw from the input distribution, we recalculate the vaccine price for which the incremental cost-effectiveness ratio (ICER) equals our defined threshold of €35,000 and summarize its distribution by taking the mean, median and 95% range. Since vaccine price and ICER have a strictly monotone relationship, the median threshold price (and other order statistics such as the 95% range) can be interpreted as the price for which the median ICER equals $€35,000$. This median price was taken as dependent variable in sensitivity analysis, to allow anticipation of price reductions by vaccine manufacturer competition in a tender system.

9.2.4 PCV13 and PPV23 versus PPV23 alone

In addition to studying the cost-effectiveness of various vaccination scenarios against no vaccination, we study possible conditions of incremental cost-effectiveness of adding a dose of PCV13 to an existing PPV23 program. The main added value of PCV13 vaccination lies in the demonstrated efficacy against non-bacteremic pneumonia. Therefore, we explore the impact of model assumptions regarding the proportion of outpatient pneumonia cases caused by pneumococcus and of non-bacteremic hospitalised pneumonia. Furthermore, model assumptions on the duration of vaccine protection and the evolution of the circulating serotypes causing pneumococcal disease are explored.

9.3 Results

9.3.1 Assuming equal uptake and duration of effectiveness for PPV23 and PCV13

Table 9.3 lists the incremental costs and effects of vaccinating 75% of the population per age group with either PCV13 or PPV23, assuming an equal duration of complete vaccine protection of 5 years without waning for both vaccines. This shows the clear advantage of PPV23 vaccination, for all age groups, in preventing invasive pneumococcal disease, indicated by the prevented number of meningitis and septicemia cases and partly by hospitalised pneumonia cases. The higher vaccine efficacy of PCV13 compared with PPV23 does not compensate for its lower serotype coverage, which is assumed decreasing by 24% yearly due to the childhood program.

In preventing pneumonia cases (hospitalised and outpatient) in contrast, PCV13 dominates PPV23 vaccination across all age groups. This is to be expected since PCV13 provides some protection against non-bacteremic pneumococcal pneumonia which is estimated to cause 75% of hospitalised pneumococcal pneumonia cases [21], while PPV23 offers no such protection. Because of the larger number of prevented pneumonia cases for PCV13, the result of vaccination on the discounted total QALY loss prevented is slightly in PCV13's advantage for all age groups investigated. The difference is most noticeable in >75 year olds where PCV13 vaccination prevents a median number of 878 QALYs (95% range: [505; 1,132]) while PPV23 prevents a median number of 613 QALYs (95% range: [498; 725]). Still these 95% ranges partially overlap. In contrast, PPV23 is clearly more cost-effective than PCV13 versus no vaccination for all age groups studied, when assuming 5 years of complete vaccine protection, equal uptake and current market prices. Both single vaccination programs are highly unlikely to reach cost-effectiveness at a willingness to pay of €35,000 per QALY gained. It is more cost-effective to vaccinate older than younger age groups. Vaccinating 75-90 year olds with PPV23 yields a median incremental cost-effectiveness ratio (ICER) of €49,760 per QALY (95% range: [40,298; 62,705]) versus 67,507 (95% range: [50,273; 124,875]) with PCV13. Since both vaccines yield comparable costs and effects, the large vaccine price difference between PCV13 (€74.55 per dose) and PPV23 (€28.46 per dose) is the main reason for the difference in cost-effectiveness.

In the next section we explicitly study vaccine prices for which a pneumococcal vaccination program might be cost-effective in relation to the duration of vaccine protection and serotype evolutions.

Table 9.3: Incremental effects, direct medical costs, vaccination costs, quality-adjusted life-years and incremental cost-effectiveness ratio (ICER) of 75% vaccination with PCV13 or PPV23 versus no program per age group, results of 1,000 simulations, presented as median (mean) [95% range], (price level 2014).

	PCV13			PPV23		
	50-64	64-75	75+	50-64	64-75	75+
Menigitis cases prevented	17 (17) [9; 21]	10 (10) [6; 13]	7 (7) [4; 9]	26 (26) [22; 30]	16 (16) [13; 18]	11 (11) [9; 12]
Hearing loss cases prevented	3 (3) [1; 3]	2 (2) [1; 2]	1 (1) [1; 1]	4 (4) [4; 5]	3 (3) [2; 3]	2 (2) [1; 2]
Sequelae cases prevented	2 (2) [1; 3]	1 (1) [1; 2]	1 (1) [1; 1]	4 (4) [3; 4]	2 (2) [2; 3]	2 (2) [1; 2]
Septicemia cases prevented	38 (39) [21; 47]	44 (45) [24; 55]	72 (75) [40; 91]	61 (61) [51; 69]	70 (71) [59; 80]	113 (113) [94; 129]
Hospitalised pneumonia cases prevented	223 (227) [123; 301]	242 (246) [133; 327]	443 (451) [244; 598]	136 (136) [107; 168]	149 (148) [116; 183]	262 (262) [205; 323]
Non-hospitalised pneumonia cases prevented	1,443 (1,478) [462; 2,287]	1,214 (1,244) [389; 1,924]	1,563 (1,601) [500; 2,477]	0 (0) [0; 0]	0 (0) [0; 0]	0 (0) [0; 0]
Menigitis deaths prevented	2 (2) [1; 2]	2 (2) [1; 2]	2 (2) [1; 3]	3 (3) [2; 3]	3 (3) [2; 3]	3 (3) [3; 4]
Septicemia deaths prevented	7 (7) [4; 8]	8 (8) [4; 10]	20 (20) [11; 25]	11 (11) [9; 12]	13 (13) [11; 15]	31 (31) [25; 35]
Pneumonia deaths prevented	14 (14) [8; 19]	27 (27) [15; 36]	77 (78) [42; 103]	9 (9) [7; 11]	17 (17) [13; 20]	46 (46) [36; 56]
Quality adjusted life years gained (discounted)	692 (705) [416; 888]	657 (669) [393; 857]	861 (878) [505; 1,132]	622 (623) [517; 723]	513 (512) [419; 603]	613 (613) [498; 724]
Medical costs prevented	5,674,115 (5,720,687) [3,295,757; 7,507,093]	5,215,622 (5,269,302) [2,933,910; 7,085,719]	8,431,525 (8,486,438) [4,632,300; 11,879,559]	4,435,087 (4,432,752) [3,669,111; 5,275,966]	3,616,790 (3,605,195) [2,886,018; 4,439,600]	5,285,196 (5,215,567) [4,057,566; 6,875,667]
Cost vaccination program	160,012,752	71,868,608	67,584,691	84,657,815	38,023,465	35,756,977
ICER (discounted)	232,352 (218,774) [172,069; 377,140]	106,399 (99,620) [76,032; 175,856]	72,556 (67,507) [50,273; 124,875]	130,051 (128,859) [110,111; 156,250]	67,791 (67,182) [55,912; 83,062]	50,263 (49,760) [40,298; 62,705]

9.3.2 Scenario analyses for separate use of the vaccines

9.3.2.1 50-64 years

PCV13 vaccination of 50-64 year olds is not cost-effective compared to no vaccination, at a willingness to pay of €35,000 per QALY, unless assuming that PCV13 type-specific incidence does not decline due to the childhood program and that the vaccine offers 11 years of full protection without waning (no waning scenario, see Figure C.2 in appendix). If we assume 5 years of complete vaccine protection followed by exponential waning (exponential waning scenario), the half life time of this exponential waning needs to exceed 6.5 years (see Figure C.3).

Likewise, PPV23 is not cost-effective for this age group unless the duration of complete protection exceeds 10 years in the no waning scenario or the half life time following 5 years of complete vaccine protection exceeds 5 years in the exponential waning scenario.

For both vaccine waning scenarios, PPV23 serotype disease incidence should remain constant; i.e. no PCV13 serotype incidence decay, or nearly complete compensation of incidence by non-PCV13 types, the most prevalent ones being captured by PPV23. No price reduction makes PCV13 or PPV23 in this age group cost-effective if PCV13 type specific incidence is reduced by the observed PCV7-type reduction in Belgium.

9.3.2.2 65-74 years

For vaccination of 65-74 year olds with PCV13 versus no vaccination to be cost-effective at the current price level we have to assume no PCV13-serotype coverage decay and a duration of complete vaccine protection exceeding 6 years (see Figure 9.1), or a half-life time exceeding 2 years when assuming exponential waning after 5 initial years of full protection (see Figure C.4 in appendix). Given a duration of complete protection of 5 years and a yearly PCV13 type incidence reduction of 24%, PCV13's price needs to decline to PPV23's level to be considered cost-effective according to our criteria. PPV23 vaccination in this age group can reach the cost-effectiveness threshold if there is no PPV23 serotype incidence reduction and the duration of complete protection is assumed longer than 5 years. If there is a reduction of PPV23 incidence by elimination of PCV13 types without replacement, cost-effectiveness can only be reached by assuming an increased duration of complete vaccine protection to 8 years (no waning) or assuming a half life of exponential waning over 8 years (exponential waning starting after 5 years).

9.3.2.3 75-90 years

The shorter remaining life span limits the influence of the duration of protection for the 75-90 year olds (see Figure 9.2). At the current vaccine prices and assuming at least 5 years of vaccine protection without waning and no vaccine preventable incidence reduction due to the childhood program, vaccination of this age group with PCV13 or PPV23 is likely to be considered cost-effective. A price reduction to about €50 is required to keep the median ICER of the PCV13 program acceptable when PCV13's preventable incidence decreases yearly by 24%. For PPV23 a reduction of vaccine price to €24, suffices to keep the median ICER of the program below the €35,000 limit. In the results above we focused on the median price for which the ICER equals a willingness to pay of 35,000 per QALY in each draw of the input distribution. In Tables C.1 and C.2 in in appendix we summarise price distributions in terms of the mean, median and 95% range for the scenario of 24% yearly PCV13 type incidence decay over a range of duration of protection (no waning) and half life values (exponential waning).

9.3.3 Scenario analyses of combined PCV13 and PPV23 use

The addition of PCV13 vaccination to PPV23 is not cost-effective at any age, when assuming a steady PCV13 serotype coverage and 5 years of vaccine protection for both PCV13 and PPV23 (Equal comparison scenario, Figure 9.3). The incidence rates of non-hospitalised pneumococcal pneumonia or of non-bacteremic hospitalised pneumococcal pneumonia have only a limited influence in this case. With 15 years of continued PCV13 protection, adding PCV13 to PPV23 is cost-effective for 65-74 year-olds, all else being equal. Given a small vaccine price reduction, this is also the case for the 75-90 year-olds. The extent of the required price reduction depends on other uncertainties which were explored in scenario analyses (Figure 9.3). The highest price is reached if all CAP is assumed pneumococcal CAP. A higher proportion of non-bacteremic pneumonia within hospitalised pneumococcal pneumonia reduces the maximum price at which the addition of PCV13 would be cost-effective, because PCV13 vaccine efficacy is higher against bacteremic pneumonia than against non-bacteremic pneumonia. However, the addition of a 12% yearly PCV13 serotype specific incidence reduction to the pro PCV13 scenario, renders this program no longer cost-effective, regardless of age group, CAP incidence (within the range) and proportion of non-bacteramic pneumonia within hospitalised pneumococcal pneumonia.

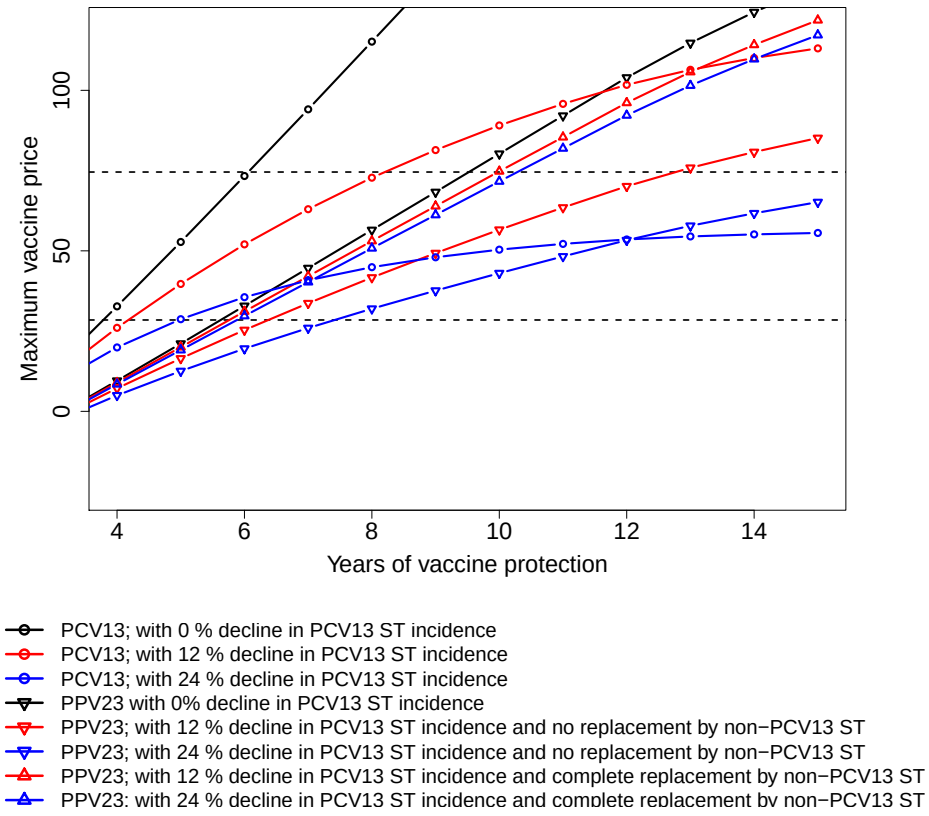

Figure 9.1: The influence of years of vaccine protection on the maximum vaccine price such that vaccinating 75% of 65-74 year-olds versus no vaccination is cost-effective (median of the distribution) at a willingness to pay of €35,000 per quality adjusted life year gained. Scenarios are shown of vaccine choice (PCV13 or PPV23), proportional yearly decline of PCV13 serotype (ST)-specific incidence in adults and complete (100%) or no (0%) replacement of PCV13-serotypes by non-PCV13 serotypes. Dashed lines represent the current PCV13 (€74.55) and PPV23 (€28.46) vaccine price, excluding administration costs.

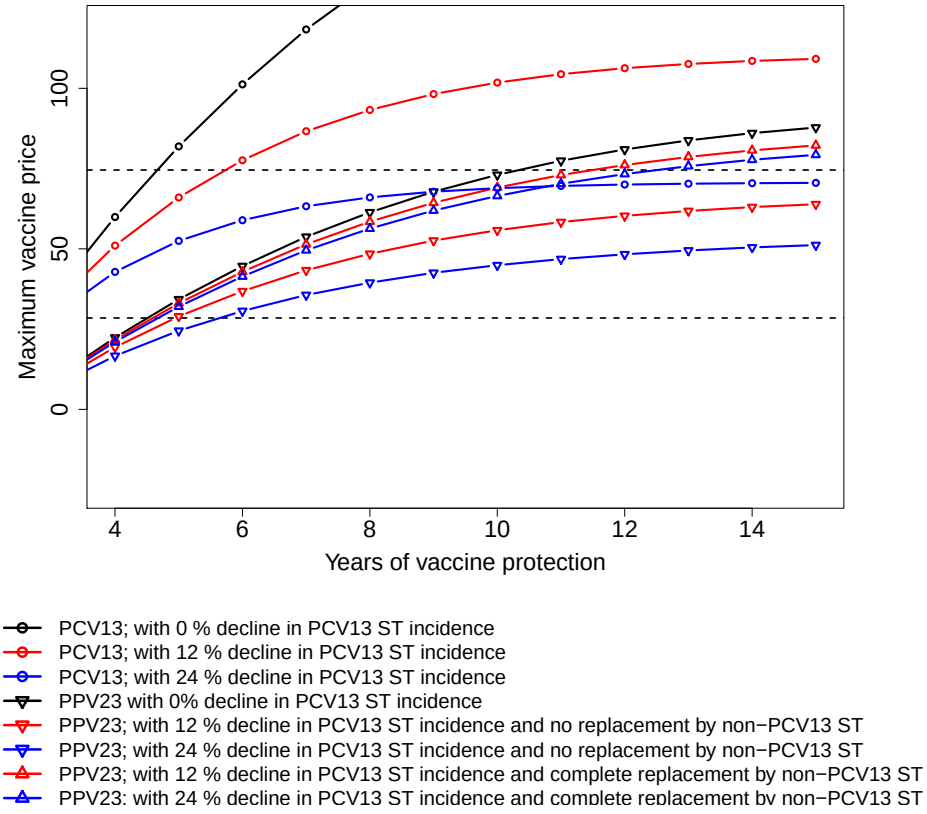

Figure 9.2: The influence of years of vaccine protection on the maximum vaccine price such that vaccinating 75% of 75-90 year-olds versus no vaccination is cost-effective (median of the distribution) at a willingness to pay of €35,000 per quality adjusted life year gained. Scenarios are shown of vaccine choice (PCV13 or PPV23), proportional yearly decline of PCV13 serotype (ST)-specific incidence in adults and complete (100%) or no (0%) replacement of PCV13-serotypes by non-PCV13 serotypes. Dashed lines represent the current PCV13 (€74.55) and PPV23 (€28.46) vaccine price, excluding administration costs.

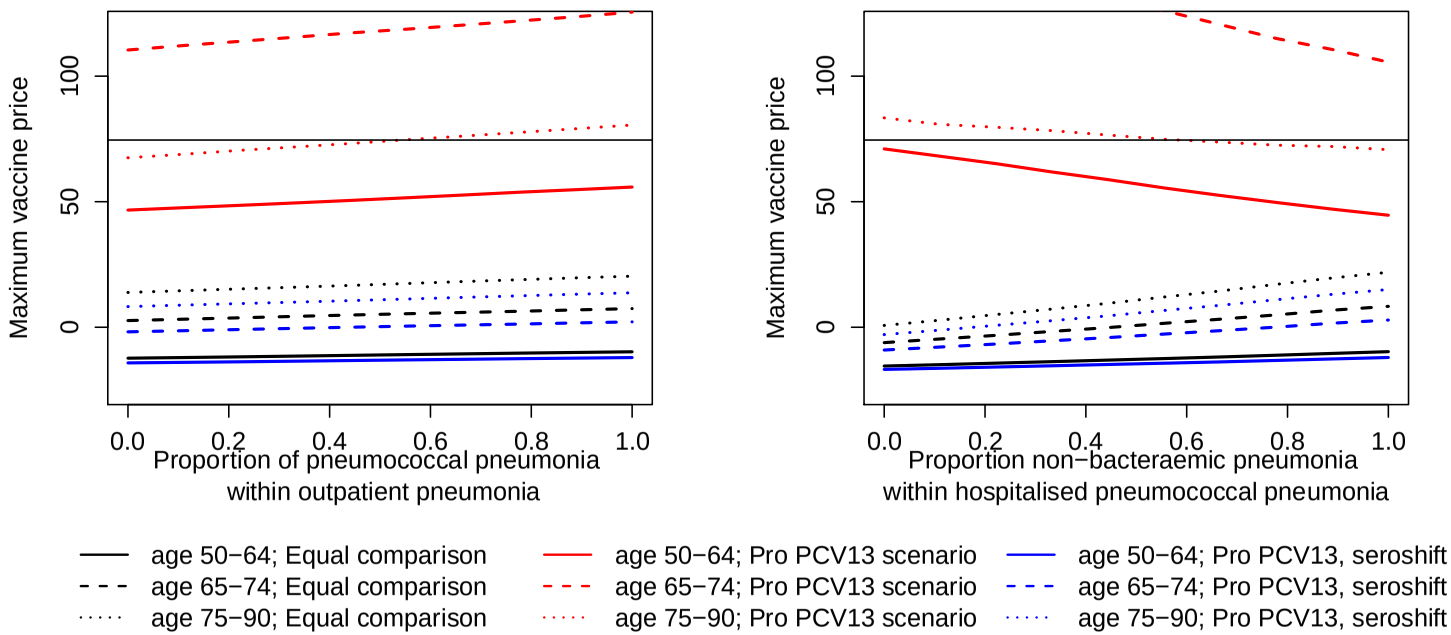

Figure 9.3: Age group dependent influence of the proportions of outpatient pneumonia caused by pneumococcus (left panel) and of hospitalised pneumococcal pneumonia that is non-bacteremic (right panel) on the maximum vaccine price such that adding PCV13 to PPV23 would be cost-effective (median of the distribution). Equal comparison scenario: 5 years duration of PPV23 and PCV13 vaccine efficacy without changes in serotypes causing disease in adults. Pro PCV13 scenario: 15 years duration of PCV13 vaccine efficacy. Pro PCV13, seroshift scenario = Pro PCV13 scenario, including a 10% reduction in PCV13 serotype specific incidence, without serotype replacement.

9.4 Discussion

We found pneumococcal vaccination programs in healthy adults > 50 to be cost-ineffective at a willingness to pay of €35,000 per QALY, using current price levels, plausible serotype incidence evolutions and assuming 5 years of complete vaccine protection (assumed to be age-independent in healthy vaccine recipients).

The strategy of vaccinating elderly adults with PPV23 only compared with no vaccination dominates PCV13 vaccination across age groups not because of higher effectiveness but because of a lower vaccine price.

Cost-effectiveness of PCV13 vaccination under a declining vaccine serotype coverage (24% yearly) due to the childhood program can realistically only be achieved in those aged over 65 years by reducing the vaccine price. Vaccinating the elderly population with PCV13 in addition to PPV23 is highly unlikely to be cost-effective at current price levels. Since the single dose programs were already relatively unattractive and relevant efficacy data are lacking, we did not explore scenarios including repetitive revaccination. Such scenarios may be explored in future analyses.

Earlier PCV13 cost-effectiveness studies in adults, before the CAPITA trial, in hindsight used unrealistically high vaccine efficacy estimates [11]. To our knowledge the only other published cost-effectiveness analysis that incorporates the CAPITA trial data, found generally highly cost-effective results for the Netherlands when incorporating relatively high vaccine efficacy of long duration in relatively common medium and high risk groups [17]. However, PCV13 efficacy in such risk groups is currently unknown. Mangen et al assumed in their main analyses that initial vaccine efficacy in high risk groups and elderly is 22%-35% lower than those observed in the subjects participating in the CAPITA trial. This assumption was based on PCV13 efficacy observed in children with HIV versus those without HIV. They also assumed that in all vaccine recipients the initial level of vaccine protection is maintained fully over 5 years, and then wanes slowly over the next 10 years (such that still about 45% of the original vaccine efficacy is maintained after 15 years). The vaccine serotype coverage also differed between Belgium and the Netherlands who had a PCV10 instead of a PCV13 childhood program in place, and therefore can expect more circulation of PCV13 specific serotypes. A drawback of the Dutch study is that it did not include the PPV23 vaccine, which we found to be more cost-effective because of the large price difference relative to a moderate effectiveness difference.

Our study has also limitations. Our pneumonia incidence data did not distinguish well between bacteremic and non-bacteremic pneumonia, which required us making assumptions in this respect. The impact of these assumptions is assessed

in Appendix C.5. We also assumed vaccine efficacies to be age independent. It is unclear to which extent the clinical trial vaccine estimates are applicable to the oldest age categories, knowing only 31.5% of subjects were aged above 75 years in the CAPITA trial [8]. Moreover, in this explorative analysis, conclusions can only be drawn for healthy adults, because at risk-groups with co-morbidities were not specifically targeted due to a lack of specific data. Especially for the oldest age groups, this is a restriction as many of them suffer from comorbidities. Lastly the model is not completely serotype specific (i.e. beyond serotypes grouped by vaccine formulation) and ignores per-serotype differences in disease incidences, severity of disease and case-fatality ratios.

In sum, our exploration focused only on three pivotal and currently largely unknown factors: (1) the evolution of serotypes causing pneumococcal disease in adults; (2) the duration of vaccine effectiveness and (3) the vaccination costs. The inclusion of age- and risk group specific vaccine efficacy estimates (including lower initial protective vaccine efficacy and more rapid waning of efficacy) will make the cost-effectiveness of older and higher risk target groups less attractive. It remains to be demonstrated whether in these groups these lower protective capacities are more than compensated by a much higher burden of disease (i.e. preventable hospitalisations and deaths) occurring over a shorter time period following vaccination to result in more favourable cost-effectiveness ratios than we have estimated for healthy adults. As outlined above, there are more unknown or uncertain elements to add to the three on which we focused here. Data to inform all these data inputs should make future explorations more detailed and accurate.

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Part V

Conclusion

Main findings and conclusions

Statistics

Generalized Estimating Equations (GEE) is a computational efficient way to determine the impact of covariates on a longitudinal response, requiring few assumptions. The method has however important drawbacks: variable selection methods and goodness of fit criteria are not well established.

In Chapter 2 we explored Penalized GEE (PGEE) with Elastic Net (EN) or L2-Smoothly Clipped Absolute Deviation (SCAD_{L2}) penalization to simultaneously select the most important variables and estimate their effects for longitudinal Gaussian data when multicollinearity is present. Asymptotic theory reveals that both the EN and the SCAD_{L2} penalty functions can achieve a consistent fit, however only the SCAD_{L2} has the additional property of selection consistency. This is also reflected in our simulation studies were the SCAD_{L2} outperformed all other methods with respect to prediction performance. Although the SCAD_{L2} displayed overall better prediction performance this might not always be the case. In practice we recommend exploring variable importance using EN-paths and base final inference on the model selected (EN or SCAD_{L2}) through cross-validation.

In Chapter 3 we reviewed the combination of either penalization methods or regression tree algorithms with linear mixed models, a likelihood based framework for longitudinal data analysis. Penalized Linear Mixed Models (PLMM) are similar to PGEE for covariate selection, but differ in their subject specific interpretation because they include random effects which also can be selected in that framework. Regression tree methods have the advantage of not requiring any assumptions regarding the functional relationship between response and covariates since the algorithm relies entirely on binary splits. Disadvantages are possible instability under multicollinearity. The extensions of data-mining methods such as penalization methods, tree based methods and others to longitudinal and clustered data merit further research and have a vast application area.

Determinants of antibiotic consumption

Antibiotics are the main treatment option for bacterial infections such as pneumococcal disease. Because of historic antibiotic use, bacterial populations have developed antibiotic resistance. In Part III we investigated possible determinants of outpatient antibiotic prescribing on the patient-prescriber level and on the country level.

For the patient-prescriber level, we investigated factors related to amoxicillin pref-

erences instead of co-amoxiclav and moxifloxacine as broad spectrum alternatives in Chapter 5. Controlling for patient characteristics, we discovered less active and female prescribers to more frequently choose amoxicillin for both children and adults, prescriber region and specialty of the prescriber to significantly interact and the age category 40-45 to have an increased preference for co-amoxiclav versus amoxicillin compared with both younger and older prescribers. Historical evidence reveals that physicians tend to stick to their prescriber habits of the past, even though the proportion or amoxicillin increased substantially for all prescriber age groups during the study period 2003-09. Female patients and patients from a less favourable social category are also observed to be prescribed more amoxicillin versus broad spectrum alternatives.

Intervention measures to promote better antibiotic prescribing can take these findings into account and focus on the age category 45-55 years of age. Since other effects are small, promoting antibiotic prescribing quality on the individual level rather than on the group level might be a more fruitful approach than targeting particular prescriber groups as a whole.

In Chapter 6 we zoomed out to the country level, where societal choices and socioeconomic, geographic and cultural differences might explain variations in antibiotic consumption. We focused on determinants of quantity of use, use of particular subgroups and antibiotic resistance. Factors describing the health care system were found to predict either higher (guidelines for treating respiratory tract infections) or lower (restrictions on the commercial conduct of pharmaceutical companies; number of antibiotics available) antibiotic use. Besides the health care system other factors contributed to explaining observed quantity of prescribing differences: Relative humidity, health expenditure as a percentage of GDP, feelings of distrust and the proportion of the population aged over 65 years were positively associated with antibiotic use. Population density, the proportion of adults who completed upper secondary education and the extent to which people describe themselves as atheistic rather than religious were negatively associated with antibiotic use.

The organisation of the health care system was the key factor to explain differences in relative consumption of antibiotic subgroups: the existence of regulations concerning the position of the GP within the health care system and incentives for seeing a GP first before a specialist physician reduces relative co-amoxiclav use. Restrictions on pharmaceutical companies reduces the relative share of amoxicillin and increased co-amoxiclav use.

Resistance analysis revealed that specific antibiotic use expressed in DIDs is not always the best predictor of current antibiotic resistance. Average household size,

life expectancy at 65 years of age of males or females, and non-religious feelings are found to be related to higher resistance levels whereas, incentives to visit a GP before consulting a specialist physician are found to be related to lower resistance levels in a country for all drug/bug combinations except for the resistance of E. coli to aminopenicillines.

This study showed that, apart from societal aspects over which policy has no control in the short run (such as population density, religiousness, and trust), there are a number of aspects that can be modified by policy makers and that might have a significant impact on antibiotic use and resistance in the short run. Such policies include strengthening the gatekeeping function of GPs and the authority of physicians over their patients. This can be done, for instance, by restricting the freedom of patients to consult many different GPs or to consult specialists directly. However, it should be accompanied by placing restrictions on direct marketing activities by pharmaceutical companies aimed at prescribing physicians, as this would also have a significant impact on consumption of antibiotics. Furthermore, it would seem prudent to provide feedback to physicians on their prescribing habits versus those of their peers. Clearly, such measures would have consequences far beyond the prescription of antibiotics. Therefore, they should be considered in their country-specific context, balancing aspects of access, quality, affordability, equity and cost-effectiveness of care.

Cost-effectiveness

In Part IV we assessed the cost-effectiveness of vaccination decisions to prevent influenza and pneumococcal disease. Chapter 8 focused on prioritising risk groups to be vaccinated against influenza using a decision tree model. We showed that increasing the coverage of influenza vaccination is likely to be cost-effective for pregnant women (median 6,589 per quality-adjusted life-year (QALY) gained [€4,073-€10,249]) and health care workers (median €24,096/QALY gained [€16,442-€36,342]), if this can be achieved without incurring additional administration costs. Assuming an additional physician's consult is charged to administer each additional vaccine dose, the cost-effectiveness of vaccinating pregnant women depends strongly on the extent of its impact on the neonate's health. For health care workers, the assumed number of preventable secondary infections has a strong influence on the cost-effectiveness. Vaccinating people with underlying illnesses is likely highly cost-effective above 50 years of age and borderline cost-effective for younger persons, depending on relative life expectancy and vaccine efficacy in this risk group compared to the general population. The case-fatality ratios of the target group, of the secondary affected groups

and vaccine efficacy are key sources of uncertainty.

A recent trail showed PCV13 to be effective against invasive and non-invasive pneumococcal disease in the adult population. Therefore in Chapter 9 we explored determinants for the cost-effectiveness of vaccinating adults over 50, with either the 23 valent polysacharide vaccine (PPV23) or the 13 valent conjugated vaccine (PCV13). A static multi-cohort model was used to simulate the impact of the duration of vaccine protection, vaccine serotype evolution and vaccine price on the cost-effectiveness of single or combined vaccination programs.

We found that at a willingness to pay of €35,000 per QALY assuming current prices, realistic serotype incidence evolutions and five years of vaccine protection elderly pneumococcal vaccination is not cost-effective. PPV23 would dominate PCV13 across age groups because of the large vaccine price difference. In above 65 year olds, a price reduction is needed to make PCV13 vaccination cost-effective under realistic serotype coverage evolutions. Vaccinating the youngest age category (50-64 years) studied with either PCV13 or PPV23 is not cost-effective unless assuming undemonstrated durations of vaccine protection. Vaccinating the elderly population with PCV13 in addition to PPV23 is not cost-effective compared with PPV23 vaccination only, unless under very strong, unrealistic conditions: long duration of protection and no decrease in PCV13 type specific incidence and a strong reduction in price.

Limitations and future research

Statistics

The PGEE estimator explored in Chapter 2 to select time dependent covariates for a longitudinal response when multicollinearity is present was limited to the Gaussian case and only cross-sectional associations can be retrieved. Moreover the working independence assumption might be inefficient. Future studies could investigate lag selection either in the PGEE or PLMM framework. This might require representing time dependent covariances by a spline function and develop new appropriate penalty functions. To better deal with multicollinearity issues, alternative penalty functions possessing the exact grouping effect, meaning putting highly correlated parameter exactly equal to each other, could be incorporated in either the PGEE or PLMM framework. This would have the additional advantage of recovering the grouping structure but might be computational intensive. For the PLMM framework new work could consider penalizing random and fixed effects jointly. From a theoretical point of view the development of significance test for penalization methods could shed

light on model and covariate selection as a whole. These issues are discussed in more detail in Chapter 3.

Antibiotic consumption

A major drawback of using administrative databases to identify patient-prescriber determinants of the choice between amoxicillin and broader spectrum alternative (Chapter 5) is the inability to take patient's underlying pathology or additional comorbidities such as HIV and cancer into account. Future studies might focus on incorporating them together with other aspects such as patient's expectations. Since found differences between prescriber groups apart from age are relatively small, future analyses may aim to identify physician groups with deviating quantity as well as quality of prescribing. This may facilitate actions targeted at the group level, additional to a personalised approach, through which individual physicians are confronted with their deviating prescribing versus that of their colleagues. The methodology and data used for identifying determinants of between-country differences of antibiotic consumption and resistance (Chapter 6) have some limitations as well: missing covariate data, short time series, rough association measures, no interactions or non-linearities allowed. The approach taken can be seen as a data mining exercise, uncovering rough material that should be worked on further. We hope to motivate future research focusing on some of the determinants separately by for example instrumental variable methods to discover potential causal effects. Another drawback of our methodology used is the instability of the stepwise variable selection procedure under multicollinearity. Multicollinearity implies that overlapping information is present in the variables, and different subsets of determinants can explain the same variation in the response. For example, female and male life expectancy are highly correlated and could be equally predictive of antibiotic resistance. In Chapter 2 we used penalization methods to perform selection for longitudinal data, which do not suffer from the instability issue. The performance of these penalization methods together with missing data remain to be investigated.

Only cross-sectional associations were investigated, whereas antibiotic resistance evolves dynamically, with current resistance levels being determined by selection pressure over time. Identifying the dynamics of resistance development would require longer and more precise data of both antibiotic consumption and resistance measurements.

Cost-effectiveness analysis

A major limitation of the cost-effectiveness analysis of both influenza and pneumococcal vaccination is the use of the vaccine efficacies irrespective of age and risk group. There was no clear evidence showing differences according to these characteristics, but future clinical trials may focus on informing vaccine efficacies for elderly and frail populations. Lower efficacy estimates would strongly influence cost-effectiveness results.

A second related uncertain factor is the extension of vaccine protection into the next season for influenza and the duration of vaccine protection in conjunction with the vaccine specific serotype distribution for pneumococcal disease. For influenza a partial extension of vaccine protection into the next seasons would make already cost-effective results even more so. For pneumococcal disease the duration of protection is a crucial factor determining possible cost-effectiveness provided the vaccine serotype coverage is not eroded in time due to the childhood program. The recording of duration of vaccine protection merits further epidemiological research as does the monitoring of pneumococcal serotype evolutions.

Part VI

Summary-Samenvatting-Dankwoord

Chapter 10

Summary

Background

Streptococcus pneumoniae or pneumococcus is a bacterial pathogen which can temporarily colonise the nose-throat area (nasospherix) of a human host, until the host's immune system clears it off. Several subspecies (serotypes) exist, to which the human immune system can react distinctively. These serotypes compete with each other to colonise human hosts by moving from one host the next by means of droplets in the air let out by sneezing or coughing colonised individuals. Usually, pneumococcal colonisation clears without symptoms. In some cases however, colonisation can cause ear infections, pneumonia, and even meningitis and septicaemia adding up to a high number of disease cases in children and adults worldwide. Influenza disease caused by the influenza virus is a key risk factor for the transition from asymptomatic carriage to pneumococcal disease.

Vaccination and antibiotics are used to prevent the influenza and pneumococcal disease burden, or treat pneumococcal disease respectively. The general aim of this PhD research is to study the treatment and prevention of pneumococcal disease from a statistical and economics point of view by (1) investigating the broader context of determinants of antibiotic consumption; (2) developing statistical methodology for variable selection in longitudinal data and (3) assessing the cost-effectiveness of influenza and pneumococcal vaccination programs in adult risk groups.

Antibiotic consumption

With the long term goal of improving antibiotic policy in mind, we studied antibiotic prescribing/use (1) at the prescription level to explain the prescriber's choice between small and broad spectrum antibiotics; (2) at the country-year level to assess the impact of the organisation of the health care system and background variables such as agriculture, culture, demography, disease burden, education and socioeconomic make up of a country. Controlling for patient characteristics, we discovered at the prescription level, less active and female prescribers to more frequently choose amoxicillin for children and adults, prescriber region and specialty of the prescriber to significantly interact and the age category 40-45 years old, to have an increased preference for co-amoxiclav versus amoxicillin. Historical evidence reveals that physicians tend to stick to their prescriber habits of the past, even though the proportion of amoxicillin increased substantially for all prescriber age groups during the study period 2003-09. From an intervention policy's point of view, the age difference is likely the only relevant finding, since other significant effect sizes are small.

At the country-year level, factors describing the health care system were found to predict either higher (guidelines for treating respiratory tract infections) or lower (restrictions on the commercial conduct of pharmaceutical companies; number of antibiotics available) antibiotic use. Besides the health care system other factors contributed to explaining observed quantity of prescribing differences: Relative humidity, health expenditure as a percentage of GDP, feelings of distrust and the proportion of the population aged over 65 years were positively associated with antibiotic use. Population density, the proportion of adults who completed upper secondary education and the extent to which people describe themselves as atheistic rather than religious were negatively associated with antibiotic use. The organisation of the health care system was the key factor to explain differences in relative consumption of antibiotic subgroups: the existence of regulations concerning the position of the GP within the health care system and incentives for seeing a GP first before a specialist physician reduce relative co-amoxiclav use.

Average household size, life expectancy at 65 years of age of males or females, and non-religious feelings are found to be related to higher resistance levels whereas, incentives to visit a GP before consulting a specialist physician are found to be related to lower resistance levels in a country.

Apart from societal aspects over which policy has no control in the short run (such as population density, religiousness, and trust), improving the organisation of the health care system in general and strengthening the gatekeeping function of the

GP in particular, might have a significant impact on reducing quantity and improving quality of antibiotic use.

Statistical methodology

In mining for the determinants of antibiotic use we relied on Generalized Estimating Equations (GEE) as a computational efficient way to determine the impact of covariates on a longitudinal response, requiring few assumptions. However variable selection methods and goodness of fit criteria are not well established within GEE. Therefore we explored Penalized GEE (PGEE) with Elastic Net (EN) or L2-Smoothly Clipped Absolute Deviation (SCAD_{L2}) penalization to simultaneously select the most important variables and estimate their effects for longitudinal Gaussian data when multicollinearity is present. Asymptotic theory reveals that both the EN and the SCAD_{L2} penalty functions can achieve a consistent fit, however only the SCAD_{L2} has the additional property of selection consistency. This is also confirmed in simulation studies were the SCAD_{L2} outperformed all other methods with respect to prediction performance.

The PGEE method together with recent extensions of the mixed model framework which includes a penalty part or incorporates a regression tree algorithm, greatly extend the tools to assess variable importance in longitudinal data.

Cost-effectiveness analysis

Increasing the coverage of influenza vaccination is likely to be cost-effective for pregnant women (median ICER[1] : €6,589 per quality-adjusted life-year (QALY) gained [€4,073-€10,249]) and health care workers (median €24,096/QALY gained [€16,442-€36,342]), if this can be achieved without incurring additional administration costs. Assuming an additional physician's consult is charged to administer each additional vaccine dose, the cost-effectiveness of vaccinating pregnant women depends strongly on the extent of its impact on the neonate's health. For health care workers, the assumed number of preventable secondary infections has a strong influence on the cost-effectiveness. Vaccinating people with underlying illnesses is likely highly cost-effective above 50 years of age and borderline cost-effective for younger persons, depending on relative life expectancy and vaccine efficacy in this risk group compared to

[1]Incremental cost-effectiveness ratio, i.e. cost per quality-adjusted life-year gained

the general population. The case-fatality ratios of the target group, of the secondary affected groups and vaccine efficacy are key sources of uncertainty.

A recent trail showed PCV13 to be effective against invasive and non-invasive pneumococcal disease in the adult population. Therefore we explored the cost-effectiveness of vaccinating adults over 50, with either the 23 valent polysaccharide vaccine (PPV23) or the 13 valent conjugated vaccine (PCV13). We found that at a willingness to pay of €35,000 per QALY assuming current prices, realistic serotype incidence evolutions and 5 years of vaccine protection, elderly pneumococcal vaccination is not cost-effective. PPV23 would dominate PCV13 across age groups because of the large vaccine price difference. In above 65 year olds, a price reduction is needed to make PCV13 vaccination cost-effective under realistic serotype coverage evolutions. Vaccinating the youngest age category (50-64 years) studied with either PCV13 or PPV23 is not cost-effective unless assuming undemonstrated durations of vaccine protection. Further research is needed on vaccine efficacy of the combination strategy, and the duration of protection for all options. The serotype distribution changes through childhood vaccination are also highly uncertain and influential and should be monitored.

Hoofdstuk 11

Samenvatting

Achtergrond

Streptococcus pneumoniae of pneumokok is een bacterie die de neus- en keelholte kan koloniseren van een menselijke gastheer, tot ze wordt teruggedrongen door het menselijke immuunsysteem. Verschillende ondersoorten of serotypen bestaan, waarop het immuunsysteem van een gastheer verschillend kan reageren. De serotypen wedijveren met elkaar om de kolonisatie van menselijke gastheren door van de ene naar de andere gastheer te verhuizen via druppeltjes in de lucht, losgelaten door het niezen of hoesten door een besmet individu. Gewoonlijk is pneumokokkendragerschap asymptomatisch. In een klein aantal gevallen, kan er echter een oor- of longontsteking optreden die uiteindelijk kan leiden tot meningitis of sepsis. Een voorgaande influenza-infectie veroorzaakt door een influenzavirus is een belangrijke risicofactor voor de overgang van asymptomatisch dragerschap tot pneumokokkenziekte. Vaccinatie en antibiotica worden respectievelijk gebruikt om de ziektelast, veroorzaakt door het influenzavirus of de pneumokok, te voorkomen of om pneumokokkenziekte te genezen. De algemene doelstelling van dit doctoraatsonderzoek is het bestuderen van het voorkomen en behandelen van de ziektelast van de pneumokok vanuit een statistische en economische invalshoek door (1) de bredere context van determinanten van antibioticagebruik te verkennen; (2) nieuwe statistische methodologie voor het selecteren van variabelen in longitudinale data te ontwikkelen en (3) de kosteneffectiviteit van influenza- en pneumokokkenvaccinatieprogramma's in volwassen risicogroepen in te schatten.

Antibioticaconsumptie

Met als algemene doelstelling het verbeteren van het antibioticabeleid, bestudeerden we antibioticavoorschrijfgedrag en consumptie (1) op voorschriftniveau om de keuze tussen smal- en breedspectra-antibiotica te verklaren; (2) het land- en jaarniveau om de impact van het gezondheidszorgsysteem en achtergrondvariabelen zoals landbouw, cultuur, demografie, ziektelast, onderwijs en socio-economische variabelen na te gaan. Wanneer we controleren voor patiëntenkarakteristieken, vinden we dat minder actieve en vrouwelijke voorschrijvers meer amoxicilline voorschrijven aan zowel kinderen als volwassenen, dat regio en specialiteit van de voorschrijver interageren en dat de leeftijdscategorie 40-45 jaar oud, een sterkere voorkeur heeft voor co-amoxiclav i.p.v. amoxicilline. Historische gegevens tonen aan dat voorschrijvers hun voorschrijfgewoonten uit het verleden gedeeltelijk aanhouden.

Op het land- en jaarniveau, vinden we organisatiekenmerken van het gezondheidszorgsysteem terug die een hoger (richtlijnen voor de behandeling van luchtweginfecties) of lager (beperkingen op het commercieel gedrag van farmaceutische bedrijven, aantal antibioticaproducten) antibioticagebruik voorspellen. Ook andere factoren buiten de organisatie van de gezondheidszorg verklaren verschillen in antibioticagebruik: gemiddelde relatieve vochtigheidsgraad, gezondheidsuitgaven als percentage van het bruto binnenlands product, gevoelens van wantrouwen tussen mensen en de proportie van de populatie ouder dan 65 voorspellen hoger antibioticagebruik. Populatiedichtheid, de proportie van volwassenen die middelbaar onderwijs volmaken en de mate waarin mensen zichzelf beschrijven als atheïstisch dan eerder religieus zijn negatief geassocieerd met antibioticagebruik. De organisatie van de gezondheidszorg was de belangrijkste factor om relatieve consumptie van antibioticasubgroepen het voorspellen: het bestaan van wetgeving die de positie van de huisarts binnen het gezondheidszorgsysteem regelt en het bestaan van stimulansen om eerst een huisarts voor een specialist te consulteren vermindert het relatieve gebruik van co-amoxiclav. Gemiddelde gezinsgrootte, levensverwachting op 65 voor mannen of vrouwen, en niet-religieuze gevoelens voorspellen hogere resistentieniveaus, terwijl het bestaan van stimulansen om eerst een huisarts vooraleer een specialist te consulteren lagere resistentieniveaus voorspellen. Los van maatschappelijke aspecten waarover het beleid geen controle heeft op korte termijn (zoals populatiedichtheid, religieuze gevoelens, en vertrouwen) kan het verbeteren van het gezondheidszorgsysteem en vooral dan het versterken van de poortwachtersfunctie van de huisarts leiden tot het verbeteren van de kwaliteit en verminderen van de kwantiteit van antibioticagebruik.

Statistische methodologie

Bij de zoektocht naar determinanten van antibioticaconsumptie, gebruikten we Generalized Estimating Equations (GEE) als een computationeel efficiënte en assumptie arme manier om de impact van covariaten op een longitudinale respons te bepalen. Een belangrijk nadeel is dat bestaande selectiemethoden binnen GEE niet goed kunnen omgaan met een grote hoeveelheid covariaten. Daarom verkennen we Penalized GEE met Elastic Net (EN) of L2-Smoothely-Clipped Absolute Deviation (SCAD_{L2}) penalisatie om zowel de belangrijkste variabelen te selecteren als hun effectgrootte te schatten voor normaal verdeelde longitudinale data waarbij er multicollineariteit bestaat binnen de verklarende variabelen. Asymptotische theorie toont aan dat beide penalisatiefuncties leiden tot een consistente schatting. Enkel de SCAD_{L2} leidt echter ook tot selectieconsistentie. Dit werd ook bevestigd door een simulatiestudie, waar de SCAD_{L2} beter presteerde dan elke andere penalisatiemethode op vlak van nauwkeurigheid en variabeleselectie. De PGEE methode samen met recente uitbreidingen van mixed models die een penalisatiefunctie of regressieboomalgorithme opnemen, hebben het gereedschap om het belang van covariaten in longitudinale data in te schatten, sterk uitgebreid.

Kosteneffectiviteitsanalyse

Het verhogen van de influenzavaccinatiegraad, is waarschijnlijk kosteneffectief voor zwangere vrouwen (mediaan ICER[1] : €6,589 per gewonnen kwaliteitsaangepast levensjaar (QALY) [€4,073-€10,249]) en gezondheidswerkers (mediaan ICER €24,096/QALY [€16,442-€36,342]), indien er geen extra vaccinadministratiekosten aangerekend worden. Als er een extra huisartsenconsultatie vereist is, wordt de kosteneffectiviteit van het vaccineren van zwangere vrouwen sterk afhankelijk van de impact op het kind. Voor gezondheidswerkers, beïnvloedt het aantal aangenomen secundaire infecties bij hun patiënten sterk de kosteneffectiviteit van vaccinatie van deze doelgroep. Het vaccineren van personen met onderliggende ziekten is waarschijnlijk sterk kosteneffectief boven de 50 jaar en mogelijk kosteneffectief voor jongere individuen, afhankelijk van de relatieve levensverwachting en vaccinefficaciteit vergeleken met de algemene populatie. De letaliteit van de doelgroepen, de invloed op secundair afhankelijke groepen en de vaccinefficaciteit zijn belangrijke bronnen van onzekerheid. Een recente trial bewees de effectiviteit van het PCV13 vaccin tegen invasieve en niet-invasieve pneumokokkenziekte bij volwassenen. Daarom verkenden we de kosteneffec-

[1] Incremental cost-effectiveness ratio, i.e. kost per gewonnen kwaliteitsaangepast levensjaar

tiviteit van het vaccineren van volwassenen boven de 50 jaar met ofwel het 23 valent polysacharide vaccin (PPV23) of met het 13 valent geconjugeerd vaccin (PCV13). We vonden pneumokokkenvaccinatie van deze doelgroep niet kosteneffectief aan een betalingsbereidheid van €35,000 per QALY tegen huidige vaccinprijzen, realistische serotype-evoluties en met 5 jaar vaccinbescherming. Door het grote prijsverschil is PPV23 vaccinatie voor alle leeftijdsgroepen kosteneffectiever. Een prijsdaling is nodig om het vaccineren met PCV13 kosteneffectief de maken, gegeven een realistische serotype-evolutie. Het vaccineren van de jongste leeftijdscategorie (50-64) met PCV13 of PPV23 is niet kosteneffectief, tenzij met een hoger dan aangetoonde duurtijd van vaccinbescherming. Verder onderzoek is nodig naar de vaccinefficaciteit van de combinatiestratiegie (PCV13+PPV23) en de duurtijd van vaccinbescherming van alle opties. Veranderingen in de serotypeverdeling door het vaccineren van kinderen zijn ook erg invloedrijk en zouden opgevolgd moeten worden.

Chapter 12

Dankwoord

Tot slot wil ik nog enkele mensen bedanken,

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Appendix A

Antibiotic prescriptions per prescriber and patient category

Table A.1: Importance of prescriber categories related to antibiotic prescriptions by GPs in Belgium to adults aged between 30 and 60 years in the period from July 2008 to June 2009

Variable	Category	Number of prescriptions of antibacterials for systemic use (ATC J01)	Number of prescriptions of amoxicillin (ATC J01CA04)	Number of prescriptions of co-amoxiclav (ATC J01CR02)	Number of prescriptions of moxifloxacin (ATC J01MA14)	Proportion of amoxicillin (ATC J01CA04) to total antibacterials for systemic use	Proportion of co-amoxiclav (ATC J01CR02) to total antibacterials for systemic use	Proportion of moxifloxacin (ATC J01MA14) to total antibacterials for systemic use	Proportion of total prescribers or patients	Proportion of prescriptions (ATC class J01)
Prescriber characteristics										
qualification	other GPs	25050	3533	7349	1334	0.141	0.293	0.053	0.093	0.011
	licensed GP	2287807	450288	568422	108747	0.197	0.249	0.048	0.806	0.9767
	GP in training	30070	7573	7535	969	0.252	0.251	0.032	0.101	0.0123
region	Brussels Capital region	153703	31395	39609	5331	0.204	0.258	0.035	0.113	0.066
	Flemish region	1318097	268998	316858	69763	0.204	0.24	0.053	0.526	0.563
	Walloon region	871127	161001	226839	35956	0.185	0.26	0.041	0.361	0.372
gender	male	1740887	332471	433510	85909	0.191	0.249	0.049	0.68	0.743
	female	602040	128923	149796	25141	0.214	0.249	0.042	0.32	0.257
age	20-29	45890	12694	10215	1613	0.277	0.223	0.035	0.032	0.02
	30-34	135780	31445	34230	5851	0.232	0.252	0.043	0.079	0.058
	35-39	222366	47296	56020	10621	0.213	0.252	0.048	0.103	0.095
	40-44	242624	46903	63145	12372	0.193	0.26	0.051	0.096	0.104
	45-49	382071	73864	98314	17385	0.193	0.257	0.046	0.139	0.163
	50-54	539514	99268	138028	26556	0.184	0.256	0.049	0.189	0.231
	55-59	444826	87111	106956	20475	0.196	0.24	0.046	0.173	0.19
	60-64	213156	40830	49542	10694	0.192	0.232	0.05	0.098	0.091
	65-69	65878	11949	15139	3109	0.181	0.23	0.047	0.043	0.028
	70+	50822	10034	11717	2374	0.197	0.230	0.047	0.048	0.022
active	non-active	148154	34888	37874	3946	0.236	0.256	0.027	0.258	0.063
	active	2194773	426506	545432	107104	0.194	0.249	0.049	0.743	0.937

Table A.2: Importance patient categories related to antibiotic prescriptions by GPs in Belgium to adults aged between 30 and 60 years in the period from July 2008 to June 2009

Variable	Category	Number of prescriptions of antibacterials for systemic use (ATC J01)	Number of prescriptions of amoxicillin (ATC J01CA04)	Number of prescriptions of co-amoxiclav (ATC J01CR02)	Number of prescriptions of moxifloxacin (ATC J01MA14)	Proportion of amoxicillin (ATC J01CA04) to total antibacterials for systemic use	Proportion of co-amoxiclav (ATC J01CR02) to total antibacterials for systemic use	Proportion of moxifloxacin (ATC J01MA14) to total antibacterials for systemic use	Proportion of total prescribers or patients	Proportion of prescriptions (ATC class J01)
Patient characteristics										
gender	male	931495	186705	270071	45480	0.2	0.290	0.049	0.421	0.398
	female	1411432	274689	313235	65570	0.195	0.222	0.047	0.579	0.602
diabetes	no diabetic	2202473	438554	544444	103524	0.199	0.247	0.047	0.948	0.94
	diabetic	140454	22840	38862	7526	0.163	0.277	0.054	0.052	0.06
reimbursement (higher reimbursement)	no higher reimbursements	1993918	398073	492549	94048	0.2	0.247	0.047	0.874	0.851
	higher reimbursement	349009	63321	90757	17002	0.181	0.260	0.049	0.126	0.149
social category	active	1615532	331391	393653	73122	0.205	0.244	0.045	0.714	0.69
	other	36699	7580	9719	1314	0.207	0.265	0.036	0.015	0.016
	PWDO	374771	59299	95687	21899	0.158	0.255	0.058	0.13	0.16
	unemployed	315925	63124	84247	14715	0.2	0.267	0.047	0.1413	0.1348
low income	no	2148508	425647	533929	102667	0.198	0.249	0.048	0.9312	0.917
	yes	194419	35747	49377	8383	0.184	0,254	0.043	0.0688	0.083

Appendix B

Country level determinants and statistical methodology

B.1 Details of the statistical methodology

B.1.1 Dealing with missing covariate data

We used multiple imputation (MI [12]) of missing covariates to limit the loss of too many observations or variables in the analysis. Multiple imputation provides valid estimates and p-values under the missing at random (MAR [13] missingness mechanism, meaning that the missingness distribution may depend on the observed data, but not the unobserved part. Even though this assumption cannot be checked MI is considered as a state of the art methodology to deal with missing data [14]. For each country-variable combination, missing values were imputed by sampling from the normal distribution, with mean equal to the weighted average of the observed data for a country, and variance equal to the pooled variance of that variable. The weights were determined by a tri-cube function, giving progressively less weight to more distant values in time. Missing values for a variable were not imputed for a country when no observations were available for that variable in the particular country. Categorical variables arising from the LNR survey were not missing and were therefore not imputed. Five imputed datasets were created to acknowledge the uncertainty of the imputation process. No information on other covariates, or of other countries was used to impute missing values for a particular variable in a particular country.

There are various methods to interpolate time series data and we opted for a

pragmatic approach. We tried several alternatives: random forests, linear model, weighted average and loess-smoothing. The imputations were compared graphically after which the weighted average was identified as giving the most reasonable values. The Normal distribution provided a convenient way to incorporate the variability of the imputation process, although this normality assumption is difficult to check.

Remaining missingness of covariate data was removed by extracting a subset of complete variables and observations using biclustering [15] on the data availability matrix. This implies selecting combinations of observations (country-years) and variables without missingness after imputation. The biclustering algorithm provided suggestions for such selections, with an advantageous trade-off between losing observations and losing variables. Overall, we retained 57 variables (see Table B.1) and 153 country-year combinations for 19 countries in each of the five imputed datasets.

B.1.2 Model selection within GEE

The selection of determinants was carried out on each of the five imputed datasets separately, using generalized estimating equations (GEE [16,17]) with a stepwise search based on Wald testing at a significance threshold of 5%, which is standard methodology for variable selection within GEE. (see for instance [18]) The GEE method yields population level parameter estimates while treating the correlation between observations within a country as a nuisance and is therefore well suited for our purpose of selecting relevant determinants. A drawback is that country specific effects and predictions are not possible as in the mixed model framework, but this is not an objective of this study. We took the union of all selected covariates in the five GEE models, and used this selection to build a multiple-imputation GEE (MI-GEE) model [12]. A final backward selection based on the Wald-significance test was performed to eliminate non-significant variables. Rather than a direct stepwise MI-GEE, the initial GEE stepwise search was performed to avoid numerical problems. Both the initial GEE search and the final MI-GEE fit were based using the independence working correlation matrix. Any other choice of the working correlation matrix would yield a biased result because of the presence of time dependent covariates [18,19]. In summary, we imputed missing covariate data wherever possible and created five imputed datasets. Using biclustering, we eliminated remaining missingness. A stepwise search within the GEE approach was then used to identify relevant predictors for each imputed dataset separately. We used MI-GEE with a backward selection step to obtain the final estimates with valid p-values.

B.1.3 Outcome distributions

MI-GEE based on the log-normal distribution was used to identify determinants of total outpatient antibiotic use. This approach yields multiplicative effects, and accounts for the observed right skewed distribution of antibiotic consumption measured in DID in Europe [20,21]. Consumption of subgroups of antibiotics was modelled using MI-GEE based on the Poisson distribution with the natural logarithm as a link function. The respective larger groups were used as an offset. Note that non-integer values were present in the amount of antibiotics used. The GEE based Poisson model for rates is however insensitive to the scaling of the amount of antibiotics consumed, and can therefore be applied for our purposes. GEE models based on the Poisson distribution with a log-link were used to model resistance counts, whereby the total counts of bacterial samples per country-year were taken as an offset. This implies that we studied the relative rate of occurrence of resistant bacterial isolates in a country. In this part of the analyses, we were mainly interested in assessing cross-sectional associations between the rate of resistance and antibiotic use in specific subclasses, expressed in DID as summarized in Table 6.1.

B.2 Determinants and data availability

Table B.1: Data availability before and after imputation by country and years selected after biclustering

Country	Data availability before imputation (mean 1999-2007)	Data availability after imputation (mean 1999-2007)	Number of years selected after biclustering
Austria	77%	92%	9
Belgium	63%	89%	9
Bulgaria	60%	77%	2
Croatia	55%	69%	8
Cyprus	32%	45%	0
Czech Republic	71%	81%	0
Denmark	75%	91%	9
Estonia	65%	78%	6
Finland	83%	97%	8
France	75%	92%	9
Germany	76%	87%	0
Greece	69%	84%	0
Hungary	73%	92%	9
Iceland	69%	81%	0
Ireland	73%	85%	9
Italy	74%	95%	9
Latvia	57%	71%	5
Lithuania	59%	74%	0
Luxembourg	69%	80%	0
Macedonia	25%	25%	0
Malta	37%	45%	0
Netherlands	79%	92%	9
Norway	75%	94%	7
Poland	65%	81%	0
Portugal	71%	89%	9
Romania	38%	46%	0
Slovakia	68%	81%	0
Slovenia	66%	82%	9
Spain	79%	99%	9
Sweden	79%	93%	9
Switzerland	68%	86%	0
United Kingdom	71%	86%	9

Table B.2: Complete list of potential determinants of antibiotic consumption and resistance

Nr	Determinant	group
	Potential determinants taken up in regression models	
1	Poverty rate: percentage of people earning less than 60% of the median income (made equivalent after social transfers) [1]	Socioeconomic factors
2	Unemployment rate of the active population (15-64 years) [1]	Socioeconomic factors
3	United Nations Development Programme (UNDP) Human Development Index (HDI) [2]	Socioeconomic factors
4	Number of different antibiotic products for sale in the pharmacy	Healthcare system
5	Number of hospital beds per 100,000 inhabitants [1]	Healthcare system
6	Patients do not have to be registered at a GP but there is a financial benefit for being registered at a GP (1=True, 0=False)[a]	Healthcare system
7	Patients have to be registered at a GP and it is easy to change between GPs (1=True, 0=False)[a]	Healthcare system
8	Patients have to be registered with a GP and it is not easy to change between GPs (1=True, 0=False)[a]	Healthcare system
9	Patients do not have to consult a GP before visiting a gynecologist and there is a financial benefit for consulting a GP first (1=True, 0=False)[a]	Healthcare system
10	Are there any restrictions towards pharmaceutical companies for providing dinners ORconferencesORbreakawaysOR presents to physicians (1=Yes; 0=No)[a]	Healthcare system
11	Do gynecologists OR pulmonologists OR GPs OR pediatricians receive any feedback on their antibiotics prescriptions (1=Yes; 0=No)[a]	Healthcare system
12	Do pulmonologists OR GPs or Pediatricians have guidelines for treating respiratory tract infections? (1=Yes; 0=No)[a]	Healthcare system
13	Do patients have to consult a GP first before seeing a gynecologist OR a pulmonologist OR a pediatrician? (1=Yes; 0=No)[a]	Healthcare system
14	Is there any incentive for consulting a GP before seeing an pulmonologist OR a paediatrician or gynaecologist (1=Yes; 0=No)[a]	Healthcare system
15	Private households' out-of-pocket payment on health as a percentage of total health expenditure [2]	Healthcare system
16	Total health expenditure in purchasing power parity per capita, WHO estimates [2]	Healthcare system
17	Number of practicing physicians per 100,000 inhabitants [2]	Healthcare system
18	Public sector expenditure on health as a percentage of total government expenditure, WHO estimates	Healthcare system
19	Percentage of infants vaccinated against rubella [2]	Healthcare system
20	Percentage of infants vaccinated against pertussis [2]	Healthcare system
21	Percentage of infants vaccinated against mumps [2]	Healthcare system
22	The number of GPs per 100,000 inhabitants	Healthcare system
23	Total health expenditure as percentage of GDP [3]	Healthcare system
24	Expected years of education over a lifetime [1]	Education and knowledge about antibiotics

Table B.2, continued

Nr	Determinant	group
25	Percentage of the adult population (25-64 years old) that has completed upper secondary education1	Education and knowledge about antibiotics
26	Percentage of people who know antibiotics do not kill viruses	Education and knowledge about antibiotics
27	Number of women per 100 man [1]	Demographic factors
28	Average household size [1]	Demographic factors
29	Female life expectancy at birth in years [1]	Demographic factors
30	Female life expectancy at 65 years of age in years [1]	Demographic factors
31	Male life expectancy at 65 years of age in years [1]	Demographic factors
32	Female life expectancy at 60 years of age in years [1]	Demographic factors
33	Male life expectancy at 60 years of age years [1]	Demographic factors
34	Male life expectancy at birth in years [1]	Demographic factors
35	Average population density per km^2 [1]	Demographic factors
36	Percentage of population aged 65 years and above [1]	Demographic factors
37	Number of births per 1,000 inhabitants [1]	Demographic factors
38	Percentage of population aged between 0-14 years of age [2]	Demographic factors
39	Percentage of people living in an urban environment [2]	Demographic factors
40	Disability-adjusted life expectancy in years [2]	Demographic factors
41	Year average dew point in degrees Celsius as measure of relative humidity of the air [4]	Demographic factors
42	Standard deviation over a year of the daily dew point in degrees Celsius as a measure of variability of relative humidity of the air [4]	Demographic factors
43	Percentage of regular daily smokers in the population above 15 years [2]	Culture and perception of illness
44	The extent to which people consider greater respect for authority undesirable [5]	Culture and perception of illness
45	The extent to which persons describe themselves as atheistic versus religious [5]	Culture and perception of illness
46	The percentage of people who feel one should be careful in trusting others [5]	Culture and perception of illness
47	Age standardized death rate per 100,000 due to influenza [6]	Burden of disease
48	Age standardized death rate per 100,000 due to due to chronic lower respiratory diseases [6]	Burden of disease
49	Age standardized death rate per 100,000 due to other acute respiratory infections [6]	Burden of disease
50	E. coli. percentage intermediate and full resistant to aminopenicillins [7]	Burden of disease
51	E. coli. percentage intermediate and fully resistant to 3rd generation cephalosporins [7]	Burden of disease
52	E. coli. percentage intermediate and fully resistant to fluoroquinolones [7]	Burden of disease

Table B.2, continued

Nr	Determinant	group
53	S. pneumoniae. percentage intermediate and full resistant to penicillins [7]	Burden of disease
54	S. pneumoniae. percentage intermediate and full resistant to both penicillins and erythromicin [7]	Burden of disease
55	E. coli. percentage intermediate and full resistant to aminoglycosides [7]	Burden of disease
56	Staphylococcus aureus percentage intermediate and full resistant to vancomycin [7]	Burden of disease
57	Age standardized death rate per 100 000 due to pneumoniae [1]	Burden of disease
	Determinants excluded by expert screening on medical relevance and overlap	
	Percentage of new born babies with weight > 2.5 kg [2]	Socioeconomic factors
	Age standardized death rate per 100,000 due to aids [1]	Socioeconomic factors
	Age standardized death rate per 100,000 due to all causes in the age group 0-14 years [6]	Socioeconomic factors
	Age standardized death rate per 100,000 due to all causes in the age group 60-74 years [6]	Socioeconomic factors
	Age standardized death rate per 100,000 due to all causes in the age group 15-29 years [6]	Socioeconomic factors
	Age standardized death rate per 100,000 due to ischaemic heart disease [1]	Socioeconomic factors
	GINI inequality index [1]	Socioeconomic factors
	The extent to which people believe it is a bad thing that experts instead of politicians make decisions about the country [5]	Socioeconomic factors
	Total pharmaceutical expenditure as a percentage of total health expenditure [2]	Socioeconomic factors
	Consumption of seafood in kg per capita [8]	Healthcare system
	Percentage of individual using the internet for seeking health-related information in the last 3 months [1]	Healthcare system
	Percentage of Women aged 25-49 years with at least one child aged 0-5 years who are employed [1]	Healthcare system
	Main source of income for physicians (see LNR survey for possibilities)	Healthcare system
	Average length of hospitalisation in days for carcinoma in situ [9]	Healthcare system
	Average length of hospitalisation in days for disease of the circulatory system [9]	Healthcare system
	Percentage of kids aged less than three that receive no form of formal care [1]	Healthcare system
	Are there treatment guidelines available to pediatricians for treating respiratory tract infections (1=True, 0=False)[a]	Healthcare system
	Are pharmaceutical companies prohibited from providing physicians free drug samples as part of their marketing strategies (1=True, 0=False)[a]	Healthcare system
	Production of turkey in kg per capita [8]	Healthcare system
	Age standardized death rate per 100,000 due to diseases of the respiratory system [6]	Healthcare system

Table B.2, continued

Nr	Determinant	group
	GDP per capita in purchasing power standards [1]	Healthcare system
	Work hours per week which is considered full time employment [1]	Healthcare system
	Infant deaths per 1000 live births [1]	Healthcare system
	Total population (on 1 Jan) [1]	Healthcare system
	Production of chicken in kg per capita [8]	Healthcare system
	Consumption of meat in kg per capita [8]	Healthcare system
	Consumption of poultry in kg per capita [8]	Healthcare system
	Percentage of population aged 16 - 74 years that use the internet to find information on goods and services1	Healthcare system
	Average living area in square meter per person [1]	Healthcare system
	Percentage of population with unmet needs for medical examination (Self-reported) [1]	Healthcare system
	Percentage of the population that assesses its own health to be good [9]	Healthcare system
	Number of hospital beds for long-term care per 1,000 inhabitants [9]	Healthcare system
	Number of doctors consultations per capita [9]	Healthcare system
	Percentage of children immunized for diphtheria, tetanus and pertussis [9]	Healthcare system
	Public expenditure on clinical laboratory as a percentage of total expenditure on health [9]	Healthcare system
	Public expenditure on diagnostic imaging as a percentage of total expenditure on health [9]	Healthcare system
	Public expenditure on prevention and public health as percentage of public expenditure on health [9]	Healthcare system
	Total health employment as percentage of total civil employment [9]	Healthcare system
	Individualism (Hofstede) [10]	Healthcare system
	Masculinity (Hofstede) [10]	Healthcare system
	Pig production in thousands of tons slaughtered [1]	Healthcare system
	Age standardized death rate per 100,000 due to chronic liver disease [1]	Education and knowledge about antibiotics
	Age standardized death rate per 100,000 due to all causes in the age group 45-59 years [6]	Education and knowledge about antibiotics
	The extent to which people agree with: “I seek to be myself rather that to follow” [5]	Demographic factors
	The extent to which people agree with: “Science and technology are making our lives healthier, easier, and more comfortable” [5]	Demographic factors
	Average length of hospital stay in hospitalisation due to alcoholic liver disease [9]	Demographic factors

Table B.2, continued

Nr	Determinant	group
	Age standardized death rate per 100,000 due to chronic diseases [1]	Demographic factors
	Age standardized death rate per 100,000 due to all causes in the age group 30-44 years [6]	Demographic factors
	Average length of hospitalisation in days for aids [9]	Culture and perception of illness
	Average length hospitalisation in days due to diseases of the nervous system [9]	Culture and perception of illness
	The extent to which people have confidence in their government [5]	Culture and perception of illness
	The extend in which people describe their country as democratic [5]	Culture and perception of illness
	Corruption index score of the public sector, higher score means less corrupt (Lambsdorff) [11]	Culture and perception of illness
	Age standardized death rate per 100,000 due to diabetes mellitus [1]	Culture and perception of illness
	Age standardized death rate per 100,000 due to alcohol abuse [1]	Culture and perception of illness
	Age standardized death rate per 100,000 due to cancer [1]	Culture and perception of illness
	Age standardized death rate per 100,000 due to disease of the nervous system [1]	Culture and perception of illness
	Pure alcohol consumption, liters per capita [2]	Culture and perception of illness
	Age standardized death rates due to bronchitis asthma and emphysema [2]	Culture and perception of illness
	Percentage of people (aged over 15) with a BMI bigger than 25 [1]	Culture and perception of illness
	Poultry production in thousands of tons [8]	Culture and perception of illness
	Average length of hospitalisation for diabetes [9]	Culture and perception of illness
	Percentage of respondents that indicated that the worst problem for their country is poor sanitation and infectious diseases [5]	Burden of disease

Table B.2, continued

Nr	Determinant	group
	The extent to which people agree with that people shape their fate themselves in contrast to everything is determined by fate [5]	Burden of disease
	Percentage of respondents that indicated that the worst problem for the world is poor sanitation and infectious diseases [5]	Burden of disease
	The extent to which people agree with "I see myself as citizen of the European Union" [5]	Burden of disease
	Age standardized death rate per 100,000 due to all causes for people over 75 years of age [6]	Burden of disease
	Percentage of households gross dispensable income that goes to gross savings [1]	Burden of disease
	Percentage of population that cannot keep its house warm [1]	Burden of disease
	Percentage of physicians working in a hospital [2]	Burden of disease
	Total inpatient expenditure as a percentage of total health expenditure [2]	Burden of disease
	Percentage of mothers still breast feeding the child when it is three months old [2]	Burden of disease
	Number of microbiological foodborne diseases per 100,000 inhabitants [2]	Burden of disease
	In-patient care admissions per 100 [2]	Burden of disease
	Number of in-patient surgical procedures per year per 100,000 [2]	Burden of disease
	Crude death rate in the ages 1-4 years old per 100,000 [2]	Burden of disease
	Crude death rate in infants ($<$ 1 year old) per 100,000 [2]	Burden of disease
	Staphylococcus aureus percentage intermediate and full resistant to methicillin [7]	Burden of disease
	Percentage of bed occupancy in acute care hospitals [2]	Burden of disease
	Average length of hospital stay in days [2]	Burden of disease
	Expenditure on inpatient care, in purchasing power parity per capita [2]	Burden of disease
	Salaries as a percentage of total public health expenditure [2]	Burden of disease
	Number of physicians per 100 hospital beds [2]	Burden of disease
	Total expenditure on pharmaceuticals & other medical non-durables as a percentage of GDP [2]	Burden of disease
	Average number of cigarettes consumed per person per year [2]	Burden of disease
	The extent to which people agree with: "Because of science and technology, there will be more opportunities for the next generation" [5]	Agricultural factors
	The extent to which people agree with: "We depend too much on science and not enough on faith" [5]	Agricultural factors
	The extent to which people agree with: "The world is better off, or worse off, because of science and technology" [5]	Agricultural factors

Table B.2, continued

Nr	Determinant	group
	The extent to which people trust people they meet for the first time [5]	Agricultural factors
	Inequality of income distribution: ratio of total income by the population of the 20% highest incomes divided by the total income of the population with 20% lowest incomes [1]	Agricultural factors
	Number of live born children who dies before the age of five per 1,000 [2]	Healthcare system
	Total capital investment expenditures on medical facilities as a percentage of total health expenditure [2]	Healthcare system
	Determinants excluded by the biclustering algorithm because of low availability	
	Average length of hospitalisation in days for acute upper respiratory infections and influenza [9]	Healthcare system
	Patients do not have to consult a GP before visiting a pediatrician and there is a financial benefit for consulting a GP first (1=True, 0=False)[a]	Healthcare system
	Do gynecologists receive individual feedback on their antibiotic prescribing behavior versus that of their colleagues (1=True, 0=False)[a]	Healthcare system
	Are pharmaceutical companies prohibited from providing physicians breakaways as part of their marketing strategies (1=True, 0=False)[a]	Healthcare system
	Are pharmaceutical companies prohibited from providing physicians personal presents as part of their marketing strategies (1=True, 0=False)[a]	Healthcare system
	Do pulmonologists receive individual feedback on their antibiotic prescribing behavior versus that of their colleagues (1=True, 0=False)[a]	Healthcare system
	Do GPs receive individual feedback on their antibiotic prescribing behavior versus that of their colleagues (1=True, 0=False)[a]	Healthcare system
	Are there treatment guidelines available to pulmonologists for treating respiratory tract infections (1=True, 0=False)[a]	Healthcare system
	Are there treatment guidelines available to GPs for treating respiratory tract infections (1=True, 0=False)[a]	Healthcare system
	Patients must consult a GP before visiting a pulmonologist (1=True, 0=False)[a]	Healthcare system
	Patients must consult a GP before visiting a gynecologist (1=True, 0=False)[a]	Healthcare system

Table B.2, continued

Nr	Determinant	group
	Patients must consult a GP before visiting a pediatrician (1=True, 0=False)[a]	Healthcare system
	Are pharmaceutical companies prohibited from providing physicians complementary dinners as part of their marketing strategies (1=True, 0=False)[a]	Healthcare system
	Patients do not have to consult a GP before visiting a pulmonologist and there is a financial benefit for consulting a GP first (1=True, 0=False)[a]	Healthcare system
	Do pediatricians receive individual feedback on their antibiotic prescribing behaviour versus that of their colleagues (1=True, 0=False)[a]	Healthcare system
	Are pharmaceutical companies prohibited from providing physicians conferences as part of their marketing strategies (1=True, 0=False)[a]	Healthcare system
	Average length of hospitalisation stay in days for other acute lower respiratory infections than pneumoniae, influenza, chronic diseases of tonsils and adenoids, COPD, bronchiectasis or bronchiectasis or asthma [9]	Healthcare system
	Power Distance Index (Hofstede) [10]	Healthcare system
	Uncertainty Avoidance Index (Hofstede) [10]	Healthcare system
	Average length of hospitalisation in days for chronic obstructive pulmonary diseases (COPD) or bronchiectasis [9]	Healthcare system
	Percentage of 15 year olds that know that antibiotic use leads to antibiotic resistance	Healthcare system
	Role between prescribing physician and pharmacists (categorical see LRN survey for possibilities)	Healthcare system
	Age standardized death rate per 100,000 due to certain infectious and parasitic diseases [9]	Healthcare system
	Age standardized death rate per 100,000 due to influenza and pneumoniae [9]	Healthcare system
	Average length of hospitalisation in days for diseases of the respiratory system [9]	Healthcare system
	Average length of hospitalisation in days for pneumoniae [9]	Healthcare system
	Percentage of private expenditure on health (out of pocket and private insurance) in total health expenditure [9]	Healthcare system
	Average length of hospitalisation in days for infectious and parasitic diseases (intestinal, tuberculosis, septicemia, HIV and others) [9]	Culture and perception of illness
	Percentage of infants vaccinated against invasive disease due to Haemophilus influenzae type B	Culture and perception of illness
	Number of hospitals per 100,000 inhabitants [2]	Culture and perception of illness
	Number of pharmacists per 100,000 inhabitants [2]	Culture and perception of illness

Table B.2, continued

Nr	Determinant	group
	Number of outpatient contacts per person per year [2]	Culture and perception of illness
	Pharmaceutical expenditure in purchasing power parity per capita [2]	Culture and perception of illness
	Average number of people per room in an occupied housing unit [2]	Culture and perception of illness
	Number of pediatricians per 100,000 inhabitants [2]	Culture and perception of illness
	Percentage of elderly population (>65 years) vaccinated against influenza [9]	Burden of disease
	Percentage of kids aged less than three that are cared for by only their parents	Agricultural factors

Determinants are sorted by whether or not they are included in the short list for statistical analysis. Excluded determinants are further split up in two groups: the first were excluded by expert screening on medical relevance and overlap, the second were excluded because of low too low availability after imputation as determined by the biclustering algorithm.
The World values survey [5] contains ordinal variables, which are summarized at the population level by taken the average. The resulting variable presents how a country balances between two extremes.
[a] Variables taken arising for the lead national representative survey. Variables in the excluded category have been summarized (in variables 10 to 14) to reduce the number of variables and improve interpretability.
In total 181 determinants, not counting summarized determinants 10 to 14.

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Appendix C

Cost-effectiveness pneumococcal vaccination

C.1 Details model structure and calculation population at risk

C.1.1 Model structure

Since adults over 50 years are not core transmitters of pneumococcal infections (in contrast with children), herd immunity effects induced by vaccinating relatively small proportions of this age group are likely to be negligible [1]. Ignoring herd immunity effects by using a static model for this analysis therefore implies that there might be a small underestimation of the benefits of vaccination, rendering this analysis conservative in this respect. We developed and applied an age-structured static multi-cohort model to simulate the costs and effects of adult pneumococcal conjugate vaccination strategies , using the R software [3]. Single year age cohorts between 50 and 90 years of age are simultaneously followed from the moment of vaccination until death of the last survivor in the youngest cohort. Cohort sizes over time are informed by age specific all-cause mortality and life-expectancy (based on life tables from the National Institute for Statistics (NIS)), and were independent of explicit pneumococcal-specific mortality (this commonly made assumption had an insignificant influence on the outcomes).

The vaccines (PCV13, PPV23 or both), their timing and the applied scenario of

duration and waning of vaccine-induced protection determines each cohort's vaccine efficacy at every age in years post-vaccination, for both IPD and non-IPD and per serotype set (VE(a,c) see Section C.1.1.1).

The decay in childhood vaccine type (PCV13) incidence per year is combined with the proportion of non-PCV13 type incidence replacement to calculate an incidence correction factor for both PCV13- and non-PCV13 serotype specific incidence. The vaccination coverage together with the calculated vaccine efficacy and serotype evolution determine the population at risk to acquire invasive or non-invasive pneumococcal disease for each cohort, at each age in years (see Figure C.1). On those calculated population sizes per cohort-age combination, we apply age- and serotype-specific yearly incidence rates of the different disease categories and their consequences in terms of hospitalisations and deaths. For non-IPD outpatient cases only pneumococcal pneumonia is included because we considered the direct vaccine impact on acute otitis media (AOM) negligible in adults. The distinction between different disease categories was made based on how physicians classified hospitalised patients based on ICD9 coding in administrative databases (see Table 9.2 in main text). Possible long-term consequences of meningitis (hearing loss or neurological sequelae) are also taken into account. Direct medical costs and Quality-adjusted life-year (QALY) losses associated with these outcome categories were included in order to compare the costs and QALYs between different possible vaccination programs. In accordance with Belgian guidelines [2], a health care payer's perspective was used under which morbidity and mortality-associated productivity losses to society are excluded. Future life-years and QALYs lost due to pneumococcal disease were discounted at an annual rate of 1.5%, and future costs were discounted at an annual rate of 3% [2].

C.1.1.1 Proportion of population at risk

We calculated the proportion of the population at risk for IPD at age a (in years) and belonging to cohort c as follows:

$$F_{IPD}(a,c) = P_{vac} \sum_{\tau} A_{\tau}(a) \left(1 - VE_{(IPD,\tau)}(a,c)\right) Q_{\tau}(a,c) + (1 - P_{vac}) \sum_{\tau} A_{\tau}(a) Q_{\tau}(a,c),$$

with P_{vac} the proportion of the population at age a belonging to cohort c that is vaccinated (i.e. vaccination coverage), τ one of four serotype categories which take values from the set $\{OPPV23, OPCV13, both, none\}$. Here "$OPPV23$" signifies all serotypes included in the PPV23 vaccine but not in PCV13; "$OPCV13$" only

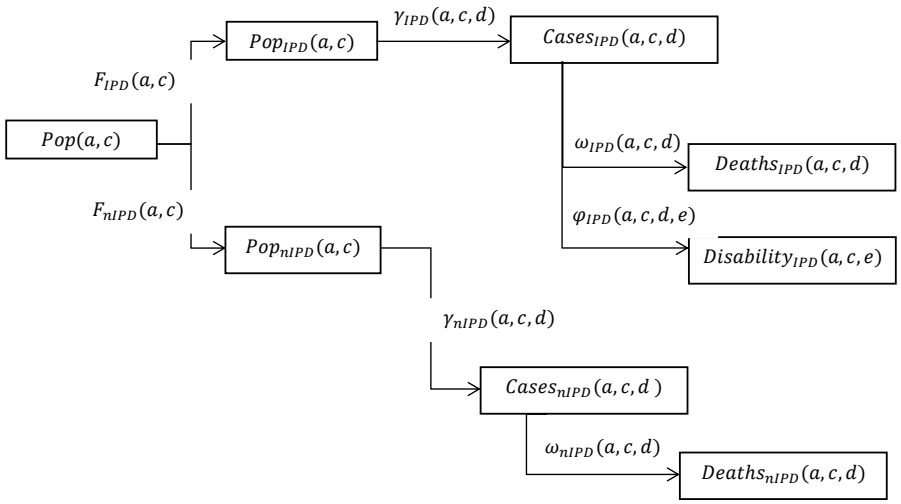

Figure C.1: Structure pneumococcal cohort model: from left to right: Population, population at risk for invasive or non-invasive pneumococcal disease, Disease cases and disease consequences: fatality or long term effects (see Section C.1.1)

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$Pop(a,c)$ is the population size of cohort c at age a. Pop(a,c) is multiplied with the proportion that is not vaccine protected against IPD or non-IPD ($F_{IPD}(a,c)$ or $F_{nIPD}(a,c)$ respectively) to calculate the number of people at risk of IPD or non-IPD disease respectively (see Section C.1.1.1 for details). $\gamma_{IPD}(a,c,d)$ and $\gamma_{nIPD}(a,c,d)$ represent the yearly rate to develop IPD or non-IPD respectively, with d indicating the disease category: bacteremic hospitalised pneumonia, septicaemia or meningitis for IPD; outpatient pneumonia or non-bacteremic hospitalised pneumonia for non-IPD (impact of otitis media is assumed negligible). $\omega_{IPD}(a,c,d)$ and $\omega_{nIPD}(a,c,d)$, are the age- and cohort-specific death rates of the different IPD and non-IPD disease categories, respectively. $\varphi_{IPD}(a,c,d,e)$ is the rate at which meningitis cases develop sequelae of category e (hearing problems or neurological sequelae). Other IPD disease categories do not have such long term outcomes attached.

serotypes in PCV13 but not in PPV23, "*both*" in both vaccines, "*none*" in neither vaccine.

- $A_\tau(a)$ is the age dependent initial proportion of incidence of serogrouping τ at the start of the vaccination program.
- $VE_{(IPD,\tau)}(a, c)$ is the vaccine efficacy against IPD for serogrouping τ of cohort c at age a. It takes into account the vaccine or combination of vaccines used, protection against IPD (as in the notation given here) or non-IPD disease types, the initial vaccine efficacy, the duration of vaccine protection and waning of vaccine efficacy over time.
- $Q_\tau(a, c)$ is the ratio of the incidence (in a susceptible population) of serotype category τ of cohort c at age a and the incidence of that serotype category at the start of the vaccination program. This factor can incorporate PCV13 specific incidence changes due to the childhood vaccination program and the possible replacement of non-PCV13 types. Serotype specific incidence changes are assumed proportional to observed serotype specific relative incidences of pneumococcal disease before implementation of the vaccination program.

For non-IPD, the fraction at risk F_{nIPD} is calculated analogously. Note that the population at risk for non-IPD and the population at risk for IPD will be largely overlapping and are only used as intermediates to calculate disease cases.

C.2 Serotype coverage data

The vaccine serotype coverage for over 50 year olds was estimated from data from the Belgian pneumococcal reference centre for the period 2012-2014. The reference centre collects all positive pneumococcal invasive isolates and determines its serogroup, but not the subtypes. For instance, serotypes 19A and 19F are therefore not distinguishable. Observations were classified and counted according to whether the sample's serogroup is captured by one of the vaccines assuming complete cross-protection within each serogroup. A limitation of this approach is that mainly IPD cases are recorded, because for non-IPD cases usually no clinical sample is taken. We assumed the same serotype distribution for both IPD and non-IPD cases. These counts were then used in a Dirichlet distribution to simulate the proportions in each of the set of serogroups (see Section C.1.1.1). Through regression analyses (not shown), no significant differences were found in the proportions of specific serotypes isolated according to age or isolation site.

C.3 PCV13 or PPV23 versus no vaccination

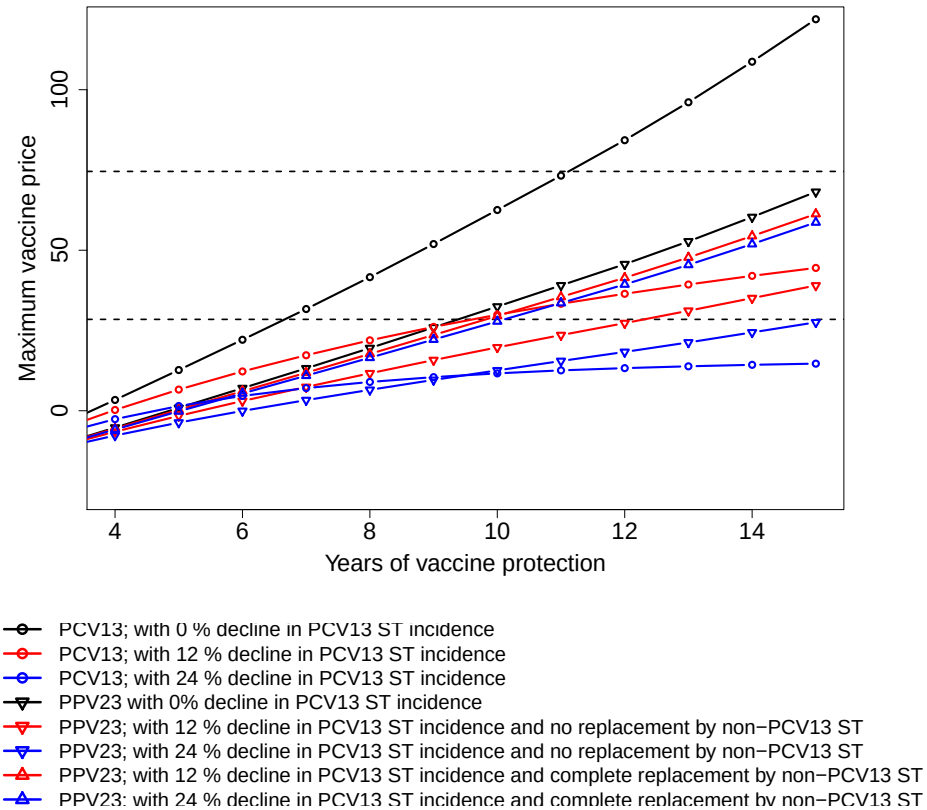

Figure C.2: The influence of years of vaccine protection on the maximum vaccine price such that vaccinating 75% of the age group 50-64 year old versus no vaccination is cost-effective (median of the distribution) at a willingness to pay of €35,000 per quality adjusted life years gained. Scenarios are shown of vaccine choice (PCV13 or PPV23), proportional yearly decline of PCV13 (ST)-specific incidence in adults and complete (100%) or no (0%) replacement of PCV13-serotypes by non-PCV13 serotypes. Dashed lines represent current PCV13 (€74.55) and PPV23 (€28.46) vaccine price, excluding administration costs.

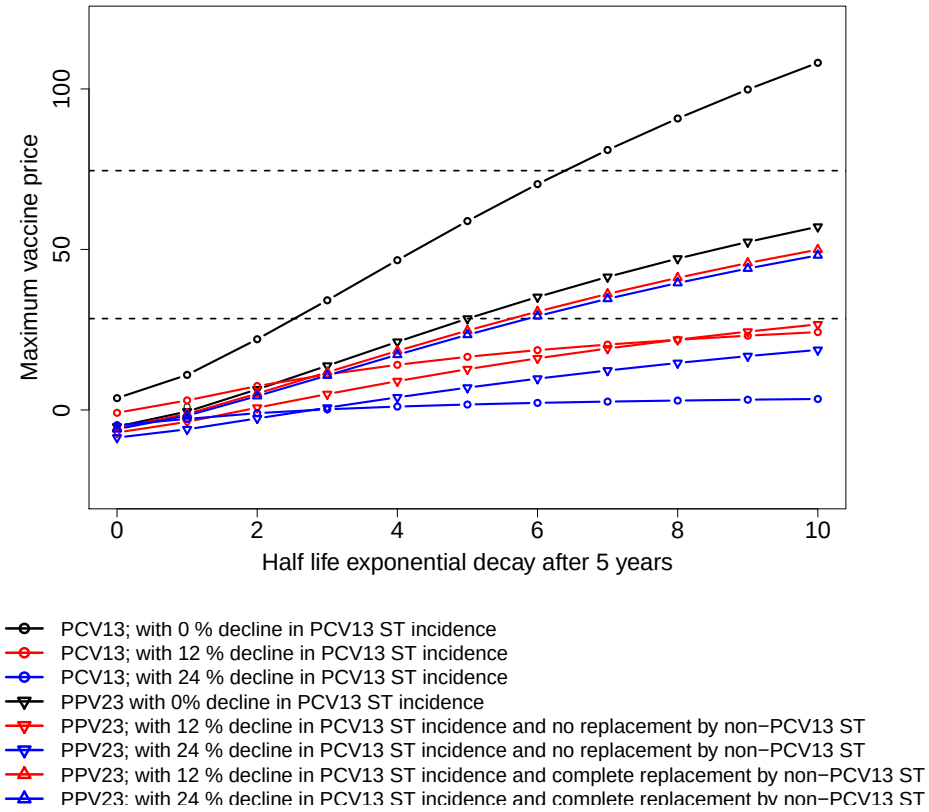

Figure C.3: The influence of the halflife time of exponential waning starting after 5 years of complete vaccine protection on the maximum vaccine price such that vaccinating 75% of the age group 50-64 year old versus no vaccination is cost-effective (median of the distribution) at a willingness to pay of €35,000 per quality adjusted life years gained. Scenarios are shown of vaccine choice (PCV13 or PPV23), proportional yearly decline of PCV13 (ST)-specific incidence in adults and complete (100%) or no (0%) replacement of PCV13-serotypes by non-PCV13 serotypes. Dashed lines represent current PCV13 (€74.55) and PPV23 (€28.46) vaccine price, excluding administration costs.

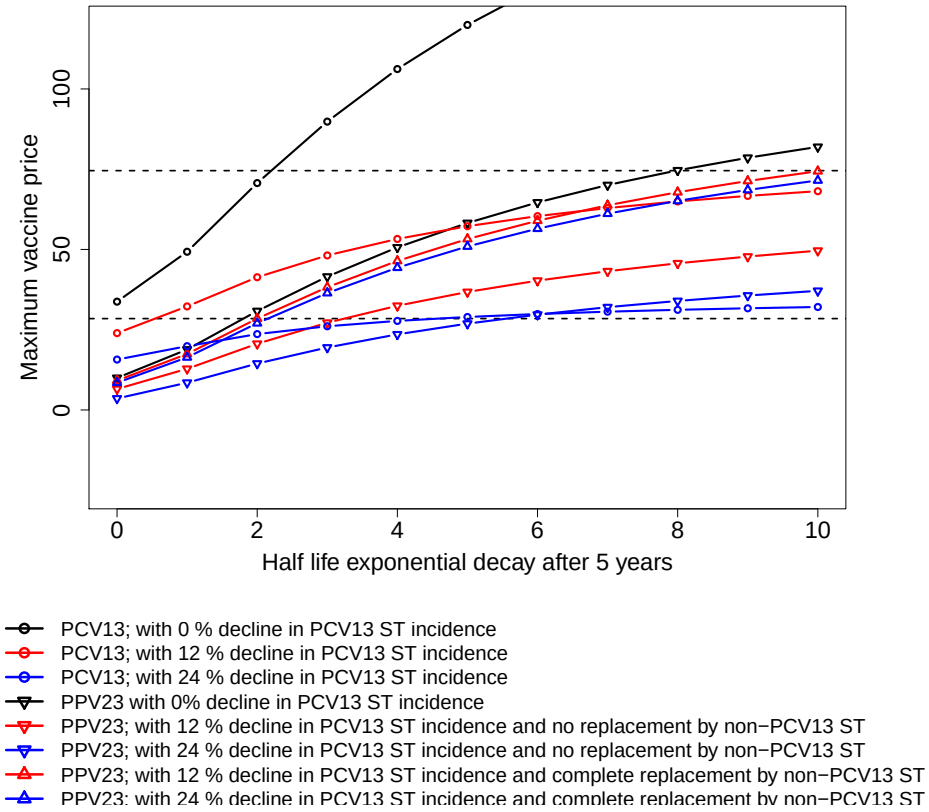

Figure C.4: The influence of the halflife time of exponential waning starting after 5 years of complete vaccine protection on the maximum vaccine price such that vaccinating 75% of the age group 65-74 year old versus no vaccination is cost-effective (median of the distribution) at a willingness to pay of €35,000 per quality adjusted life years gained. Scenarios are shown of vaccine choice (PCV13 or PPV23), proportional yearly decline of PCV13 (ST)-specific incidence in adults and complete (100%) or no (0%) replacement of PCV13-serotypes by non-PCV13 serotypes. Dashed lines represent current PCV13 (€74.55) and PPV23 (€28.46) vaccine price, excluding administration costs.

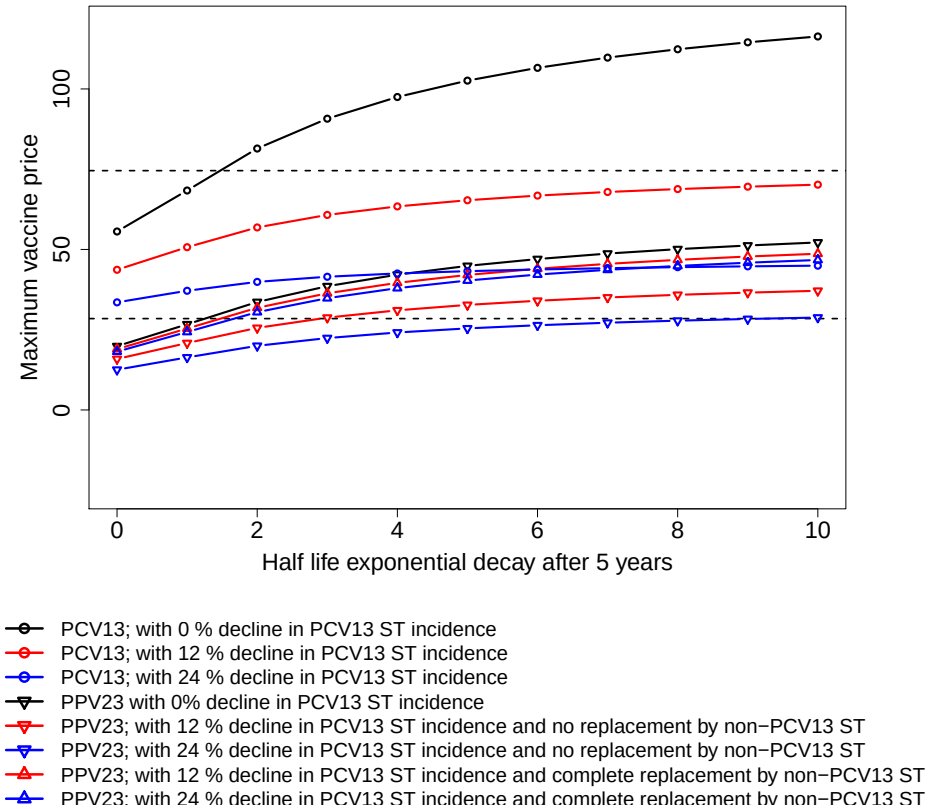

Figure C.5: The influence of the halflife time of exponential waning starting after 5 years of complete vaccine protection on the maximum vaccine price such that vaccinating 75% of the age group 75-90 year old versus no vaccination is cost-effective (median of the distribution) at a willingness to pay of €35,000 per quality adjusted life years gained. Scenarios are shown of vaccine choice (PCV13 or PPV23), proportional yearly decline of PCV13 (ST)-specific incidence in adults and complete (100%) or no (0%) replacement of PCV13-serotypes by non-PCV13 serotypes. Dashed lines represent current PCV13 (€74.55) and PPV23 (€28.46) vaccine price, excluding administration costs.

C.4 Uncertainty price threshold analysis

Table C.1: Summary statistics simulated distribution of vaccine price per dose for which the incremental cost-effectiveness ratio of vaccinating 75% of the age group with a single vaccine versus no vaccination, equals €35,000 per QALY gained at each draw of the input distrubution (1,000 draws), assuming 24% PCV13 serotype incidence decline . Results displayed as: mean [median] [95% interval], in function of duration of vaccine protection (T) and age group, asuming no waning.

	PCV13			PPV23, no replacement			PPV23, full replacement		
T	50-64 years	65-74 years	75-90 years	50-64 years	65-74 years	75-90 years	50-64 years	65-74 years	75-90 years
5	1.05 (1.47)	27.91 (28.71)	51.11 (52.48)	-3.7 (-3.7)	12.56 (12.55)	24.56 (24.49)	-0.2 (-0.19)	19.1 (19.09)	32.1 (31.99)
	[-8.69;8.03]	[7.11;43.35]	[19.93;74.14]	[-6.96;-0.48]	[6.36;19.03]	[15.85;33.77]	[-4.07;3.55]	[11.73;26.67]	[22.02;42.89]
6	4.15 (4.62)	34.64 (35.57)	57.44 (58.92)	-0.06 (-0.06)	19.51 (19.53)	30.73 (30.64)	5.36 (5.39)	29.74 (29.71)	41.53 (41.39)
	[-6.89;12.03]	[11.08;52.11]	[23.61;82.5]	[-3.95;3.74]	[12.15;27.33]	[20.91;41.18]	[0.55;10]	[20.54;39.21]	[29.69;54.21]
7	6.53 (7.05)	39.8 (40.84)	61.7 (63.27)	3.29 (3.3)	25.91 (25.95)	35.72 (35.62)	10.88 (10.92)	40.26 (40.26)	49.74 (49.55)
	[-5.51;15.11]	[14.13;58.83]	[26.07;88.14]	[-1.19;7.7]	[17.42;34.99]	[24.97;47.2]	[5.13;16.37]	[29.14;51.67]	[36.33;64.07]
8	8.42 (8.97)	43.8 (44.91)	64.4 (66.03)	6.49 (6.51)	31.94 (31.96)	39.59 (39.46)	16.47 (16.51)	50.82 (50.8)	56.52 (56.31)
	[-4.42;17.55]	[16.48;64.03]	[27.62;91.75]	[1.45;11.5]	[22.3;42.01]	[28.11;51.93]	[9.76;22.89]	[37.72;64.18]	[41.83;72.3]
9	9.91 (10.47)	46.83 (48)	66.14 (67.8)	9.57 (9.6)	37.61 (37.6)	42.68 (42.53)	22.14 (22.18)	61.24 (61.18)	62.2 (61.93)
	[-3.51;19.48]	[18.26;67.97]	[28.62;94.07]	[3.99;15.15]	[26.95;48.84]	[30.61;55.72]	[14.45;29.51]	[46.31;76.55]	[46.46;79.24]
10	11.07 (11.64)	49.15 (50.37)	67.22 (68.9)	12.55 (12.57)	43.06 (43.04)	45.08 (44.9)	27.84 (27.83)	71.67 (71.62)	66.8 (66.48)
	[-2.8;20.98]	[19.63;71]	[29.24;95.53]	[6.5;18.67]	[31.46;55.43]	[32.55;58.68]	[19.18;36.18]	[54.79;88.89]	[50.19;84.89]
11	11.97 (12.57)	50.91 (52.17)	67.91 (69.6)	15.45 (15.49)	48.27 (48.25)	47.01 (46.81)	33.57 (33.55)	81.98 (81.92)	70.61 (70.27)
	[-2.25;22.14]	[20.65;73.29]	[29.64;96.46]	[8.95;22.11]	[35.73;61.76]	[34.1;61.06]	[23.93;42.9]	[63.25;101.15]	[53.28;89.51]
12	12.67 (13.27)	52.25 (53.54)	68.32 (70.03)	18.29 (18.31)	53.36 (53.31)	48.5 (48.29)	39.34 (39.34)	92.29 (92.2)	73.64 (73.29)
	[-1.81;23.05]	[21.43;75.04]	[29.88;97.02]	[11.35;25.49]	[39.92;67.94]	[35.3;62.92]	[28.72;49.68]	[71.69;113.41]	[55.72;93.12]
13	13.24 (13.84)	53.17 (54.49)	68.58 (70.29)	21.25 (21.27)	57.85 (57.8)	49.7 (49.49)	45.46 (45.45)	101.59 (101.49)	76.11 (75.76)
	[-1.46;23.79]	[21.96;76.24]	[30.02;97.37]	[13.79;29.04]	[43.56;73.29]	[36.26;64.4]	[33.78;56.88]	[79.31;124.47]	[57.75;96.05]
14	13.7 (14.31)	53.81 (55.13)	68.74 (70.45)	24.34 (24.4)	61.78 (61.7)	50.65 (50.44)	51.95 (51.92)	109.84 (109.72)	78.11 (77.75)
	[-1.17;24.39]	[22.33;77.07]	[30.12;97.58]	[16.32;32.74]	[46.73;77.96]	[37.02;65.53]	[39.12;64.52]	[86.06;134.29]	[59.39;98.51]
15	14.07 (14.67)	54.24 (55.57)	68.84 (70.55)	27.51 (27.54)	65.3 (65.18)	51.37 (51.17)	58.68 (58.66)	117.32 (117.21)	79.65 (79.29)
	[-0.94;24.87]	[22.58;77.64]	[30.17;97.7]	[18.92;36.55]	[49.59;82.14]	[37.59;66.39]	[44.69;72.45]	[92.18;143.18]	[60.65;100.43]

Table C.2: Summary statistics simulated distribution of vaccine price per dose for which the incremental cost-effectiveness ratio of vaccinating 75% of the age group with a single vaccine versus no vaccination, equals €35,000 per QALY gained at each draw of the input distrubution (1,000 draws), assuming 24% PCV13 serotype incidence decline . Results displayed as: mean [median] [95% interval], in function of half life exponential decay (τ).

	PCV13			PPV23, no replacement			PPV23, full replacement		
τ	50-64 years	65-74 years	75-90 years	50-64 years	65-74 years	75-90 years	50-64 years	65-74 years	75-90 years
0	-5.04 (-4.73)	15.1 (15.7)	32.5 (33.53)	-8.6 (-8.6)	3.59 (3.58)	12.59 (12.54)	-5.98 (-5.97)	8.5 (8.48)	18.25 (18.16)
	[-12.34;0.19]	[-0.5;26.68]	[9.12;49.77]	[-11.05;-6.19]	[-1.06;8.44]	[6.06;19.49]	[-8.88;-3.17]	[2.97;14.18]	[10.69;26.34]
1	-3.14 (-2.79)	19.2 (19.88)	36.05 (37.13)	-6.03 (-6.03)	8.47 (8.49)	16.44 (16.37)	-1.8 (-1.78)	16.41 (16.38)	24.41 (24.3)
	[-11.25;2.65]	[1.92;32.01]	[11.18;54.46]	[-8.93;-3.2]	[3;14.28]	[9.21;24.13]	[-5.4;1.68]	[9.52;23.51]	[15.68;33.74]
2	-1.38 (-1)	22.88 (23.64)	38.75 (39.9)	-2.64 (-2.63)	14.44 (14.46)	20.06 (19.98)	4.31 (4.33)	27.04 (27.02)	30.62 (30.47)
	[-10.24;4.93]	[4.09;36.81]	[12.74;58.06]	[-6.14;0.84]	[7.85;21.32]	[12.15;28.51]	[-0.34;8.77]	[18.15;36.12]	[20.71;41.25]
3	-0.19 (0.2)	25.26 (26.07)	40.32 (41.5)	0.69 (0.71)	19.45 (19.45)	22.5 (22.39)	10.75 (10.74)	36.45 (36.41)	34.98 (34.82)
	[-9.55;6.46]	[5.49;39.91]	[13.64;60.14]	[-3.36;4.8]	[11.96;27.36]	[14.13;31.5]	[5;16.33]	[25.86;47.29]	[24.27;46.59]
4	0.66 (1.06)	26.91 (27.74)	41.32 (42.53)	3.91 (3.93)	23.56 (23.55)	24.24 (24.13)	17.21 (17.19)	44.39 (44.32)	38.16 (37.95)
	[-9.03;7.56]	[6.46;42.05]	[14.22;61.49]	[-0.64;8.63]	[15.36;32.34]	[15.53;33.64]	[10.35;23.93]	[32.36;56.68]	[26.84;50.49]
5	1.29 (1.7)	28.1 (28.96)	42.02 (43.24)	6.94 (6.96)	26.93 (26.89)	25.53 (25.41)	23.43 (23.41)	51.01 (50.93)	40.55 (40.32)
	[-8.64;8.38]	[7.16;43.61]	[14.63;62.42]	[1.86;12.27]	[18.14;36.43]	[16.57;35.23]	[15.49;31.26]	[37.78;64.54]	[28.78;53.39]
6	1.78 (2.21)	29.01 (29.89)	42.54 (43.76)	9.75 (9.75)	29.72 (29.69)	26.53 (26.39)	29.26 (29.24)	56.54 (56.47)	42.41 (42.17)
	[-8.34;9.02]	[7.69;44.79]	[14.92;63.11]	[4.16;15.64]	[20.4;39.79]	[17.38;36.46]	[20.28;38.14]	[42.31;71.12]	[30.28;55.61]
7	2.18 (2.61)	29.72 (30.61)	42.93 (44.16)	12.32 (12.29)	32.05 (32.02)	27.32 (27.18)	34.64 (34.62)	61.21 (61.15)	43.9 (43.66)
	[-8.1;9.53]	[8.11;45.71]	[15.15;63.63]	[6.28;18.69]	[22.29;42.57]	[18.01;37.43]	[24.71;44.5]	[46.13;76.66]	[31.49;57.39]
8	2.5 (2.93)	30.29 (31.2)	43.24 (44.48)	14.65 (14.64)	34.03 (33.96)	27.96 (27.82)	39.57 (39.55)	65.19 (65.13)	45.11 (44.87)
	[-7.9;9.94]	[8.45;46.46]	[15.33;64.05]	[8.22;21.46]	[23.89;44.92]	[18.53;38.22]	[28.73;50.33]	[49.38;81.38]	[32.48;58.84]
9	2.76 (3.2)	30.76 (31.68)	43.5 (44.74)	16.78 (16.77)	35.73 (35.65)	28.49 (28.35)	44.06 (44.06)	68.61 (68.54)	46.12 (45.88)
	[-7.74;10.28]	[8.72;47.07]	[15.47;64.39]	[9.99;23.97]	[25.25;46.93]	[18.96;38.88]	[32.4;55.64]	[52.18;85.43]	[33.31;60.04]
10	2.99 (3.42)	31.15 (32.08)	43.7 (44.95)	18.71 (18.71)	37.19 (37.11)	28.94 (28.79)	48.15 (48.16)	71.58 (71.5)	46.98 (46.72)
	[-7.6;10.58]	[8.95;47.58]	[15.59;64.67]	[11.6;26.27]	[26.43;48.67]	[19.32;39.43]	[35.74;60.49]	[54.61;88.93]	[34;61.06]

C.5 Impact pneumococcal pneumonia assumptions

C.5.1 Introduction

Even though PCV13's protection against non-bacteremic pneumonia is a major reason for considering vaccinating adults with it instead of the PPV23 vaccine, in our model strong assumptions have been made for these pneumonia parameters. In the absence of specific data we assumed the proportion of hospitalised pneumococcal pneumonia cases with bacteremia to be age independent and we used an overall case-fatality ratio for all hospitalised pneumococcal pneumonia. The latter implicitly assumes an equal case-fatality for bacteremic and non-bacteremic pneumonia. In this section we assess the impact of these two assumptions by sensitivity analysis, while taking other parameter settings the same as in Section 9.2.2 in main text and limiting the analysis to single vaccine programs (see Section 9.2.3). Sensitivity analysis is performed under 2 constraints: (C1) the adult average proportion of bacteremic pneumonia within hospitalised pneumococal pneumonia remains constant; (C2) the age dependent total case-fatality ratio of bacteremic and non-bacteremic pneumoccal pneumonia combined remains the same (see Table 9.1 in main text).

C.5.2 Age dependent proportion bacteremic pneumonia

We make the proportion of bacteremic pneumonia within hospitalised pneumonia (P_{bact}) age dependent by multiplying its age independent value with an age dependent factor ($f(a)$):

$$P_{bact}(a) = P_{bact} * f(a).$$

We choose a logisitic curve to simulate age dependency:

$$f(a) = \frac{A}{1 + e^{-k(a-a_0)}}, \tag{C.1}$$

with A the scale parameter, k the steepness parameter and a_0 the point were the curve reaches 50% of the scale parameter. In the absence of data, this curve is quite arbitrary a choice. But it has useful properties: monotone increasing with a, symmetric about the reflection point $a = a_0$ and with $A = 1$, bounded between 0 and 1 which is suitable for a proportion. We will fix $a_0 = 70$ to study the increase of relative bacteremic proportions of above 70 year olds compared to below 70 year olds. The scale parameter A is calculated following (C1): $A = 1/\sum_a f(a) * freq(a)$, with $freq(a)$ the incidence frequency of hospitalised pneumonia in adults, which was calculated by multiplying the population size at age a with the hospitalisation rate of

pneumococcal pneumonia and dividing by the total over age. The parameter k was varied from 0 over 1/30 to 1/10 to assess its impact (see Figure C.6).

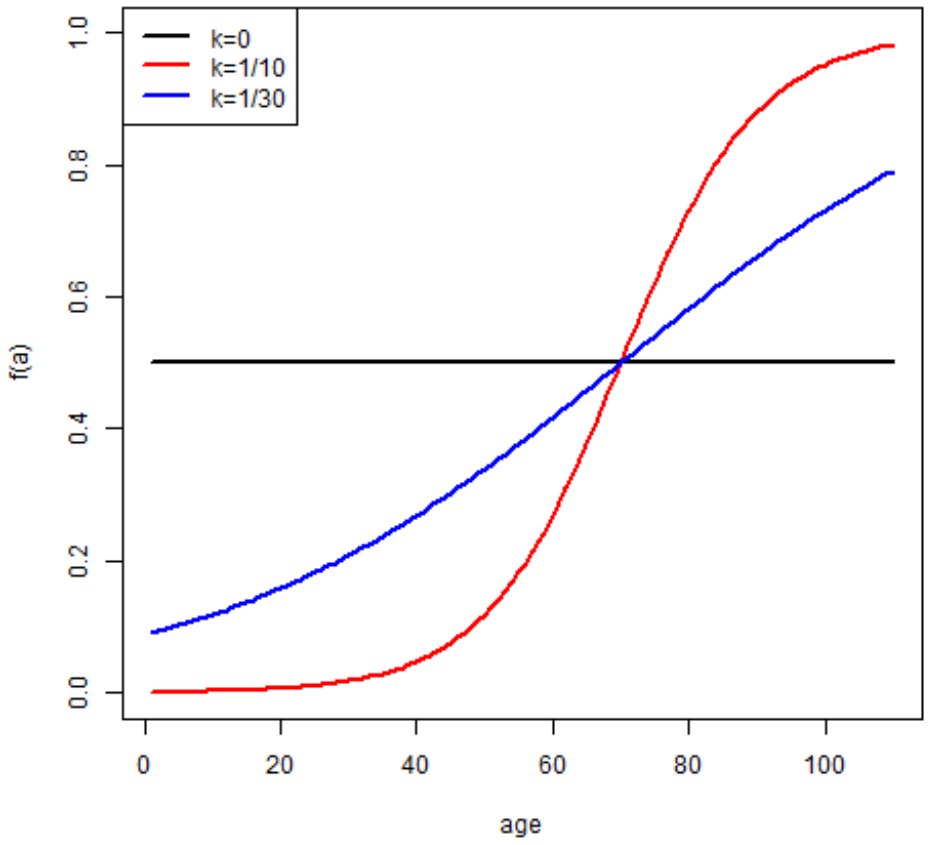

Figure C.6: Logistic curves with $A = 1$ and a_0 equal to 70 years. $k = 0$ represents age independency.

C.5.3 Bacteremic versus non-bacteremic death rates

To assess the impact of different death rates of bacteremic and non-bacteremic pneumonia, we vary the parameter λ defined as the ratio of both:

$$\lambda = \frac{\omega_{IPD}(a,d)}{\omega_{nIPD}(a,d)}, \tag{C.2}$$

With d indicating the disease category pneumococcal pneumonia, ω_{IPD} and ω_{nIPD} the case-fatality ratio in hospitalised pneumonia patients with bacteremic or non-bacteremic pneumonia respectively. In the model we included a factor to distinguish between the case-fatality of bacteremic and non-bacteremic pneumonia: $\omega_{IPD} = fact_{bact}(a) * \omega_{overall}(a)$ and $\omega_{nIPD}(a) = fact_{nbact}(a) * \omega_{overall}(a)$, with $\omega_{overall}(a)$ the overall case-fatality ratio of bacteremic and non-bacteremic pneumonia.

We vary the parameter λ from 1 over 2 to 4 and calculate "case-fatality factors" from λ under constraint (C2):

$$fact_{bact}(a) = \frac{1}{P_{bact}(a) + \frac{1-P_{bact}(a)}{\lambda}}$$

and

$$fact_{nbact}(a) = \frac{fact_{bact}(a)}{\lambda}.$$

Notice these factors depend on the proportion of bacteremic pneumonia (P_{bact}), therefore in the simulation study we first simulate $P_{bact}(a)$ and then $fact_{bact}(a)$ and $fact_{bact}(a)$.

C.5.4 results

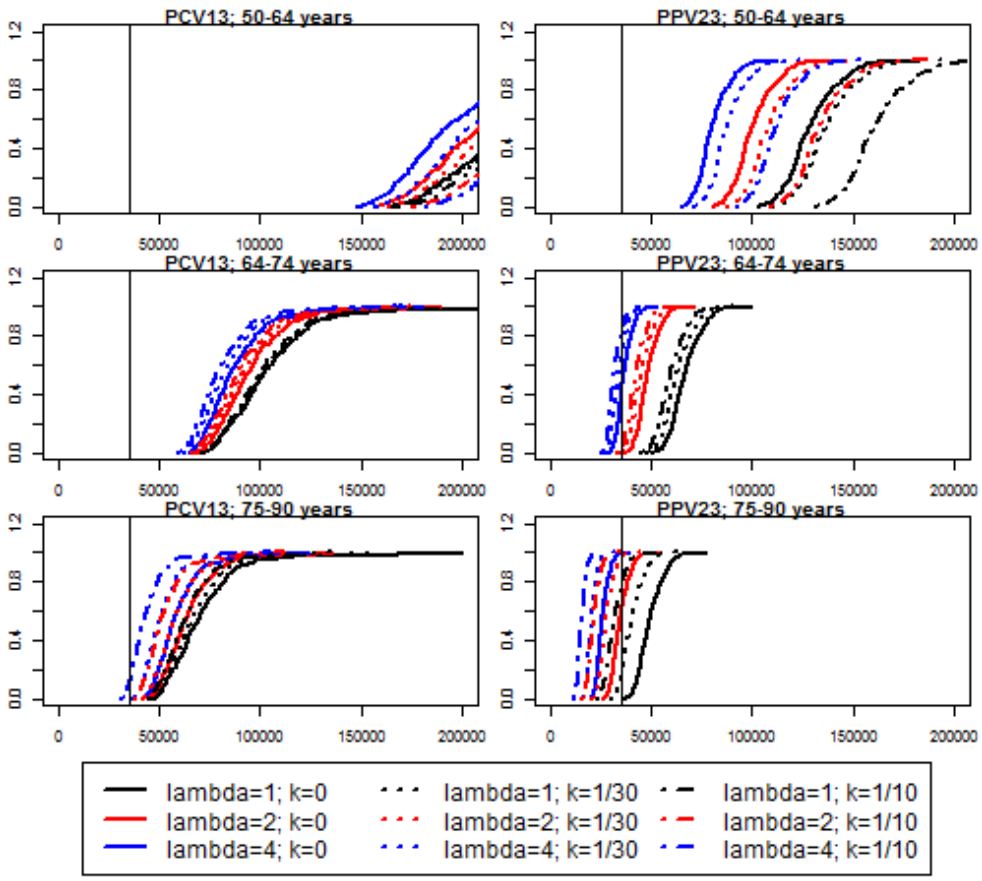

Figure C.7: Cost-effectiveness acceptability curves for vaccinating 70% of the target group with a pneumococcal vaccine versus no vaccination in function of the age dependency of the proportion of hospitalised pneumococcal pneumonia that is bacteremic (k, see Equation C.1) and the relative death rate of bacteremic versus non-bacteremic pneumonia (λ, see Equation C.2). Each panel represents an age group-vaccine combination, indicated by the title above the panel. The vertical line represents a willingness to pay of €35,000 per quality adjusted life year gained

Figure C.7 displays the cost-effectiveness acceptability curves (CEACs) for single vaccine scenarios in function of the age dependency of the proportion bacteremic pneumonia and the ratio of case-fatality ratios of bacteremic versus non-bacteremic pneumonia. We see that for the oldest age category (75-90 years old) a higher proportion of bacteremic pneumonia together with an increased relative case-fatality ratio of bacteremic pneumonia can possibly make PCV13 vaccination cost-effective at a willingness to pay of €35,000 per QALY, under conditions outlined in Section 9.2.3 in main text. However, PPV23 still remains more cost-effective under the same conditions.

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