Chapter 15
Health Economics of Infectious Diseases

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15.1 Introduction

Due to technical innovations and demographic changes, many industrialized countries are facing problems in financing health-care costs. One way to guide decision makers in the allocation of their limited health-care budget is the use of economic evaluation. The economic evaluation of health technologies is a special discipline of health economics, which compares the technical efficiency of technologies in the health-care sector. The term technology covers everything from drugs to medical equipment to the design of intervention programs. Technical efficiency is achieved if with a minimum input (of resources) a given output is produced or if with a specific input a maximum of output (e.g., life years) is produced. Hence, technical efficiency considers both effectiveness and resource utilization. Only an effective technology can be efficient. Typically, in economic evaluations the incremental cost-effectiveness ratio (ICER) of a technology is estimated. The ICER is a measure for the technical efficiency of a technology and can be expressed, for example, as € 30,000 per life year gained (LYG) or US $ 15,000 per quality-adjusted life year (QALY) gained, reflecting the net costs (costs minus savings) of gaining one life year or QALY, respectively.

Several specific aspects characterize economic evaluations of infectious diseases. The main differentiating characteristic of infectious diseases is obviously their infectiousness. Hence, the prevention of an infection in one individual can decrease the infection risk of another individual. Next, many important infectious diseases occur at young ages, most notably during childhood which makes the measurement of quality of life (QoL) losses very difficult and raises questions about the estimation of the loss of future productivity. Furthermore, prevention programs against several infectious diseases require immediate investment of costs but render prevented

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sequelae and associated savings years later. Thus, the results of economic evaluations of prevention programs are often greatly influenced by the applied analysis horizon and the discount rates.

This chapter considers these special challenges, which are posed by the economic evaluation of infectious disease prevention. The main elements of economic evaluations are shortly described and the specific requirements of the prevention measures against infectious diseases are discussed. The cost-effectiveness analysis (CEA), which is the most common study type in the economic evaluation of infectious diseases, will be used as a case example.

15.2 Elements of Economic Evaluation with a Special Focus on Infectious Disease Prevention

15.2.1 Effectiveness

The effectiveness of a technology is one of the most important parameters for a CEA. Typically, effectiveness – aimed to reflect the drug's performance in real life conditions – differs from efficacy estimated from controlled studies, such as randomized clinical trials. Effectiveness may generally be plausibly approximated from efficacy estimates by accounting for possible non-compliance, non-adherence, and non-persistence. In the case of infectious diseases this approximation is, however, more difficult. As infectious diseases are transmissible, the direct aversion of an infectious disease in one person might also lead to the indirect aversion of the disease in other persons. These indirect protection effects can occur if an intervention, such as vaccination, reduces the force of infection in the population. The force of infection has been defined as the rate at which susceptibles acquire infection (Edmunds et al. 1999). As a consequence, incidence decreases beyond the immediate effect of the intervention under study. The overall effectiveness of a prevention measure against an infectious disease is made up of the direct effectiveness (the vaccinated person is protected) and the indirect effectiveness (the risk of non-vaccinated persons becoming infected is decreased). Hence, the overall effectiveness cannot be derived from a randomized clinical trial alone – instead it is necessary to look at the population level. Of course, the exact relative size of the indirect effect depends on the specific infectious disease and intervention under study.

There are two ways of obtaining the overall, i.e., direct and indirect effectiveness of an infectious disease prevention measure:

Retrospective data analysis: The disease incidence or prevalence before and after the intervention is analyzed. For instance, De Wals et al. calculated retrospectively the overall effectiveness of meningococcal C vaccination in Quebec in 1992–1993 (De Wals et al. 2001). Similarly, Ramsey et al. estimated the overall effectiveness for meningococcal serogroup C conjugate vaccination in England retrospectively (Ramsay et al. 2003).

Prospective simulation using mathematical modeling (see Section 15.3)**:** This is the typical method of estimating the overall effectiveness of introducing a new prevention intervention. For parameterization and validation of the model

retrospective data are typically used. A good example is the meningococcal C simulation model by Trotter et al. which estimates the effectiveness of serogroup C meningococcal C vaccination in the UK (Trotter et al. 2005).

To generate indirect protection effects, the pathogen and technology must meet the following conditions: (a) the pathogen is mainly transmitted between humans and (b) the intervention influences the spread of the pathogen in the population (Welte 2007). Examples for which the first condition is not fulfilled are rabies or tetanus. Interventions targeting only a part of a population which contributes marginally to the spread of the infection in the population do not fulfill the second condition, e.g., hepatitis B vaccination as travel prophylaxis of probably predominantly monogamous individuals in Germany. This intervention will not result in substantial indirect protection effects, as hepatitis B in Germany is mostly spread via sexual contacts with multiple partners.

Typically, indirect protection effects represent positive externalities of the intervention. The protection of one individual simultaneously reduces the risk of other individuals to become infected, and thus extends the benefit beyond the treated individual. As such, indirect protection often leads to an improved cost-effectiveness of the intervention. Examples are shown in Tables 15.1 and 15.2

Table 15.1 Examples of the impact of indirect protection effects on the cost-effectiveness of vaccination programs

Pathogen	Vaccination program	Country	Cost-effectiveness ratio		Reference
			With indirect protection effects	Without indirect protection effects	
Hepatitis A virus	Routine childhood	USA	Cost saving	US$ 228,000/LYG	Armstrong et al. (2007)
Human papillomavirus 6,11,16,18	Routine girls	USA	US$ 3,906/QALY	US$ 8,137/QALY	Chesson et al. (2008)
Influenza virus	Working population	ESP	Cost saving	∈ 76/influenza case avoided	Pradas-Velasco et al. (2008)
Meningococcus C	Routine childhood	UK	£ 8713/LYG	£ 44,639/LYG	Trotter and Edmunds (2006)
Bordetella pertussis	Routine adolescents	USA	20%*: US$ 6253/LYG	5%*: US$ 187,081/LYG	Caro et al. (2005)
Streptococcus pneumonia	Routine childhood	GER	∈ 164/LYG	∈ 100,636/LYG	Lloyd et al. (2008)
	Routine childhood	NL	∈ 15,600/LYG	∈ 58,700/LYG	Hubben et al. (2007)
	Routine childhood	UK	£ 4360/LYG	£ 33,687/LYG	McIntosh et al. (2005)
	Routine childhood	USA	$ 7500/LYG	$ 112,000/LYG	Ray et al. (2006)

* Caro et al did not show the results with and without indirect protection effects, instead, they showed them with 20% (baseline) and 5% indirect protection effects

Table 15.2 The impact of indirect protection effects on the cost-effectiveness of screening programs using genital *Chlamydia trachomatis* infections as case example (Welte et al. 2005a)

	Cost-effectiveness ratio of screening	Incremental cost-effectiveness ratio for extending the screening to	
	Females aged 15–24 years (baseline)	Females aged 15–29 years	Females aged 15–34 years
With indirect protection effects	Cost saving	Cost saving*	Cost saving*
Without indirect protection effects	US $ 700/MOA	US $ 1800/MOA	US $ 2520/MOA

* Both strategies strictly dominate screening females aged 15–24 years, i.e., they render more MOAs and savings
MOA = Major outcome averted

Sometimes, these effects can cause a less attractive ICER, as have been shown for meningococcal C conjugate vaccination in the Netherlands: The ICER for routine childhood vaccination at ages 2 + 3 + 4 months (three vaccine doses in total) versus at 14 months (one vaccine dose) strongly increased when the likely indirect protection effects of the catch-up vaccination program (all persons aged 14 months to 18 years) was considered. These indirect protection effects lowered the number of avoidable meningococcal cases in the age group 0–14 months and thus reduced the health benefit of vaccinating during the first year of life versus at the beginning of the second year of life (Welte et al. 2004c).

Moreover, in some cases indirect protection effects can also turn out as negative externalities if an age shift occurs or if the exposure of immune persons to the pathogen is important for boosting their immunity:

Age shift of infection: The indirect protection effect of a mass infant vaccination program can result in a shift of the age at infection. Vaccination of most infants against a childhood disease reduces the force of infection in the population considerably. Thus, non-immunized individuals have a decreased infection risk and therefore tend to be older when they get infected. For diseases, which are more severe in adulthood than in childhood, such as polio, hepatitis A virus, mumps, rubella, and varicella, this age shift might lead to additional health problems and thus to a worsening of the economic attractiveness of a vaccination program. For instance, after the implementation of infant vaccination against rubella in Greece an age shift was observed that resulted in an increase of congenital rubella (Panagiotopoulos et al. 1999). On the other hand, for diseases which are less severe in adulthood than in childhood, this age shift leads to an improved cost-effectiveness of the vaccination program. Examples are pertussis and hepatitis B vaccination: Pertussis is less severe in older children and adults than in infants and a higher age of infection with hepatitis B virus results in fewer chronic infections (Welte 2007).

Reduction in boosting of immunity. The indirect protection effect may decrease the exposure of immune persons to the pathogen yielding to a reduction in the rate of reactivation and boosting of immunity. This has been observed for varicella zoster (Brisson and Edmunds 2002; Thomas et al. 2002) and its negative influence on the

economic attractiveness of routine infant varicella vaccination has been simulated for Canada, England and Wales, and the USA (Brisson and Edmunds 2002; Brisson and Edmunds 2003; Goldman 2005). Modeling results show that in the short and medium term (35–50 years) after the introduction of a mass infant varicella vaccination program, herpes zoster would increase in the population. However, in the long term (50–70 years), as the immunized children aged further, a decrease of herpes zoster was predicted (Thomas et al. 2002). So far, there is mixed evidence in the USA whether the incidence of zoster has increased or not since the introduction of universal varicella vaccination (Heininger and Seward 2006). The time period since vaccination is still too short to really obtain practical evidence of the accurateness of the simulated results.

Currently, vaccination and screening programs are the primary prevention measures against infectious diseases. For vaccination programs, indirect protection effects are commonly labeled herd immunity effects and have been frequently defined as the indirect protection of non-immune individuals by the presence and proximity of immune individuals (Fine 1993). Typically, a vaccinated person leaves the susceptible pool of the population as most vaccinations result in protection from the infectious pathogen for several years. Herd immunity also implies that full vaccination coverage is not required to achieve elimination of an infectious disease in a population. Based on the concept of herd immunity, the critical level of vaccination in a population for elimination of infection has been estimated for various infectious diseases, such as measles (coverage of about 83–94%), pertussis (92–94%), and rubella (83–85%) (Fine 1993).

For screening programs, indirect protection effects have been less investigated than for vaccination programs. Screening programs for sexually transmitted diseases (STDs) lead to the identification and subsequent treatment of asymptomatic infected persons. After eradication of the pathogen the body is usually not immune against reinfection and the individual is susceptible again. Examples are genital infections with *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Thus, STD screening programs differ from vaccination programs with respect to the susceptibility to a disease. This difference might influence the impact of an intervention on the spread of disease and thus on the force of infection.

Besides these indirect protection effects, the effectiveness of an infectious disease prevention programs can also be influenced by cross protection, waning immunity, serotype replacement, and development of treatment resistance:

Cross protection may occur, with the vaccine providing protection beyond the serotypes explicitly included in the vaccine, as has been recently shown for human papillomavirus vaccines (Herrero et al. 2009). Clearly, cross protection will improve the effectiveness and cost-effectiveness of the respective vaccines.

Waning immunity, i.e., decreasing vaccine-induced immunity over time, has been observed for many vaccines, e.g., diphtheria, pertussis, or tetanus vaccines. It may result in the necessity of booster vaccine shots and a worsening of the cost-effectiveness of the vaccination program.

Serotype replacement means that the virus or bacteria serotype(s), contained in the vaccine, is (are) replaced by other types not covered in the vaccine. In case the

replacing type is pathogenic, the (cost)effectiveness of vaccination against the specific disease will decrease. This has been observed in Alaska after the introduction of routine infant pneumococcal vaccination in 2001. At first the invasive pneumococcal disease rate decreased but subsequently increased due to serotype replacement (Singleton et al. 2007).

Development of treatment resistance: Another problem in the optimizing of strategies against infectious disease may emerge over time in cases where effective treatment exists for infected persons, but its broad, intensive, and long-term use nourishes the development of treatment-resistant strains of the infective agent. The treatment of one generation of susceptibles may increase the risks of a next generation of susceptibles for whom effective treatment may no longer be available. Tuberculosis is an example of a disease incurring problems of this type (Maartens and Wilkinson 2007).

15.2.2 Comparator and Cost-Effectiveness ratio

In an economic evaluation, the costs and effects of the investigated technology are compared with costs and effects of the most common or best available technology. Thus, the incremental costs and effects are evaluated and typically integrated into the ICER. If no intervention is the most plausible comparator the comparator is "no intervention" and hence the incremental costs and effects compared to "no intervention" are calculated. The resulting cost-effectiveness ratio (CER) is often called the average cost-effectiveness ratio (ACER) or also the ICER versus "no intervention" (Welte et al. 2004c). Commonly, the results of an economic evaluation are shown in the cost-effectiveness plane (Fig. 15.1). It shows the incremental costs (ΔC) and effects (ΔE) per patient. The slope of a straight line from the origin through the coordinates of a technology (e.g., point A for technology A) gives the ICER for technology A.

The difference between the ICER and ACER is at the heart of health economics. A small example may help illustrate the difference between the ACER and ICER further. Let us assume two technologies F and G for averting a disease. Technology F costs € 1000 and leads to 5 LYGs, technology G costs € 1800 and renders 6 LYGs. The ACER of technology F is € 1000/ 5 LYGs = € 200 per LYG, the ACER of technology G is € 300 per LYG. However, the ICER of technology G versus technology F is (€ 1800–€ 1000)/(6 LYGs – 5 LYGs) = € 800 per LYG.

The ACER has become a rather uncommon measure in the economic evaluation of therapeutics, as effective treatments are usually available for the respective diseases. Yet, in the field of vaccination and screening programs the ACER is still often encountered as there is generally no implemented screening or vaccination program for comparison. Nevertheless, even in cases, where the relevant alternative is really "no intervention", the ICER can still be important for identifying the best vaccination strategy. An example is meningococcal C conjugate vaccination in the Netherlands. First the ACER of universal childhood vaccination at 14 months was estimated to be € 1900 per LYG. Subsequently, the ICER of different possible

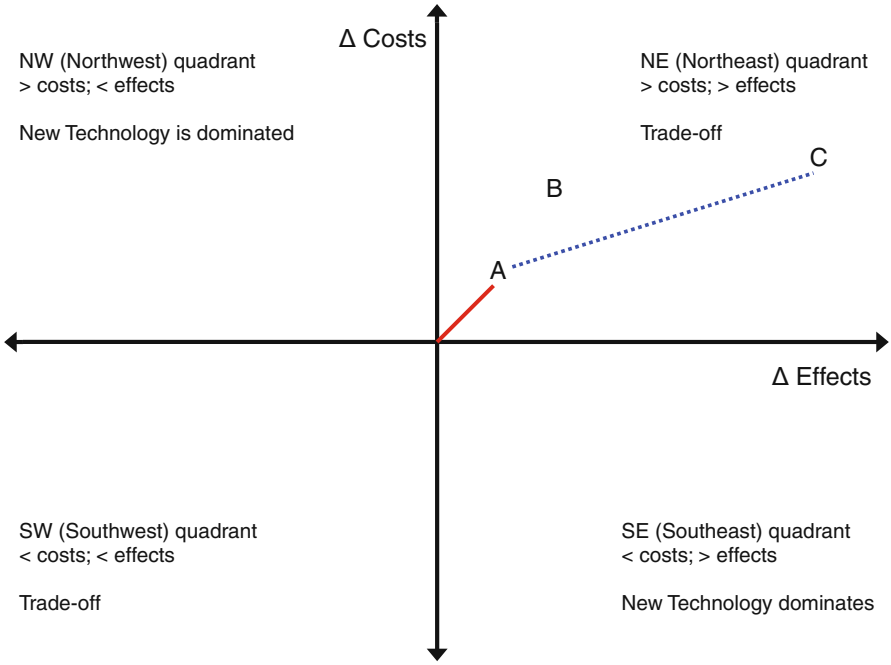

Fig. 15.1 The cost-effectiveness plane

vaccination strategies was calculated, e.g., each additional LYG by vaccination at 2, 3, and 4 months versus vaccination at 14 months was estimated to incrementally cost about € 147,000 (Welte et al. 2004c).

Consistent application of the ICER concept may reveal cases of so-called dominance. One strategy can be dominated by another strategy, either by strict or extended dominance. A strategy is strictly dominated when it is both less effective and more costly than another strategy, i.e., it lies in the northwest quadrant of the cost-effectiveness plane (Fig. 15.1). A strategy is extended dominated when it is both less effective and more costly than a linear combination of two other strategies with which it is mutually exclusive (Gold et al. 1996; Postma et al. 2008). This can be graphically illustrated by plotting the incremental costs and effects of different technologies (using the same comparator) on a cost-effectiveness plane. In Fig. 15.1, technology B is extended dominated by A and C (see dotted line). Examples of dominance are chlamydial and HIV screening as well as pneumococcal vaccination: In the Netherlands chlamydial screening every 10 years only was extended dominated by a combination of one–off screening and screening every 5 years (de Vries et al. 2008). Universal HIV screening among pregnant women in Chicago results in a decreased number of HIV-infected newborns and also cost savings, i.e., it strictly dominates no screening (Immergluck et al. 2000). Similarly, universal childhood vaccination with the pneumococcal conjugate vaccine in Germany renders health gains and cost savings (Claes et al. 2009).

15.2.3 Perspective

The perspective determines which costs (and effects) are relevant and should be considered in an economic assessment. For prevention measures against infectious diseases, commonly both the societal and the health-care payer perspective are taken. Typically, the former leads to a more attractive CER than the latter. However, this is not always the case and hence should be checked for each strategy individually (Welte 2007). For diseases causing relevant absenteeism, sometimes also the perspective of an employer is applied, e.g., for influenza vaccination (Postma et al. 2005). While the productivity loss is relevant to the employer it is often not of interest to the health-care payer. Oppositely, the direct medical costs are not always important to the employer, whereas they clearly are for the health-care payer. For the societal perspective, which is recommended in most guidelines for economic evaluation, the cost of all resource consumption is relevant, no matter who causes or pays for it.

15.2.4 Costs

Costs in economic evaluations are usually divided into direct and productivity costs.

Direct costs are the valued resource consumptions of tangible goods and services actually delivered to address the consequences of a disease (e.g., acute medical care) or to prevent the disease (e.g., vaccination). They are often distinguished into direct medical (e.g., hospital visit, vaccine) and non-medical (e.g., transport cost to the hospital) costs.

Productivity costs (also called indirect costs) are the value of productive services not performed. They can be caused by a disease (e.g., absenteeism, early retirement, and mortality) or a technology (e.g., taking time off to receive a vaccine shot). Productivity costs occur in both the paid and unpaid work sector. Those in the paid work sector can be defined as all work activities that contribute to the gross domestic product (GDP), while unpaid work is not recognized in the classical system of national accounts. Unpaid work mainly consists of household work, caring for family and non-family members (informal care), maintenance of transport, consumer items and homes, and engagement for society (work in an honorary position and voluntary work) (Welte et al. 2004b).

In economic evaluations of prevention measures against infectious disease, productivity costs frequently represent one of the major categories of averted costs as infectious diseases often occur in young children (childhood diseases) and can lead to severe life-long sequelae or even death. Typical examples are infant vaccination programs. In particular, productivity costs make up 54% of the estimated cost savings for pneumococcal conjugate vaccination in the USA (Welte 2007). Productivity costs are typically either measured with the human capital approach or the friction cost method.

The *human capital approach* is the standard approach for estimating productivity costs and can be used for assessing the productivity costs due to paid and unpaid work loss. It estimates the maximum potential loss of production as a consequence

of disease or death. In particular, the full extent of output that a person cannot produce due to a disease is assessed. For long-term work absence, the present value of the future net product has to be calculated with discounting (Welte et al. 2004b).

The *friction cost method* can also be applied to estimate the actual loss of paid work. It assumes that the paid work of any long-term absent person can be undertaken by a previously unemployed person. The time span required to find and train a replacement worker is defined as the friction time. For any work absence longer than the friction time, only the friction time is taken into account for the calculation of the production loss. It is further assumed that during work absence, about 80 % of the production of a person will be lost, as the other 20 % is assumed to be taken over by colleagues or made up for by the sick person after recovery. The value of lost production plus the costs for finding and training a replacement worker plus the costs of the negative medium-term macro-economic consequences of absence and disability render the friction costs, i.e., the productivity costs based on the friction cost method (Koopmanschap et al. 1995; Koopmanschap and Rutten 1996).

If the infectious disease causes only short-term work loss (work-loss time shorter than the friction time), the two methods render rather similar results for the paid work sector. Uncomplicated cases of diarrhea are one example of this. Otherwise, results may differ substantially, especially for diseases that cause mortality and inability to work, such as meningococcal disease. With the human capital approach, the productivity costs of a child's death are valued at the present value of the future net product of an average child at the same age, rendering considerable productivity costs. The same event is valued at € 0 with the friction cost method. The strong impact of the measurement method has been demonstrated for a routine childhood meningococcal vaccination program in the Netherlands: Applying the human capital approach instead of the friction cost method decreased the costs per life year gained by almost 700% and was identified as the most sensitive assumption in the model (Welte et al. 2004c).

Health technologies typically lead to a net decrease of productivity costs, i.e., the productivity loss caused by a disease is exceeded by the productivity gains attributable to preventing the disease. However, this cannot be taken for granted and should be checked for each technology case by case. A CEA for a meningococcal vaccination catch-up program in the Netherlands rendered higher productivity costs than productivity savings (Welte et al. 2004c).

Childhood diseases often result in parental work loss which in turn can influence the cost-effectiveness of prevention measures. The respective productivity costs are typically included in the CEA of childhood vaccination programs, such as for meningococcus (Welte et al. 2004c), pneumococcus (Hubben et al. 2007), rotavirus (Jit and Edmunds 2007), and varicella (Brisson and Edmunds 2002).

15.2.5 Effects

The effects of a technology can be measured in natural clinical (e.g., prevented deaths, LYGs, or major outcomes averted (MOAs) for *C. trachomatis*) and non-clinical (e.g., avoided work-loss days) outcomes or in combined outcomes such as

QALYs. For the measurement of QoL there are several disease-specific and some generic instruments. They can be grouped into profile and index instruments. The former describe single dimensions of QoL with values for each dimension, while in the latter all QoL dimensions are summarized in a single value using a specific algorithm. This single value represents a QoL weight, which can then be used for calculating QALYs (see below). Many authors consider the QoL weight a utility if it is being measured by methods with an axiomatic base in utility theory – as for example, the standard gamble method. Examples of index instruments are the EQ-5D of the EuroQol group, the Health-Utility-Index Mark III (HUI Mark III), and the Quality of Well-Being Scale. Specific health profiles include the Medical Outcome Study 36 – Item Short Form Health Survey (SF-36). Methods exist to map the SF-36 results into a single value or QoL weight (Brazier et al. 2002; Brazier et al. 2007).

While the LYG only considers mortality, the QALY takes both morbidity and mortality into account. For the calculation of QALYs, the time a person spends in a specific health status is multiplied with the QoL weight that ranges from 0 (death) to 1 (perfect health). One QALY equals 1 year in perfect health. There are two different theories of the QALY: The welfarist theory interprets the QALY as a representation of individual utility over health. The extra-welfarist approach sees the QALY as a measure of health as a social desideratum, i.e., as a measure of social good in health policy (Brazier et al. 2007). For the determination of QALY weights different methods can be applied, of which the standard gamble method, the time trade-off method, and the visual analogue or rating scale method are common (Berger et al. 2003). As the application of these methods is very resource consuming, index instruments such as the EQ-5D are used more often. For each possible health status indicated by these instruments (e.g., 243 possible health states for the EQ-5D) there are already QALY weights for several countries available (Greiner et al. 2003). For example, the EQ-5D QoL-weights have been estimated using the time trade-off method in the UK, Germany, Denmark, Japan, Spain, Zimbabwe, and the USA (Szende et al. 2006).

Besides the QALY there is the DALY (disability-adjusted life year) which is also a combined measure of morbidity and mortality. In the DALY approach each health state is assigned a disability weighting on a scale from 0 (perfect health) to 1 (death). Furthermore, while QoL weights in the QALY are based on preferences of either the general public or the patients, the disability weights in the DALY are person trade-off scores elicited from a panel of health experts. Unlike QALYs, DALYs are age-weighted in order to take into account welfare interdependence, i.e., individuals support others during adulthood while they are supported by others during infancy and at an advanced age (Robberstad 2005; Drummond et al. 2005). The World Health Bank introduced DALYs to measure the global burden of disease in 1993 (Robberstad 2005) and the World Health Organization recommends the use of DALYs for CEAs (WHO 2003). While in developed countries the QALY is the health effect of choice for CEA, DALYs are primarily used in developing countries. From the standpoint of economic theory, the preferences of those affected, as used in the QALY approach, and not those of experts are preferable. The weighting of QoL by DALYs may provide a substitute in population-oriented approaches where a data basis for QALYs is lacking.

Many infectious diseases occur in childhood. The measurement of QoL in children, especially of infants and toddlers, is very difficult as almost all generic index instruments have been developed for the QoL measurement of adults. Parents or doctors have often been used as proxies for indirectly estimating the QoL of children. Recently, new instruments have been specifically developed for children, such as the EQ-5D-Y (for children between 8 and 14 years), the KIDSCREEN (8–18 years), or the KINDL-R (4–16 years), which directly measure the QoL of children (Ravens-Sieberer et al. 2006). At the time being the value of all these instruments designed for the use in children cannot be considered as utilities. Therefore, the development of QoL measurement in children and especially very young children (before school age) can be considered to be still in its infancy. The QoL loss due to childhood diseases may not be limited to the affected children but may also impact their caregivers. For example, a recent study estimating the cost-effectiveness of rotavirus vaccination in England and Wales applied QALY losses for a child and two caregivers for each episode of rotavirus gastroenteritis (Jit and Edmunds 2007). It should be noted that taking into account the caregivers' QoL loss is rarely seen in economic evaluations.

The prevention of a disease leads not only to the utility gain by the avoided disease itself but also to a gain due to utility-in-anticipation. In the case of a vaccination program, the latter is the utility yielded immediately after vaccination due to the risk reduction until the time the infectious disease was expected (Drummond et al. 2007). Obviously, the utility-in-anticipation depends on the severity of the disease, the risk of non-immunized persons getting the disease, and the effectiveness of the vaccination. It is typically not considered in economic evaluations.

15.2.6 Time Horizon

The time horizon of an analysis determines how long the costs and effects of an intervention shall be measured. It is usually assumed that the current method of diagnosis and treatment will remain the same during the assessed time period in an economic evaluation. Clearly, new diagnostics and treatments can be expected to be introduced in the near future. Hence, a longer analysis horizon increases the uncertainty of the results. In general, the time horizon of an economic evaluation should be long enough to capture all relevant costs and effects of the investigated technology and the identical time horizon should be applied for both costs and effects. For interventions aimed at infectious diseases, this time span may vary from very short to very long. Medications to treat uncomplicated cases of common cold or diarrhea are examples for which a short time frame may apply. On the other hand, vaccination programs in childhood against hepatitis B or in adolescents against cervical cancer require a life-long span. If the aim of an intervention is eradication, the time horizon might even be longer to allow the model sufficient time to achieve the new steady-state of eradication. The Viral Hepatitis Prevention Board suggested in its consensus statement that the analysis horizon for economic evaluation of vaccination programs should not be less than the time required for the decrease in incidence to stop and

for the ICER to plateau, i.e., a new epidemiological equilibrium has been reached. It postulated that the necessary time span may roughly range from 1 to 100 years, depending on the intervention and the disease (Beutels et al. 2002). Given the potential long time spans investigated, one should be aware of the following issue: The actual payments and the health gains obtained per period may deviate significantly from the ICER that is calculated over the whole time span. In populations with long-term dynamic factors beyond those integrated in the model framework the estimated ICER may never be achieved.

The analysis horizon has a strong impact on the economic attractiveness of interventions when they lead to a decreased force of infection or even to the eradication of a disease in a population. Prolonging the analysis horizon will lead to the avoidance of more negative health outcomes and associated costs compared to the "no intervention" scenario and hence to a better cost-effectiveness (Welte et al. 2000).

15.2.7 Discounting

Individuals have a positive time preference for money, i.e., they would choose to get a specific amount of money rather today than tomorrow, irrespective of the presence of inflation. In order to adjust for this positive time preference, future costs are discounted to their current present net value. Thus, the further in the future the costs occur, the lower is their present value. Typically, costs are discounted on a yearly basis and exponentially, i.e., at a constant rate. The respective equation for discounting is

$$\text{Present value} = (\text{Future cost at year } t)/(1 + \text{discount rate})^t$$

There are two main theoretical approaches for estimating the discount rate for future costs of health technologies:

(a) Social rate of time preference approach: It measures the willingness of the society to forgo consumption today to enable greater consumption in the future. It can be estimated by the rate on a risk-free investment (e.g., long-term government bonds) adjusted for inflation.

(b) Social opportunity cost approach: It takes into account that public investments can displace private investments or consumption. It uses the real rate of return forgone to society in the private sector which can be empirically estimated by calculating a weighted average of discount rates of those sectors of the economy that contribute resources to the investigated health technologies (Drummond et al. 2005).

Internationally, there is no consensus on which discount rate should be used for costs and different guidelines ask for different discount rates (e.g., 5% in Canada, 4% in the Netherlands, and 3% in the USA). There is even less clear evidence on whether and how health effects should be discounted. Currently, there is an ongoing scientific debate whether the same discount rate should be applied for costs and for effects or whether differential discounting should be applied. At this time, almost all guidelines ask for equal discounting of costs and effects. However, the

Belgium and Dutch guidelines request differential discounting with 3% (Belgium) and 4% (Dutch) for costs and 1.5% for effects. Common arguments for using the same discount rate for costs and effects are as follows:

- Economic theory implies that in a perfectly competitive, risk-free, tax-free world in which all commodities (including something called "health") are perfectly divisible – so that individual decision makers could precisely adapt their consumption of goods and services over time – there would be but one discount rate (Gold et al. 1996).
- Consistency argument contends that using different discount rates for costs and effects can lead to inconsistent reasoning. Example: Intervention K costs € 10,000 this year and renders 1 QALY this year, Intervention L costs € 10,000 in 10 years and renders 1 QALY in year 10. Using the same discount rate for costs and effects would lead to the same CER and hence would give the same priority to both interventions. On the other side, applying different discount rates for costs and effects would render different CERs (Brouwer et al. 2005; Claxton et al. 2006).
- Keeler and Cretin paradox: A higher discount rate for costs than effects would result in a better CER the later the technology is implemented. Hence, it might lead to an eternal delay of the introduction of investigated technologies (Brouwer et al. 2005; Claxton et al. 2006).

Typical arguments for using different discount rates are as follows:

- Time preference might be different for effects.
- The world is not perfectly competitive, risk-free, and tax-free (Gold et al. 1996) and neither is health perfectly divisible nor is it a fully tradable good.
- The monetary valuation of health effects might change over time, invalidating the consistency argument (Brouwer et al. 2005; Gravelle et al. 2007).
- Keeler and Cretin paradox is usually not relevant for decision makers as the typical decision is not when but whether a medical technology should be implemented (Brouwer et al. 2005; Cairns 2001).
- The problem of double discounting of QALYs if calculated from time trade-off-based preferences. In the time trade-off method, the preferences already include discounting (MacKeigan 2003).
- Inter-generational discounting: Discounting effects gained in the future gives more weight to the current generation compared to the future one (Cairns 2001). This argument is especially relevant for infectious disease prevention. From any program that aims at the eradication of a disease, future generations will strongly benefit – but this benefit is basically discounted away. For example, smallpox was a major threat to people until its successful eradication and all current and future populations have an obvious benefit from the successful eradication campaign.

Finally, we note that for both money and health the functional form for discounting is questioned. In particular the time preference might not be linear considering different time periods. For instance, hyperbolic discounting has been suggested as an alternative for the linear relationship described above.

Discounting can have a profound impact on the results of economic evaluation. It always has an influence if there is a differential timing of costs (and effects), e.g., investment costs occur now while the health effects and associated savings with a technology occur later.

The impact of discounting strongly depends on two factors:

(a) The time interval between the investment (e.g., vaccination) and the health effect (e.g., averted death). As the interval increases, the impact of discounting becomes more profound. This is the case for most prevention programs against infectious diseases. For example, cervical cancers may occur on average at ages 35–55 years while HPV vaccination might take place at 12 years of age.
(b) The exact rate of discounting applied: The higher the discount rate, the less the future is valued and thus the less the future health effect and associated savings are valued. The impact of the discount rate can be easily seen in Fig. 15.2. At a discount rate of 5% the present value of any savings or effects occurring after more than 50 or 100 years is less than 10 or 1% of the future value, respectively. As a result, discounting leads to a restriction of the time horizon.

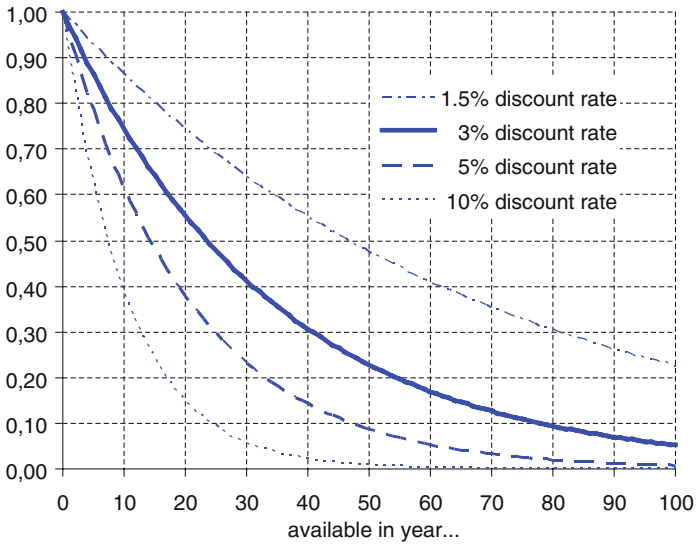

Fig. 15.2 Present value of € 1 or 1 life year

The question has been raised whether a different discounting method should be applied for prevention measures for infectious diseases. Bos et al. propose that the timing of the risk reduction and not the timing of the avoided morbidity or mortality should be incorporated in the discounting (Bos et al. 2005). This would lead to more attractive CERs for prevention measures as the benefit would be valued from the time of risk reduction and not from the later time of exposure. However, instead

of trying to address this topic by changing the discounting procedure, it could also be addressed using the utility-in-anticipation concept (see above) (Drummond et al. 2007).

15.2.8 Uncertainty

In an economic evaluation, first the base case or baseline analysis is performed (Gold et al. 1996). The most likely values are used as model input parameters to yield the main results. Second, the sensitivity analysis is conducted to assess the robustness of the results, i.e., what is the probability that the results are correct or that the outcomes are robust when changes in parameters are made? Different types of uncertainty are commonly distinguished:

- *Parameter uncertainty:* What is the true value of an input parameter, whereby the available information on the parameter is merely conceived as one possibility out of a broader set (a random draw from a distribution)?
- *Methodological uncertainty:* Are the appropriate methods used, e.g., what is the correct perspective and discount rate, what approach should be used for measurement of productivity costs, which time horizon should be applied?
- *Model (or structural) uncertainty:* Has the right model been designed, have the right relations been specified, and have the right modeling assumptions been made?

Uncertainty can be reduced through collecting more data. This is, however, not the case with variability, e.g., the variation of patient outcomes such as QoL. Variability has also been called first-order uncertainty while parameter uncertainty has also been defined as second-order uncertainty. In the sensitivity analysis, parameter and methodological uncertainty and sometimes also model uncertainty are explored but not variability. There are two main approaches for conducting a sensitivity analysis, as specified in Sections 15.2.8.1 and 15.2.8.2.

15.2.8.1 Deterministic Sensitivity Analysis

In deterministic sensitivity analysis alternative values for the point estimates of key parameters are explored and compared to those values used in the base case analysis.

- Univariate sensitivity analysis involves the variation of one input parameter at a time. This is a relatively simple but very important method to identify the most important model input parameters as well as the influence of the applied methodology. Typically, the results are presented as a tornado diagram, showing the most sensitive parameters at the top and the least at the bottom.
- Multivariate sensitivity analysis involves the variation of several parameter at a time, e.g., all parameters are set to the advantage or to the disadvantage of the investigated technology leading to a best and worst case scenario, respectively.

15.2.8.2 Probabilistic Sensitivity Analysis (PSA)

Instead of using point estimates probability distributions can be assigned to the specified ranges for the key parameters, i.e., probabilities, costs and effects to represent uncertainty. Multiple samples are drawn at random from these distributions, e.g., by Monte Carlo simulation, to generate an empirical distribution of the CER. If probability distributions are used for all uncertain input parameters, the model is called a full probabilistic model.

Typically, the results are presented as a scatter plot on the cost-effectiveness plane where each point presents one simulation. Subsequently, the results can be summarized in a cost-effectiveness acceptability curve (CEAC) where the horizontal axis represents the maximum willingness to pay and the vertical axis the probability that the technology is cost-effective (Fig. 15.3). The CEAC is derived from the joint uncertainty of incremental costs and effects of the investigated technology. It shows the probability that an intervention is more cost-effective than its comparator. Thus, the CEAC can provide a decision maker with the probability that, if the intervention is funded or reimbursed, this will be the correct decision. Moreover, the curve contains additional information: The 50% probability point on the CEAC corresponds to the median CER. Note that this median will only correspond to the mean-based CER when the CER is distributed symmetrically. The CEAC cuts the vertical axis at the probability that the investigated intervention is cost saving. When the curve is monotonically increasing, the $(1–2X)\%$ cost-effectiveness confidence interval can be obtained by cutting $X\%$ from either end of the vertical axis and using the curve to map these values on the horizontal axis. Using this approach, the 95% confidence interval in Fig. 15.3 can be determined as € 10,000–50,000 per QALY.

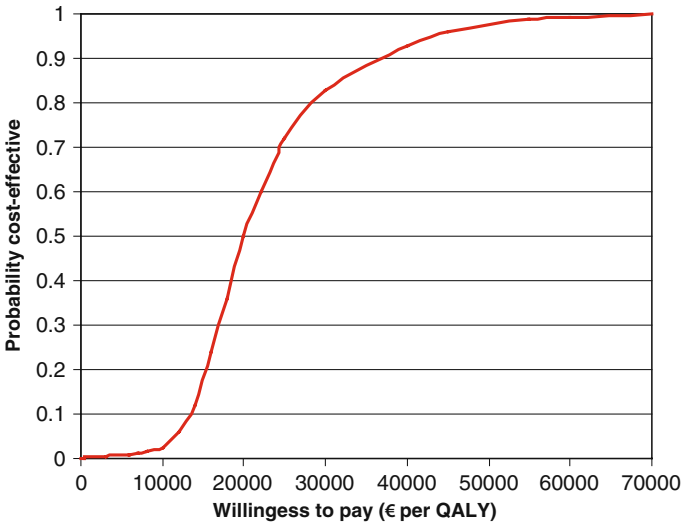

Fig. 15.3 Example of a cost-effectiveness acceptability curve

The CEAC in Fig. 15.3 represents only one of many shapes the CEAC can take; i.e., a monotonically increasing form is not the only possibility (Fenwick 2004).

While the PSA is the state of the art method for assessing overall parameter uncertainty, it is not suitable for assessing model or methodological uncertainty and hence its confidence interval omits the latter two uncertainties.

To account for methodological uncertainty the univariate sensitivity analysis is still the method of choice. Often, a combination of the PSA and univariate sensitivity analysis is applied: Running a PSA one time with the baseline estimates and subsequently with upper and lower values. For example, in the baseline PSA, a 3% discount rate might be applied and then a discount rate of 0 or 5% is used. In order to check model uncertainty, different models or parts of models need to be compared, as has been recently done for HPV vaccination (Chesson et al. 2008).

The evaluation of prevention measures against infectious diseases has to cope with two additional uncertainties: Fluctuating incidences (e.g., meningococcal or pneumococcal disease) and the disease transmission dynamics. Both represent very sensitive parameters for CEA and especially the latter is tricky to include in a PSA, given the already time- and computing consuming character of analyzing dynamic disease transmission models. PSA itself further adds to the huge time and computing requirements for such models. Furthermore the (appropriate) consideration of indirect protection effects, the perspective, the approach for productivity cost measurement, and the applied discount rate, i.e., the model and methodological assumptions, often have a great impact on the cost-effectiveness. For instance, a recent case study with varicella vaccination showed that a combination of model choice (in- or exclusion of zoster) and perspective (health-care payer or societal) can lead to the exact opposite conclusions: Either vaccination is almost certain to dominate the current strategy of no vaccination and vice versa (Brisson and Edmunds 2006). For vaccination programs where benefits occur in the medium-to-long term, e.g., hepatitis B and cervical cancer, the discount rate is typically one of the most sensitive model parameters.

15.2.9 Transferability

Not every country can perform an economic evaluation for each technology due to resource restrictions. Therefore, the assessment of the transferability of CEA results from one country to another country is often requested by decision makers. Currently, there are checklists (Boulenger et al. 2005; Welte et al. 2004a) and also a decision chart (Welte et al. 2004a) available for this assessment. The transfer of study results between countries is difficult but it is even more difficult to transfer prevention measures against infectious diseases due to possible differences in disease transmission. Nevertheless, transferring the health economic model or at least parts of it has been shown to be very efficient and helpful (Welte et al. 2004a). Making a model available via the Internet seems to be a promising way to help decision makers and researchers to adjust a model. Examples are the cost-effectiveness models used for the report “Vaccines for the 21st century” by the

Institute of Medicine (Institute of Medicine 2000), "Socrates (Screening Optimally for Chlamydia: Resource Allocation, Testing and Evaluation Software)," "Fluaid," "Flusurge" and "Fluworkloss" by the Centers for Disease Control and Prevention (CDC), "Quickflu" by the University of Tübingen or the pneumococcal conjugate vaccine cost-effectiveness model by the University of Groningen (Hubben et al. 2007).

15.3 Modeling

Models are an important tool for the economic evaluation of infectious diseases. The intervention's influence on the force of infection and the indirect protection effects can only be simulated using models (Ferguson et al. 2003). Furthermore, modeling is also required to combine the data and results from different sources and to predict the impact of different intervention strategies. Models are also necessary to extrapolate from short-term results to the long-term and to determine the effectiveness in the real world. Often they are used to estimate the uncertainty of the results and sometimes to transfer the results to other settings (Welte 2007). Finally, it has also been shown that highly flexible models are needed to support decision makers when deciding about a new vaccination program (Welte et al. 2005b).

15.3.1 Common Models for Economic Evaluation

In economic evaluations, most often decision tree or Markov models are applied. If diseases include different disease states and movements between them, Markov models are suitable, otherwise decision trees can be applied.

In a decision tree, the strategies to be compared are represented by the primary branches rising from the initial decision node. Each strategy branch has a series of probability nodes that reflect uncertain events. Payoffs such as costs, utilities, life years, QALYs are entered at terminal nodes. The decision tree is averaged out and rolled back to derive the expected value for each strategy. The expected value equals the sum of products of the path probabilities multiplied by the payoffs. Figure 15.4 shows a simple decision tree: Against a specific disease a healthy individual can either be vaccinated or not. Without the vaccination, he has a risk of 20% of falling sick. Vaccination halves this risk to 10%. The probability of staying healthy equals 1 minus the probability of falling sick. The vaccination costs € 200 while the treatment of the disease costs € 10,000. The expected costs of the vaccination strategy are € 200 × 0.9 + € 10,200 × 0.1 = € 1200. Similarly, the expected costs of the no vaccination strategy are € 0 × 0.8 + € 10,000 × 0.2 = € 2000. Thus, the expected costs of the vaccination strategy are € 800 less than the one of the no vaccination strategy.

The Markov model is the model of choice for representing random processes that evolve over time and is suited for calculating long-term outcomes. It is especially useful for modeling chronic diseases such as Hepatitis B or HIV. It leads to a simplification of "bushy" decision trees. For creation of a Markov model, the disease states

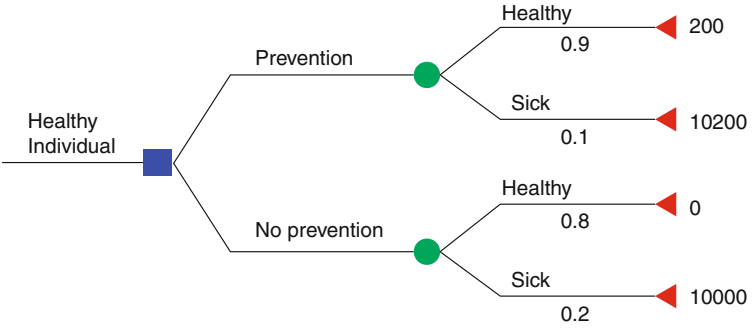

Fig. 15.4 Example of a decision tree

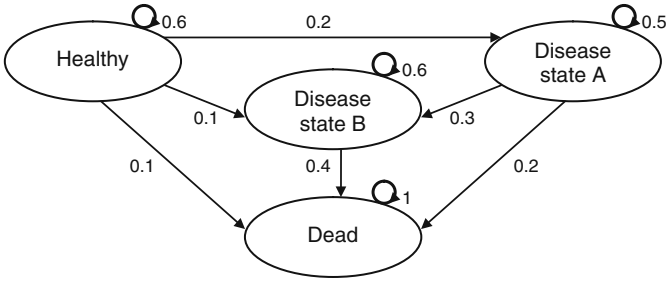

Fig. 15.5 Example of a Markov model

Table 15.3 Matrix of the transition probabilities per cycle

Health state	Healthy	Disease state A	Disease state B	Dead	Total
Healthy	0.6	0.2	0.1	0.1	1
Disease state A	0	0.5	0.3	0.2	1
Disease state B	0	0	0.6	0.4	1
Dead	0	0	0	1	1

are divided into distinct health states and absorbing states (e.g., death). Transition probabilities are assigned for movement between states over a discrete time period (=Markov cycle). Payoffs are attached to the states and transitions in the model and the model is run over a large number of cycles to obtain the long-term costs and effects. A simple Markov model is shown in Fig. 15.5, representing four health states – Healthy, Disease state A, Disease state B, and Dead. The arrows present the different possible pathways while the numbers show the assigned transition probabilities. For example, a healthy person can either stay healthy (probability = 0.6), move to Disease state A (0.2) or B (0.1), or can die (0.1). A person in Disease state A can either stay there or move on to Disease state B or die. A person in Disease state B can either stay there or die. The respective probabilities are also given in Table 15.3.

They are not depending on the states a patient might have experienced before entering this health state. Thus, a Markov model is without memory which has also been described as the Markovian assumption. However, by adding more health states or by using multidimensional transition probability matrices "memory" can be added (Briggs et al. 2007).

Decision trees and Markov models are the two basic models commonly used in the economic evaluation of all types of health-care technologies. Typically, they are analyzed as cohort models. However, there are also other models that can be applied, such as mathematical models using sets of differential equations or discrete-event simulation models. In fact, a whole taxonomy of model structures has been developed for health economic modeling which takes into account the level of aggregation by which the disease problem is analyzed (from individual to cohort level) and the degree of interaction that is being considered between individuals in a model (Brennan et al. 2006). In the case of infectious diseases, models are in addition differentiated by the way how they consider indirect protection effects.

Over the last years, the use of modeling in the economic evaluation of medical technologies has significantly benefited from discussion on a standardized, transparent documentation and motivation of the approaches used, the data used for model parameters, and the consistency checks to be conducted for improved model validity (Philips et al. 2006).

15.3.2 Approaches to Consider Indirect Protection Effects

For modeling health economics in infectious disease prevention, it is important to note whether indirect protection effects are included in the model or not. In particular, two types of models can be distinguished that differ with respect to considering the force of infection:

15.3.2.1 Static Models

Static models assume a constant force of infection. To include indirect protection effects, the increased effectiveness of the treatment is superimposed upon the core model. For example, if one knows from epidemiological studies that a herd immunity effect of 50% was observed in a specific age group then this percentage is directly put into the model. Thus, one can use this model nicely to simulate the cost-effectiveness of prevention programs in the past. However, they are less suitable for assessing the cost-effectiveness of current or future interventions due to the following reasons:

(a) They can only be used for an initial approximation of the expected herd immunity effects, e.g., based on observations for similar infections and types of vaccines.
(b) They are not able to simulate the potential absolute age shift caused by the indirect protection effects of mass infant vaccination programs.

(c) They are not an appropriate tool for CEAs of prevention measures that influence the force of infection but do not lead to a smaller number of susceptible individuals (i.e., successfully treated persons can be reinfected). In these cases, the transmission dynamics are far too complex to approximate them with a static model as has been demonstrated for chlamydial screening (Welte et al. 2005a). Whether net costs or net savings were simulated when including older women into the screening program depended, respectively, on whether only a portion (static model) or all indirect protection effects (dynamic model) were included into the analysis (Table 15.2). Hence, by taking into account the full indirect protection effect the authors identified a different optimal screening strategy, which rendered more savings and more health effects. Similarly, only by using a dynamic model the ICER of repeated chlamydial screening at various time intervals can be assessed (de Vries et al. 2008).

15.3.2.2 Dynamic Models

Dynamic models simulate the changes in the force of infection, i.e., they model the dynamic transmission of the infectious pathogen in the population. As a result, they are population and not cohort models. Often, a Markov model or decision tree is used for the progression of disease and is subsequently being coupled with a transmission model.

There are different types of dynamic models, based on their level of complexity included. They span from rather simple SIR or SIS models to highly sophisticated and complex individual-based models. The choice of model strongly depends on the type of disease, population, and intervention (Ferguson et al. 2003).

All dynamic models share one major challenge. Unlike static models they require detailed information about transmission routes and infectiveness, are more complex, and more difficult to understand. Thus, they take much more time and resources to build. Furthermore, because of the added information needs, there is more uncertainty surrounding the results. However, as stated above, for many situations they represent the only way to obtain meaningful results.

15.4 Supporting Decision Making

In the field of infectious diseases the cost-effectiveness of prevention measures has been investigated since several years. A special focus has been the evaluation of large-scale measures such as vaccination and screening programs due to their typical substantial budget impact. The cost-effectiveness of vaccination programs has even been systematically investigated in some countries such as the Netherlands (Van der Zeijst et al. 2000) and the USA (Institute of Medicine 2000). Currently, economic evaluations are done on a regular basis for new vaccines in several countries as they are requested by the national authorities to support decision making.

Economic evaluations can have a major impact on decision making in infectious disease prevention as has been demonstrated for meningococcal C conjugate

vaccination: A study investigated the role economic evaluation played in the decision process to introduce this vaccine into either the routine childhood vaccination schedule, as a mass vaccination "catch-up" campaign, or not at all for 21 developed countries. Economic evaluations for meningococcal C conjugate vaccination were identified for Australia, Canada (Quebec), The Netherlands, Portugal, Switzerland, and the UK. In all except the UK the economic evaluation had an important role in the decision-making process, especially with respect to the vaccination strategy (Welte et al. 2005b).

A further example is the assessment of the pneumococcal conjugate vaccine in the Netherlands: At the time of its initial cost-effectiveness analysis there was not enough evidence to simulate any indirect protection effects and hence they were not included. The results rendered an unfavorable CER which was one of the major reasons why it was not included in the routine vaccination schedule in 2002 (Bos et al. 2003). However, the vaccine showed surprisingly strong indirect protection effects in countries where the vaccine was included in the routine vaccination program, such as the USA. Based on these new findings, the CEA was repeated, this time including indirect protection effects. The results showed that the program would be cost-effective and this analysis supported the subsequent decision to introduce the vaccine in the Dutch routine childhood vaccination program in 2006 (Hubben et al. 2007).

Which cost-effectiveness threshold should be applied, e.g., until which CER should a technology be considered cost-effective? This is one of the questions regularly raised by decision makers (Welte et al. 2005b). Table 15.4 gives an overview of different values often used or cited.

Most thresholds lack a theoretical foundation. The most frequently used threshold by health economists seems to be US $ 50.000 per QALY or LYG, which has been often applied after 1996 (Grosse 2008). The WHO advice is unique by recommending thresholds that are depending on the economic power of countries. The gross domestic product (GDP) per capita is suggested as reference point. For the Netherlands and the UK, there are different thresholds published.

It should be noted that cost-effectiveness is never the only reason for implementing a new technology or not. For instance, the medical need, public anxiety, the availability of other treatment options, the budget impact, and budget constraints are all typical factors that are also often taken into consideration.

15.5 Conclusions

The economic evaluation of prevention measures against infectious diseases is typically more complex and difficult than for other technologies. Especially the simulation of disease transmission represents a major challenge for each new pathogen. Neglecting the externalities and hence the indirect protection effects of prevention measures can lead to wrong results and conclusions. The additional parameters needed for the disease transmission also contribute an additional complexity in the sensitivity analysis. Furthermore, as prevention programs typically require initial investments but will render health effects and resource savings in the future, the

Table 15.4 International thresholds for cost-effectiveness

Organization/group	Cost-effectiveness thresholds	Reference
Australia*	Costs per LYG < AU $ 42,000 – 76,000 (costs per LYG < AU $ 42,000: reimbursement likely, costs per LYG > AU $ 76,000 reimbursement unlikely)	George et al. (2001)
The Netherlands	Costs < € 20.000 per QALY or LYG: cost-effective* Costs < € 80.000 per QALY: cost-effective**	Welte et al. (2004c); Raad voor de Volksgezondheid & Zorg (2007)
UK National Institute of Clinical Evidence (NICE)*	Costs per QALY < £ 20,000–30,000: cost-effective Costs per QALY < £ 45,000: cost-effective	Devlin and Parkin (2004); Appleby and Devlin, Parkin (2007)
US Institute of Medicine (IOM)**	Saves money and QALYs: most favorable Costs per QALY < US $ 10,000: more favorable Costs per QALY > US $ 10,000 and < 100.000: favorable Costs per QALY > US $ 100,000: less favorable	Institute of Medicine (2000)
World Health Organization (WHO)**	Costs per DALY < GDP per capita: highly cost-effective Costs per DALY = 1x – 3x GDP per capita: cost-effective Costs per DALY > 3x GDP per capita: not cost-effective	WHO (2008)
International and especially US decision analysts**	Costs per QALY or LYG < US $ 50.000: cost-effective	Grosse (2008)
US and British health economists**	Costs per LYG < US $ 60.000: cost-effective	Newhouse (1998)

* Thresholds derived from past decisions
** Officially stated thresholds
LYG = Life year gained
QALY = Quality-adjusted life year
GDP = Gross domestic product

choice of the discount rate for costs and effects as well as the time horizon are of high importance. Finally, the approach for measuring the productivity costs has often a strong impact on the results.

15.6 Looking to the Future

Due to the better understanding of disease transmissions and the availability of epidemiological models and sophisticated software, dynamic models are likely to become the standard in the economic evaluation of infectious diseases. The QoL

measurement in children will progress further and so will the transferability of models. Finally, more countries are likely to use the tool "economic evaluation" for supporting decision making. Improved standardization and transparency in the modeling approaches may support the future assessment and appraisal of the economic evidence on intervention into infectious disease. In result, the effectiveness and cost-effectiveness of health care in this field may be further promoted.

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