Health-economics of interventions aimed at infectious diseases

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Summary
Health-economic cost-effectiveness analyses can be performed at various levels and using various sources of data. It is often argued that ideally these economic evaluations should be conducted alongside randomized clinical trials, based on such a single data source. However, more and more it is now believed that such a perspective may be too limited. In particular, relying on a single clinical trial, where data on efficacy and resource use are collected simultaneously, may have several limitations which are discussed in chapter 1 of this thesis. To overcome these problems, nowadays modeling is widely used in economic evaluations in order to structure all available evidence in a form that can assist the decision maker in taking the right decisions about clinical practice and resource allocations.

In this thesis, the emphasis is on the different modeling techniques which can be used to estimate the cost-effectiveness of (preventive) interventions aimed at infectious diseases. In contrast to other diseases, many infectious diseases possess the unique characteristic of being transmittable. Consequently, prevention programs for infectious diseases (e.g. screening, vaccination or prophylaxis) will not only reduce the incidence of disease in those participating, but also indirectly protect the non-participating individuals against infection as there will be less persons ”available to infect”. The concept of this indirect protection is defined as ‘herd-immunity’. Although these herd-immunity effects are not estimated in a clinical trial, they should be included in a cost-effectiveness analysis as the appropriate perspective of most economic evaluations is now often stated to involve the society rather than the individual. However, the inclusion of these herd-immunity effects requires a different, more complex, modeling approach.

Part I

A health-economic cost-effectiveness study consists of both an epidemiological part to assess the clinical effects and an economic part to assess the monetary outcomes. Part I of this thesis addresses both aspects separately.

In chapter 2, a back-calculation model was designed to estimate the future Dutch HIV and AIDS incidences by using current incidence numbers together with incubation time distributions. New incubation time distributions were estimated using a Markov model as obviously these have been changed since 1997 due to the introduction of HAART (Highly Active Anti-Retroviral Therapy) in the Netherlands. Future incidences were estimated for three different risk-groups: (i) homosexual men; (ii) drug users; and (iii) others. Summarized, instead of estimating the epidemiological outcomes of a new medical intervention, in chapter 2 future incidences were predicted assuming that the current course of the disease
and treatment effectiveness will not change over time.

In situations in which interventions under consideration can validly be assumed to be equivalent in terms of effectiveness and tolerability, the analysis basically reduces to a comparison of costs only. This type of analysis is often referred as ”cost-minimization analysis”. A specific difficulty in cost comparisons arises from the fact that distributions of resource use and associated costs are often highly skewed. In the literature, several methods were proposed for comparing costs which deal with these skewed distributions and these are reviewed in chapter 3. Here it is concluded that in general the t-test is often a reasonable method in order to compare the costs of alternative strategies. Furthermore, if individual data on resource use and costs are available, parametric modeling is indicated as an appropriate method for comparing costs and resource use. In annex 1 we applied parametric modeling in order to examine the difference in costs between two antibiotics, teicoplanin and vancomycin, in the treatment of Gram-positive hospital infections. The analysis did not reveal a statistically significant difference between the total costs of both treatment groups.

Part II

In part II of this thesis two examples of the use of ‘static models’ to estimate cost-effectiveness were given. In contrast to ‘dynamic models’, static models can not take the herd-immunity effects explicitly into account. The two most commonly applied static model structures are the ‘decision tree’ and the ‘Markov model’. Both structures are discussed in chapter 4 and 5, respectively.

In chapter 4 a decision tree was designed to assess the cost-effectiveness of itraconazole compared with both fluconazole and no prophylaxis for the prevention of invasive fungal infections in haematological patients in Germany and the Netherlands. According to our probabilistic model, itraconazole was estimated cost-saving (i.e. both more effective and more economically favorable) compared with both fluconazole and no prophylaxis in both countries. From a health-economic point of view, cost-saving interventions should always be adopted.

The cost-effectiveness of a potential future Helicobacter pylori (HP) vaccine for the Dutch situation was estimated in chapter 5. Additionally, the impact of the discount rate for health on the outcomes was assessed, as this influence can be profound for vaccines. Here, a Markov model was chosen for modeling long term effects as the risk of acquiring both gastric cancer and peptic ulcer continues over a life-time period. The cost-effectiveness appeared to be highly dependent on the HP prevalence in the population. When applying the
current discount rate of 1.5% for health, the expected cost-effectiveness is estimated below the informal Dutch threshold of €20,000 per life year gained when the HP prevalence is assumed ≥20%. Furthermore, a large impact of the discount rate for health was shown on the cost-effectiveness, illustrative for other vaccination programs as well.

In both analyses described in part II a static approach was justified. Itraconazole prophylaxis does not affect the force of infection (i.e. rate at which susceptible individuals acquire an infection). In other words, the probability of acquiring an invasive fungal infection for those who do not receive prophylaxis will not change as a result of providing antifungal prophylaxis to others. In chapter 5 it concerned a cohort study in which interest was only in the health benefits and economic consequences in the birth cohort to be vaccinated. As both a high vaccine effectiveness was assumed and re-infection to be of no interest (assuming the prophylactic HP vaccine to provide lifelong protection), indirect effects in the target group due to vaccination were negligible and therefore in this particular study the use of a static approach was legitimized. Obviously, if the effectiveness was assumed considerable lower or if the vaccine was not assumed to provide lifelong protection and affects the transmission in the population, a dynamic approach would be preferable as due to indirect herd-immunity effects the (re-)infection rate would probably change over time in the target population.

**Part III**

Part III of this thesis covers the dynamic modeling of infectious diseases. In these models the herd-immunity effects are explicitly modeled by incorporating of a time-dependent force of infection parameter. In chapter 6 (part III) we designed a dynamic SIS (Susceptible-Infected-Susceptible) model to estimate the cost-effectiveness of a one-off systematic *Chlamydia trachomatis* (CT) screening program in the Netherlands. The overall CT incidence was estimated to decrease from 1.78% to 1.05% as result of the screening program directed at both men and women aged 15-29 years. The resulting cost-effectiveness was estimated at €373 per major outcomes averted (e.g. infertility and chronic pelvic pain). Additionally, restricting the screening to women only resulted in cost savings. Furthermore, we showed that most (>90%) of the averted costs and averted complications due to CT screening resulted from the indirect herd immunity effects which would have been neglected in a static model. As a CT infection is transmitted through sexual intercourse and is not solely restricted to certain groups in the population, the only appropriate method for fully predicting all consequences of a screening program would be a dynamic approach that also takes the indirect effects into account.
Before implementation of such a screening program the frequency of subsequent screening is a logical topic of discussion. Hence, in chapter 7 we present additional research on the cost-effectiveness of repeated systematic screening at various time intervals compared to the one-off screening. From a health-economic point of view, for the Dutch situation, we estimated screening men and women every 2 years as the optimal strategy among the options investigated. As nicely illustrated in chapter 7, for the estimation of the optimal intervention(s) (or screening frequency) in terms of cost-effectiveness certain options possibly can be ruled out due to ‘extended dominance’. The concept of extended dominance is explained in annex 2.

In chapter 8 we designed a stochastic individually based DES (Discrete Event Simulation) model in order to estimate the cost-effectiveness of pertussis booster vaccination strategies. Here, the cost-effectiveness of vaccinating adolescents at the age of 12 years was estimated. A DES differs from a SIS model as developed in chapter 7. The latter is deterministic and population-based, whereas the former is stochastic and individually based. As the exact duration of immunity acquired by natural infection is not known two scenarios that differ in the duration of immunity after a natural pertussis infection were considered. For both scenarios, the cost-effectiveness of adolescent booster vaccination was estimated below €10,000 per quality adjusted life year. Although adolescent vaccination leads to a decrease in total incidence of pertussis in the population, it causes an increase in absolute numbers of recidive infections in the older age groups (>20 years). This stresses the importance of dynamic modeling as these indirect outcomes would never have been predicted within a static approach.

Finally, in chapter 9 the current role of dynamic modeling in national and international guidelines for health-economic research is discussed. As nowadays modeling is widely used in economic evaluations of pharmaceuticals and other health-care interventions specific guidelines on modeling have been published and are often included in the general guidelines for health-economic research. Unfortunately, these guidelines on modeling most often only apply for non-infectious-disease related health care interventions. Therefore, additional specific guidelines are needed for economic evaluations of interventions directed at infectious diseases as this requires different and more complex modeling techniques to capture the indirect herd-immunity effects.

In the Netherlands, health-economic and pharmacoeconomic cost-effectiveness studies has to be performed according to the national guidelines for pharmacoeconomic research formulated by the ”College Voor Zorgverzekeringen” (CVZ). However, nothing specifically is written about the modeling of infectious diseases in particular. In practice, the Dutch
drug-reimbursement authority (i.e. CVZ) will not even assess pharmacoeconomic studies that include dynamic modeling. CVZ demands economic models that are easy to understand, highly transparent and which are designed in either Excel [Microsoft, Redmond, US] or TreeAge [TreeAge Software, Inc., Williamstown, US] software packages. However, those software packages are not suitable for the dynamic modeling of infectious diseases. Summarized, this means that currently the CVZ preferably evaluates the cost-effectiveness of interventions aimed at infectious diseases that are produced by static approaches.

This thesis concludes with recommendations for adjustment of the national guidelines for pharmacoeconomic research in order to improve medical decision making within the field of infectious diseases. I would strongly advise the Dutch drug-reimbursement authority to add specific guidance on the modeling of infectious diseases in their guidelines. As fully described in chapter 9, neglecting the herd-immunity effects can lead to very misleading results. Consequently, dynamic modeling is inevitable to obtain reliable outcomes when interventions show considerable influence on the herd-immunity. To support this process I developed a guide on choosing the appropriate health-economic model for economic evaluations on interventions for infectious diseases. Figure 1 graphically depicts the flowchart to help determine the appropriate modeling approach (i.e. static or dynamic). The primary and most important decision in modeling infectious diseases is the choice to use either a dynamic or a static model. Unfortunately, there is not one type of model that is suitable for all situations. Static models are attractive because of their relative straightforward approach and could be appropriate as shown in chapters 4 and 5. However, sometimes a more time-consuming and complex dynamic approach is inevitable as indicated in chapters 6 to 8.

The most important message of this thesis is to treat infectious diseases according to their unique nature of being INFECTIOUS!
Figure 1: Guide on choosing the appropriate modeling approach. Pathogen are bacteria, viruses and fungi.