Economic Evaluation of Vaccination Programmes:

A Special Reference to Varicella Vaccination

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Declaration

This thesis is the result of original research conducted by myself unless stated otherwise in the text. The research was conducted under the supervision of Dr. John Edmunds and Professor Alistair McGuire at City University. All sources of information and individuals who provided data sets have been fully acknowledged. No part of this thesis has been submitted for a degree at any other university. The articles that have been published and which are based on work from this thesis are cited at the end of each chapter.

Abstract

The thesis has two broad aims. The first aim is to evaluate the effectiveness and "cost-effectiveness" of routine childhood varicella vaccination in the UK. To do so, a deterministic realistic age-structured model was built which incorporated herd-immunity effects and the indirect impact of varicella vaccination on zoster. The model predicts that although the overall morbidity due to varicella is likely to decrease following infant vaccination, these benefits will be offset by a significantly increase in zoster cases. These modelling results were used to explore the possible economic desirability of mass varicella vaccination. To do so, we perform the three major types of economic evaluation. The economic analysis predicts that using cost-utility and cost-effectiveness analysis, routine infant varicella vaccination is unlikely to be ''cost-effective'' and may produce an overall increase in morbidity. On the other hand, varicella is highly cost-beneficial when using £ as the outcome measure. Finally, we show that results are less sensitive to parameter estimates than model and methodological assumptions

The second aim of the thesis is to address the major methodological issues related to the economic evaluation of vaccination programs using varicella vaccination as an example. Firstly, we compare results from a dynamic model with those of a static model to illustrate the impact of including herd-immunity and to help provide guidance on which model should be used when assessing the impact of vaccination. Secondly, we assess the average willingness to pay for varicella vaccination and the QALY lost due to chickenpox using various elicitation techniques. We then identify important attributes of vaccination and what elicitation techniques can capture these components. Results are compared to investigate what valuation techniques should be used in the economic evaluation of vaccine programmes. Thirdly, we assess the sensitivity of economic analysis to the choice of model, methodological assumptions and parameter estimates. Finally, we propose guidelines for the economic evaluation of vaccination programmes based on the various findings of the thesis.

Introduction

Few health programmes have been as successful as immunisation both in terms of public health impact and cost-effectiveness. Policy decisions about the implementation of early vaccines such as polio, pertussis and measles were relatively easily made due to the high mortality and morbidity attached to these diseases. However, policy decisions about the use of new vaccines, such as varicella, are more difficult due to the lower public health impact of these vaccines and capped health budgets. Economic evaluation is useful under such conditions. It provides an analytical framework in which to assess the desirability of vaccination compared with other uses of the same scarce resources.

To ensure the quality/comparability of methods/results, it has been suggested that specific guidelines are needed for the economic evaluation of vaccination programmes (Edmunds *et al.*, 1999; Beutels *et al.*, 2002). The main reasoning behind this stems from the unique characteristic of vaccination against infectious disease:

> *Mass vaccination not only reduces the incidence of disease in those immunised, but also indirectly protects non-vaccinated susceptibles against infection.*

The concept of indirect protection of susceptibles (e.g. non vaccinees), termed herd-immunity, is the textbook example of externality in the consumption of healthcare. Predicting herd-immunity effects requires the use of dynamic mathematical models, which are rarely used as part of economic evaluation of vaccination and there are no guidelines as to how and when they should be applied.

The thesis has two objectives. The first aim is to evaluate the effectiveness and "cost-effectiveness" of routine childhood varicella vaccination in the UK. The second aim is to address the major methodological issues related to the economic evaluation of immunisation programmes, using varicella vaccination in the United-Kingdom as an example.

Chapter 1 gives brief background information necessary to understand the rationale behind the thesis. Further background is given at the beginning of subsequent chapters. Chapter 2 examines the epidemiology and natural history of varicella zoster virus.

In Chapter 3, we use a dynamic mathematical model to estimate the overall effectiveness of varicella vaccination taking into account herd-immunity externalities. In doing so, we examine the different dynamical effects of vaccination and present which parameters are most influential on model results. Finally, we illustrate how herd-immunity externalities influence the benefit of vaccination.

In Chapter 4, we estimate the value of varicella vaccination programmes from both the individual and population perspectives. We estimate the average willingness to pay for varicella vaccination and the QALY lost due to chickenpox (individual perspective). We then attempt to identify what attributes of vaccination are important to vaccinees and what elicitation technique can capture these components. Finally, we explore different methods of aggregating individual revealed preferences to the population level taking into account herd-immunity as well as the non-health attributes of vaccination.

In Chapter 5, we estimate the cost-effectiveness, cost-utility and cost-benefit of varicella vaccination and investigate using univariate and multivariate sensitivity analysis, the impact of model and methodological assumptions on results of economic evaluation. This, to better understand how the results of economic evaluation of vaccination programs are influenced by the methods used.

Finally, Chapter 6 is divided into three sections. First, we summarise the main findings of the thesis. Secondly, we present guidelines for the evaluation of immunisation programmes. Finally, we discuss future work.

Chapter 1
Background and Rationale

1.0 GENERAL INTRODUCTION

The aims of the thesis are two-fold. 1) to assess the public health and health economic impact of introducing routine varicella vaccination in the United-Kingdom, 2) to investigate the methodological challenges related to the unique characteristics of vaccination in the context of economic evaluation. In this first chapter we give brief background information necessary to understand the rationale behind the second aim of this thesis. Further, detailed, background is given at the beginning of each chapter.

1.1 EPIDEMIOLOGY OF INFECTIOUS DISEASE

The focus of this thesis is to address the challenges related to the economic evaluation of vaccination programmes. These challenges stem from the unique characteristics of infectious disease: transmission and herd-immunity. In this first section we describe the basic principals of infectious disease epidemiology and how these concepts can be applied using models to predict and understand the impact of control programmes on infectious diseases.

This section is largely based on publications by Beutels (2002), Anderson and May (1991), Halloran (1998) and Begg and Gay (1996). Unless stated otherwise, the material presented in this section can be found in these sources.

1.1.1 INFECTION AND NATURAL HISTORY OF DISEASE

There are many stages of infection and disease (see Figure 1.1). Both infection and disease begins with exposure/infection of the susceptible individual. Not all exposure results in infection and not all infection results in symptomatic disease. The first stage of infection is the *latent period*, which can be defined as the time from infection to infectiousness (when the individual is infectious to others). The next stage is the *period of infectiousness*. The final stage is the one where the host becomes non-infectious. Non-infectious individuals can be dead, immune, return to be susceptible or return to the latent class.

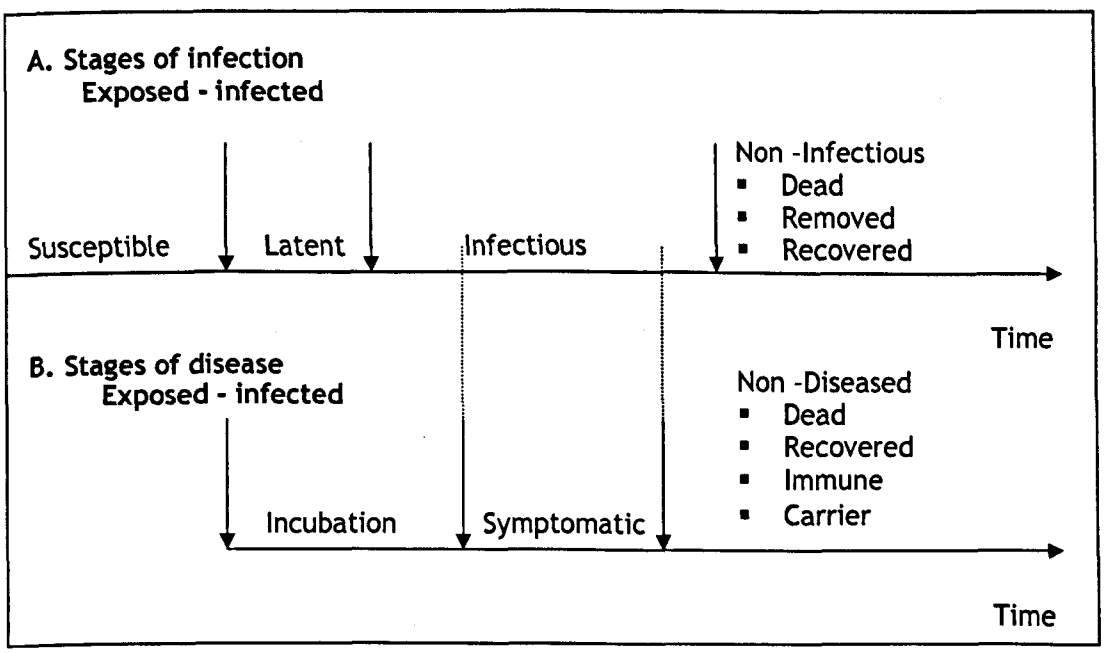


Figure 1.1. Time Line for a) infection and b) disease (adapted from Halloran (1998)).

The different stages of disease also commence at the time of infection. During the *latent* and beginning of the *period of infectiousness* the host typically does not have symptoms. This first stage of disease, between exposure and symptomatic disease, is called *incubation period.* The second stage of disease is the *symptomatic period.* The host can leave the symptomatic stage through death, by recovering from symptoms, becoming immune or a carrier. It should be noted that not all infection results in symptoms or disease.

It is important to note that, although it is the effectiveness at reducing the burden of disease which is used to substantiate intervention, it is the characteristics of infection that determine the pattern of infectious disease before and after intervention as well as the approach that should be used. Hence,

> *it is the natural history of infection that is modelled when studying the effectiveness of intervention programmes against infectious disease.*

The key parameters of transmission are duration of the latent infection and infectious periods, the probability of exposure and transmission and whether or not individuals develop immunity following infection. The Basic Reproduction number R_0, which we describe in the next section, encompasses the impact of many of the above parameters. It is also a key parameter to understand the basic concepts of infectious disease theory.

1.1.2 BASIC AND EFFECTIVE REPRODUCTION NUMBER

Basic reproduction number. The basic reproduction number, R_0 (reproductive rate is also used in the literature), is defined as the number of secondary infections that would be produced in a completely susceptible large population by

a typical infectious individual (Anderson and May, 1991). R_0 can be formally written as (adapted from Anderson and May, 1991):

$$R_0 = cpd \qquad (1)$$

where, c is the average number of new contacts (exposure with infection) made by an individual per unit of time; p is the probability of transmission per contact and; d is the duration of infectiousness. Hence, R_0 is composed of both infectious disease (p, d) and socio-demographic (c) characteristics and therefore its value not only varies between infectious agents, but also between different populations (e.g. rural vs. urban). This is important as the effectiveness of an intervention may vary from one population to another or within a population.

Effective reproduction number. R_0 assumes that all individuals in the population are susceptible which is, most often, clearly not the case. In most situations (the recent SARS outbreak being a notable exception) not all individuals are susceptible to infection, as some are immune through previous infection or vaccination. In such populations the expected number of new cases produced by an infectious individual is less than R_0, since contact with an immune individual does not result in infection. The effective reproduction number, R(t), is defined as the number of secondary cases an infectious individual causes on average in a population at time t (adapted from Anderson and May, 1991). R(t) can formally be written as:

$$R(t) = R_0 S(t) \qquad (2)$$

where, S(t) is the time-dependent proportion of contacts (population) that are susceptible to infection. It should be stated that this formal representation of R(t) represents a simplified case where the population mixes homogeneously without immigration or emigration.

R(t), the state of infection in a population and impact of vaccination. R_0 and R(t) provide us with a simplified conceptual framework to understand the important issues of infection in a population as well as the effects of intervention against infectious disease. The value of R(t) indicates whether the number of new infections are increasing (R(t)>1), at equilibrium (R(t)=1) or decreasing (R(t)<1) in a population. For an infection to establish itself in a population R_0 must be greater than 1. If the infection becomes endemic and is at equilibrium (average incidence does not change) then R(t)=1 (each infectious case produces on average one new infection). Given equations (1) and (2) the proportion of susceptibles (S(t)) at equilibrium will be:

$$R = R_0 S(t) = 1$$

$$S(t) = 1/R_0 \qquad (3)$$

R(t) must be lower than 1 for transmission to be reduced in the population (R(t)<1). Since, R_0 does not change within a population unless its characteristics or the infection changes, it is by reducing the fraction (S(t)) of susceptibles that R(t) can be kept lower than 1. If the proportion of the population that is susceptible (S(t)) is maintained (by preventing new susceptible of entering) so that R(t) remains lower than 1, the number of new cases in each successive generation of cases will be insufficient to sustain infection in the population and would eventually lead to elimination.

The necessary fraction of susceptibles for elimination can be maintained by vaccinating a proportion of the birth cohort. The necessary coverage (proportion immunised), *p*, can formally be written as:

$$R = R_0 x = R_0(1-p) \leq 1$$

$$p \geq 1-1/R_0 \qquad (4)$$

This means that a higher R_0 requires higher vaccine coverage for elimination. A higher R_0 can correspond to a mix of higher contacts (exposure), transmission probability per exposure or increased duration of infectiousness.

It should be noted that if infection is controlled but not eliminated by vaccination (coverage and therefore threshold of susceptible is not attained), in the long run the infection will reach a new lower equilibrium of infection ($R^*=1$).

1.1.3 HERD-IMMUNITY

As seen in the previous section, it is possible to eliminate an infectious disease in a population without vaccinating everyone. This is the classic example of the indirect effect produced by herd-immunity. There are many definitions for Herd-immunity. In this thesis we use the definition proposed by Fox *et al.* (1971), which is as follows:

> *''Herd-immunity is the resistance of a group to the attack by a disease to which a large proportion of the members are immune, thus lessening the likelihood of a patient with a disease coming into contact with a susceptible individual.''*

We use this definition as it includes both total and partial protection. Total protection produced by herd-immunity, also known as the threshold concept of herd-immunity, is when a typical primary infection produces less than one secondary case (i.e. $R(t)<1$). That is, when the number of susceptibles in the population is below the epidemic threshold. Partial protection is when the presence of immune individuals lessens the risk of infection in susceptibles. In Chapter 3 we illustrate and describe in detail the effects of herd-immunity on the dynamics of infection using routine varicella vaccination as an example.

1.1.4 FORCE OF INFECTION

The force of infection is defined as the instantaneous incidence rate of infection amongst susceptibles. Formally, in a homogeneously mixed population it can be defined as:

$$\lambda(t) = pcI(t)$$

where c is the average number of new contacts made by an individual per unit of time, p is the probability of transmission per contact and I(t) is the number of individuals at time t that are infected. The force of infection at any time depends on the number of infectious individuals in the population at that time. Vaccination can significantly reduce the number of infective individuals in a population reducing the force of infection and therefore the risk of new infection amongst susceptibles. As described in the previous section, this mechanism can be defined as Herd-immunity (partial protection).

Please refer to Grenfell and Anderson (1985) and Farrington *et al.* (1990) for more details on the different methods that can be used to measure the force of infection. In Chapter 2, we formally present the method developed by Farrington *et al.* (1990) using varicella as an example.

1.1.5 IMPACT OF VACCINATION

The overall impact of vaccination is dependent on the type of strategy that is adopted to control the infectious disease. There are three main strategies: 1) Routine Targeted Vaccination, 2) Routine Mass Vaccination, 3) Vaccination Campaigns (or Catch-up). These programmes are designed to achieve one or all of the three main goals of vaccination: 1) reduction of morbidity (through control of infection), 2) elimination and 3) eradication (Allwright, 1988). Herd-immunity can

play an important factor in reaching these goals. However, its impact depends on the vaccination strategy.

Routine Targeted Vaccination. The goal of routine targeted (or selective) vaccination is to reduce infection/transmission and/or morbidity in a specific sub-group of a population that is either more at risk of infection, transmission or disease. Vaccination can be targeted at core transmitters of the virus (core groups). Such a policy has an aim of substantially reducing overall morbidity in the population by immunising a limited sub-group of the population. In these cases herd-immunity is the basis of the vaccination strategy. An example of this is vaccination of highly sexually active individuals (e.g. prostitutes) to reduce sexually transmitted disease in the overall population.

Vaccination can also be targeted at sub-groups, which are at greater risk of infection or disease but are not core transmitters. Example of this can be targeted vaccination of health care workers, travellers or the elderly against influenza, pneumococcal disease or zoster. Vaccination in such instances does not have a significant impact on transmission in the population (does not significantly reduce the force of infection) and therefore herd-immunity is not a factor of influence. In Chapter 3, we investigate the impact of targeted vaccination of susceptible pre-adolescents against varicella and illustrate how herd-immunity has little impact on overall reduction of infection and disease.

Routine Mass Vaccination. Routine Mass (Universal) vaccination has historically been the most common vaccination strategy (although this is changing due to scarcity of resources and the smaller impact of new vaccines). Universal vaccination consists of vaccinating most individuals in a population when they

reach a target age. The age at vaccination is chosen to minimise the time individuals in a population are susceptible. Usually, such a strategy is given to very young children. However, with vaccines that are being developed to prevent sexually transmitted infection/disease (i.e. Human Papillomavirus and HIV) routine mass vaccination could be targeted at adolescents before the start of sexual activity. Routine mass vaccination usually requires the maintenance of an infrastructure to ensure high coverage to increase the effectiveness of the programme and to limit the chances of adverse effects.

There are three levels of control that can result from routine mass vaccination. The most common is control of infection (infection remains endemic but at a lower level than before vaccination). If vaccine coverage is sufficient and it protects against infection it will affect the transmission and thus produce herd-immunity effects (externalities). The main herd-immunity externalities are: 1) reduction of infection in susceptibles (e.g. non vaccinees), and 2) shift in the age at infection and possible increase in overall morbidity (usually from children to adults). In Chapter 3, we describe in detail and illustrate these herd-immunity effects using varicella vaccination as an example.

The second level of control through universal vaccination is elimination. Elimination of an infectious disease occurs when there is no longer endemic transmission within a population (De Serres *et al.*, 2000). Only when cases are imported do isolated outbreaks occur. As described in section 1.1.2, this occurs when the herd-immunity threshold is surpassed. An example of this is measles in developed countries such as Canada and the USA (De Serres *et al.*, 2000).

Finally, the highest level of control from routine vaccination is eradication. This occurs when the virus, bacteria or other pathogen that causes infection is eradicated from the planet. Eradication can also allow cessation of routine immunisation and thus can produce infinite savings and benefits (although in practice discounting negates this effect). Smallpox is the only disease that has been eradicated. However, a programme is underway to eradicate poliomyelitis.

Vaccination Campaigns (Catch-up). Vaccination campaigns consist of vaccinating a target age range within a short period of time. It is usually used in addition to routine mass vaccination to accelerate the effectiveness of such programmes. We show, in Chapter 3, the effect of Catch-up campaigns using varicella vaccination as an example.

In the thesis, we have chosen to investigate the public health and health economic impact of introducing routine targeted and mass varicella vaccination in the United-Kingdom (with or without catch-up), rather than targeted vaccination of at risk populations such as healthcare workers. This is due to three main reasons. First, previous evidence has shown that a vaccination strategy for healthcare workers has the potential to be a cost-effective use of health care resources (Gray et al., 1997; Nettleman & Schmid, 1997). Secondly, the main policy question regarding varicella vaccine in Australia, Canada, the United Kingdom, and many countries in Europe currently is whether mass vaccination is desirable (Canada, 1999; England and Wales, 2002). Although the United-States introduced routine varicella vaccination in 1994 (Committee on Infectious Diseases, 1995), some important concerns have prevented the introduction and implementation of routine vaccination in many developed countries such as Australia, the United-Kingdom and most countries in Europe. Finally, the second main aim of the thesis

is to investigate the methodological challenges related to the unique characteristics of vaccination (e.g. herd-immunity externalities) which are mainly present in the evaluation of mass vaccination.

1.2 MODELLING THE EFFECTIVENESS OF VACCINATION PROGRAMMES

There are many types of epidemiological models that are used to assess the impact of vaccination. The choice of an adequate model should depend on the type of population, infectious disease and vaccination programme being evaluated. There are two main classes of model that are used in the evaluation of vaccination programmes: 1) static and 2) dynamic models. Both classes can model the natural history of infection (Figure 1.1). The main difference between these two models is the way in which the force of infection (per-susceptible rate of infection) is calculated. Using the dynamic approach the force of infection is dependant on the number of infectious individuals in the population (Edmunds *et al.*, 1999; Anderson and May, 1991; Nokes and Anderson, 1988), whereas static models treat this rate as a fixed parameter (Edmunds *et al.*, 1999). Since mass vaccination results in fewer infectious individuals in the population, under the dynamic framework the force of infection will decline over time producing herd-immunity externalities. On the other hand, under the static framework the force of infection remains unaltered and therefore herd-immunity is not included. Presently, the majority of economic analysis of vaccination programmes use static models. Although these models do not take into account the effects produced by herd-immunity, authors occasionally claim to be taking account this externality.

An in-depth description of the different types of infectious disease transmission models is beyond the scope of this thesis. For a comprehensive textbook on the

subject please refer to Anderson and May (1991) or Bailey (1975). For more information on the difference between static and dynamic models please refer to Edmunds et al. (1999). In Chapter 3, we quantify and illustrate the difference between static and dynamic deterministic models, using varicella vaccination as an example.

1.3 MEASURING THE BENEFIT OF VACCINATION

1.3.1 FRAMEWORK FOR JUDGING VALUATION TECHNIQUES

In health economics, there are, at least, two competing views of what should be measured when estimating the benefit of health interventions: 1) Welfarism and 2) Extra-Welfarism (Tsuchiya and Williams, 2001; Brouwer and Koopmanschap, 2000). Welfarists believe that the output of health intervention should be judged according to the extent to which it contributes to overall welfare, as determined by individual preferences over health relative to arguments in the utility function (Dolan 2001) and that monetary valuation of benefits should be used. Extra-Welfarists believe that other types of measure can be used, and would be more pertinent, than individual preferences in the context of resource allocation (Culyer, 1990; Wagstaff, 1991; Brouwer and Koopmanschap, 2000) and that the benefits of health interventions should be based on quantifiable and comparable health outcome measures such as Life-years and QALYs gained (McGuire, 2001). The aim of this thesis is not to examine which theoretical foundation is most justified. Rather, we examine from an empirical perspective, what are the advantages and disadvantages of the different valuation methods in the context of vaccination.

Vaccination is different from most health interventions found in the literature because it:

1) *is a preventative intervention (in contrast to curative or palliative),*
2) *protects against infectious disease,*
3) *often prevents diseases that are short-lived and/or self-limiting (and can be mild),*
4) *is usually given to young children from whom it is very difficult to elicit health/program preferences.*

Because of this unique combination of characteristics, vaccination may possess its own valuation problems. Brazier and Deverill (1999) proposed a checklist for judging the merits of measures of interventions, which include: 1) Practicality, 2) Reliability, 3) Validity (description, valuation and empirical) (see Table 1.1a). In this thesis we modify this and concentrate on Practicality, Validity (Content and Empirical) and Sensitivity (Responsiveness) in the context of vaccination (See Table 1.1b for the checklist for judging valuation techniques). Below we define these different components in the context of vaccination.

Practicality

An instrument must be acceptable to the responder and to those representing him/her, such as ethics committees (Brazier and Deverill, 1999). Measures of *practicality* can be duration of questionnaire, response rate and completion rate (refusal rates) and ethical refusal.

Validity

Validity is defined as the degree to which a valuation technique (test) is measuring what it is supposed to measure (*Empirical validity*) (Streiner and Norman, 1989). Furthermore, it is concerned with the relationship of the measure and the purpose to which it is being used (*Content validity*) (Streiner and Norman, 1989). That is, whether what is valued is relevant to the purpose of the study.

Content validity. *Content validity* consists of determining (through value judgement) whether the instrument (technique) used takes into account all relevant/important domains or attributes (Streiner and Norman, 1989; Brazier and Deverill, 1999). Although this validity exercise is dependent on value judgements, it is important that the user of the instrument (as well as decision-makers) consider whether the assumptions and attributes being measured are appropriate for the intervention being evaluated.

Table 1.1a. Checklist for judging the merits of preference-based measures of health (Brazier and Deverill, 1999).

	Components
Practicality	▪ How long does the instrument take? ▪ What is the response rate? ▪ What is the completion rate
Reliability	▪ What is the test-retest reliability? ▪ What are the implications for sample size? ▪ What is the inter-rater reliability? ▪ What is the reliability between places of administration?
Validity	

Description	▪ Content Validity:
	  ▪ Does the instrument cover all dimensions of health of interest?
	  ▪ Do the items seem sensitive enough?
	▪ Face Validity:
	  ▪ Are the items relevant and appropriate for the population?
	▪ Construct Validity:
	  ▪ Can the unscored classification of the instrument detect known or expected differences or changes in health?

Valuation	▪ Do the assumptions about preferences seem credible?
	  ▪ What is the model of preferences being assumed?
	  ▪ What are the main assumptions of this model?
	  ▪ How well are the patient/general population/decision-makers likely to conform to these assumptions?
	▪ Was the technique of valuation choice-based?
	▪ Quality of data
	  ▪ What were the background characteristics of the respondents to the valuation survey?
	  ▪ What was the degree of variation in the valuation survey?
	  ▪ Did respondents' understand the valuation task?
	  ▪ What was the method of estimation (where relevant)?
	▪ Whose values have been used?

Empirical	▪ Is there any evidence for the empirical validity of the instrument against:
	  ▪ Revealed preferences?
	  ▪ Stated preferences?
	  ▪ Hypothesised preferences?

Table 1.1b. Framework for judging measures of the benefit of vaccination.

	Components
Practicality	▪ How long does the instrument take? ▪ What is the response rate? ▪ What is the completion rate?
Validity	
Content Validity	▪ Does the instrument cover or capture all relevant/important domains or attributes? ▪ Direct Health effect? ▪ Current use Non Health effects? 1. Caring (Altruistic externality) among vaccinees. 2. Security (Insurance type benefit) ▪ Non-Current use Attribute 1. Altruism among individual who is not at risk of disease 2. Option Value 3. Uncertainty of the outcome of intervention 4. Herd-Immunity Externality (Selfish externality)
Empirical Validity	▪ Criterion Validity: ▪ How do results compare to the "Gold Standard" or observed preferences? ▪ Convergent Validity: ▪ What is the correlation of the instrument with others within similar populations? ▪ Construct Validity: ▪ Are results consistent with expected theory? ▪ Technical quality of the study ▪ Is the sample size adequate? ▪ Is the method of administration of the questionnaire appropriate (e.g. ? ▪ Whose values are elicited?
Sensitivity	▪ Is the instrument sensitive to small changes in well fare?

It has been demonstrated that health is not the only source of well-being that can be derived from public health interventions (Mooney, 1994; Birch *et al.*, 1999; Olsen and Smith, 2001)). Individuals may find benefit in the characteristics of an intervention which do not affect the health outcome (Mooney, 1994). We classify intervention attributes according to three mutually exclusive categories: 1) Heath related attributes, 2) "Current use" non-health attributes and 3) "Non current use" attributes (Olsen and Smith, 2001).

1) Direct effect on health; The principal benefit that can be derived from vaccination is that it prevents the vaccinee from acquiring disease and thus losing health related quality of life. Health related quality of life being defined as a state of physical, mental and social well-being and not merely absence or presence of disease (World Health Organisation, 1947). Hence, an individual's health state should comprise not only of main quantitative health outcomes such as physical function, social function and mortality but also qualitative outcomes such as, health perception and psychological function. Other direct effects on health from vaccination could also be the side-effects related to the vaccine itself.

2) "Current use" non-health attributes: As mentioned above, individuals may find that an intervention can yield benefits beyond improvement in health (Mooney, 1994). In the literature the most commonly measured non-health attribute is "process utility" (Berwick and Weinstein, 1985; Donaldson et al., 1995; Donaldson and Shackley, 1997; Donaldson et al., 1997; Ryan, 1996) in which patients gain utility from the process by which the intervention is provided (e.g. content or delivery of a programme)(Mooney, 1994). There are two potential non-health

attributes specific to vaccinees: 1) Caring externality (Altruism) and 2) Security (Insurance type benefits).

Caring externality (Altruism): Externalities can be classified into two broad categories: selfish and altruistic (Labelle & Hurley, 1992; Johannesson, 1996). Altruism occurs when individual A cares about individual B's consumption of health care and/or health status and this enters A's utility function. Selfish externalities exist when individual A cares about individual B's consumption of health services because B's consumption of health services affects A's (expected) health status. Vaccinees may derive benefit from the knowledge that by being vaccinated they will not infect others. Such a benefit can be called caring (paternalistic or altruistic Altruism). It should be noted that this externality should be considered different to the herd-immunity externality, which can be considered a selfish externality among non-users (i.e. individuals find benefit in that others are vaccinated because it indirectly protects them against disease (see below for more details)). For non-infectious disease, caring externalities (Altruism) are usually "non-current use" attributes, which are derived from individuals (not at risk) finding benefit from the knowledge that others in the population have access to an effective intervention (O'Brien et al., 1998; Neumann and Johannesson, 1994)).

Security (Insurance type benefits). Immunisation is a preventative intervention against the uncertain future event of catching disease. Thus, being vaccinated can be viewed as taking insurance against disease. Because individuals are generally risk averse in relation to health, they may find an added benefit in the knowledge that they are protected against disease (i.e. a potential for improving welfare by reducing or eliminating uncertainty). This type of attribute is similar to the "Non

current use" attribute referred to as Option value, where individuals find value in the presence of a programme because they may need it in the future (O'Brien and Gafni, 1996; Birch et al., 1999).

3) "Non-current" use attributes: The types of Non current use attributes most addressed in the health economic literature are: 1) caring externality, in which individuals find benefit in vaccination although they are not at risk of the disease, 2) Option value and 3) Uncertainty of the outcome of intervention (Olsen *et al.*, 2001; O'Brien and Gafni, 1996; O'Brien *et al.*, 1998; Birch *et al.*, 1999). Apart from these, vaccination also produces Herd-Immunity Externalities (Selfish Externality).

Herd-Immunity Externalities (Selfish Externality): As described above, the herd-immunity externality (Weisbrod, 1961), comes from the benefits of being partially protected to infectious disease because a proportion of the population is vaccinated. However, as will be shown in Chapter 3, herd-immunity can produce both positive and negative effects (e.g. protects non-vaccinated susceptibles against infection but can increase overall morbidity and mortality by shifting the age at infection).

In Chapter 4, we examine whether some of the attributes of vaccination mentioned above exist, are measurable and, if so, assess their relative importance compared to direct health effects. We now concentrate on *Empirical Validity*.

Empirical Validity. Empirical validation of valuation techniques in health care are very difficult due to the hypothetical nature of many of the questions (Drummond, 1997). Ideally, results should be compared to a "gold-standard" or

criterion (*criterion validity*). Furthermore, if the aim is to measure individuals' preferences then the goal is to verify if the values elicited reflect practice. Because of the difficulty measuring *criterion validity* (due to the lack of a "gold standard"), other validation tests have been suggested. First, if other valuation instruments exist, *convergent validity* can be used, which consists of measuring the correlation of the instrument with others within a same sample population. The second approach is to measure *construct validity*. This consists of examining whether the instrument produces results that are consistent with expected theory (i.e. the value of preventing a disease increases with its severity).

Many economic instruments for measuring the benefit of intervention will use data elicited from valuation studies. These studies vary in terms of their respondents, the size of the sample, response completion, and the method of administering the questionnaires (e.g. interview or self-administered questionnaire, paper vs. electronic questionnaire, and use of props), which have important implications on the *internal* and *external validity* of results. Hence, an important component of validity is what is termed *technical quality of the study*.

The validity of an instrument is also dependant on whose values are elicited (Brazier and Deverill, 1999). Valuations can vary by disease experience, state of health, age, education and sex. Whose values should be used? Should it be those who are at risk or affected by the disease or the general public? De Wit *et al.* (2000) consider this question in detail. Our aim here will not be to argue which value should be used but to show the divergence/convergence of responses according to responders' characteristics. As described above, an added problem with vaccination is that it is usually given to young children from whom it is very difficult to elicit health/program preferences due to measurability (too young to

answer questionnaires) and comparability issues (ability to comprehend questions evolves over time for children) (Petrou S, 2003). The use of proxies is thus needed, which adds an additional level of complexity. See Petrou (2003) and Eiser and Morse (2001) for more information on the methodological challenges of measuring the health status of children using preference based approaches.

Sensitivity to change (Responsiveness)

The goal of a valuation technique, in economic evaluation, is to measure changes in well-being (or change in welfare) following intervention. Hence, valuation techniques must be sensitive to change. This is of particular importance with vaccination, as many of the diseases it prevents are short-lived, self-limiting and/or mild.

1.3.2 INTERVENTION OUTCOMES AND VALUATION TECHNIQUES

There are three predominant types of economic analysis (Drummond *et al.*, 1997):

- ***Cost-Benefit***: Analysis in which both costs and consequences (benefits) of alternatives are measured in dollars.
- ***Cost-Effectiveness***: Analysis in which costs are compared to a single, common effect which may differ in magnitude between the alternative programmes (e.g. Cost per life-year gained, Cost per case averted).
- ***Cost-Utility***: Analysis in which utilities are employed to measure the value of an intervention (e.g. Cost per Quality-Adjusted Life-Year).

The feature that distinguishes among techniques of economic evaluation is the way in which the benefit of health care programmes are valued.

In the following section we describe the different valuation instruments/techniques and outcomes that can be used to measure the benefit of interventions, focussing on the potential advantages and disadvantages of their use in the valuation of vaccination programmes (using the checklist proposed in Table 1.1b).

1.3.2.1 Monetary Values

The main advantage of using monetary values is that it values benefits in the same unit as the costs and therefore allows direct comparison (Olsen and Smith., 2001, Birch *et al.*, 1999, Bala *et al.*, 1998; O'Brien and Viramontes, 1994; O'Brien and Gafni, 1996; Klose, 1999). Furthermore, it allows intersectoral comparisons (e.g. transport and environment) of resource use (O'Brien and Gafni, 1996). On the other hand, the main disadvantage is the widespread reluctance of policymakers in the healthcare sector to evaluate health changes in monetary terms (Drummond *et al.*, 1997; Johannesson, 1996; Brouwer and Koopmanschap, 2000).

Here, we define and discuss the properties of the three general approaches to the monetary valuation of the benefit health interventions: 1) Human Capital, 2) Revealed preferences, 3) Stated preferences (Contingent valuation) (Drummond *et al.*, 1997). See Table 1.2 for details.

Human Capital Approach. The Human Capital approach consists of measuring monetary weights on healthy time using market wage rates and the value of the programme is assessed in terms of the Present Value of future earnings (Drummond et al., 1997). Monetary valuation of the benefit of health interventions started with this approach which was popularised in the early 1960s by Becker (1964). One of the more cited examples of Human Capital was for the

evaluation of Rubella vaccination (Schoenbaum *et al.*, 1976). The Human Capital approach was widely criticised in the 1970s by economists who argued that the approach was not rooted in welfare economics or the economic concept of opportunity cost (Shelling, 1968; Mishan, 1971). This combined with its many other disadvantages (Table 1.2) lead empirical work on monetary valuation of health intervention in two main directions: 1) Revealed preference and 2) Contingent valuation (Stated preference).

Revealed preference. The Revealed preference approach measures individual observed trade-offs (e.g. conscience choice to buy/not to buy or use/not use a good or service) (Viscusi, 1978; Marin and Psacharopoulos, 1982). Its major advantage is that it is based on observed consumer choices rather than the stated preferences (e.g. Contingent valuation, see below) (Drummond et al., 1997). However, it is difficult and often impossible, to find an occupation where the relevant outcome is the focus of compensation. This is particularly true when evaluating the benefit of vaccination where the disease prevented is infectious, often mild and acute. Furthermore, because of the many imperfections in the labour market and limitations in how individuals perceive occupational risk, it may not reflect the rational choice revealing preferences wanted (Viscusi, 1992). Because of theses limitations Revealed preferences are very seldom used in economic evaluation. See Viscusi (1992) for an in-depth review of Revealed preference.

Contingent Valuation (CV). The use of Monetary values to assess benefit, and therefore Cost-Benefit analysis, has had renewed interest among health economists due to the increased popularity of CV which, was first developed in environmental economics to estimate the value of environmental changes (Olsen

and Smith, 2001; O'Brien and Gafni, 1996; Klose, 1999; Diener *et al.*, 1998; Johannesson, 1993; Johannesson and Weinstein, 1996). CV consists of presenting to respondents hypothetical scenarios about programmes and asking them to express their maximum Willingness to Pay (WTP) to have the programme in place (or some variation of this which we will present later) (Diener et al., 1998; O'Brien and Gafni, 1996; Johannesson and Weinstein, 1996; Drummond et al., 1997). There is enormous diversity on how a CV study in health care can be performed. To describe the methodological questions and considerations we present in Table 1.3 the framework proposed by O'Brien and Gafni (1996) (for more detailed information on CV and WTP please refer to Johannesson (1993), O'Brien and Gafni (1996), Johannesson and Weinstein (1996), Drummond *et al.* (1997), Olsen (1997), Dienar *et al.* (1998), Klose (1999), Bala *et al.* (1999) and, Olsen and Smith (2001)).

Table 1.2. Monetary values in the context of vaccination

	Human Capital	Revealed Preference	Contingent Valuation
Definition	▪ Healthy time measured as the Present Value of future earnings	▪ Wage-Risk trade-off.	▪ Respondents are given hypothetical scenarios about the programme or problem under evaluation.
Theoretical basis	▪ Not rooted in welfare economics (1,2).	▪ Rooted in welfare economics: Measures consumer choice involving heath versus money (6).	▪ Based on welfare economic theory (7-11).
Practicality	▪ NA	▪ NA	▪ Good response and completion rates (8,10), except when open-ended questions are used (11,12,13)).
Validity			
Content	▪ Cannot measure non-health attributes of an intervention. ▪ Raises problems on how to place shadow prices on non-market resources (e.g. child health time) (3,4,5).	▪ Cannot measure non-health attributes of an intervention. ▪ Difficult or impossible to find an occupation where the relevant outcome is the focus of compensation.	▪ No restrictions on which dimensions of a programme people are allowed to express a value for (7,9-11).
Empirical	▪ Criterion, Convergent or Construct validity not demonstrated.	▪ Does not reflect the rational choice revealing preferences wanted due to many imperfections in the labour market (6). ▪ Estimates vary widely and values are very context and job-specific (6).	▪ *Criterion Validity*: Hypothetical WTP exceeds observed WTP (14). ▪ *Construct Validity*: Strong Correlation with health gain and income. (10,13,15-17) ▪ *Convergent Validity*: Week correlation with other monetary (13) and non-monetary health measures (10,13,18,19). ▪ *Bias*: Evidence of warm-glow effects and strong evidence of starting point bias (14,20,21)
Sensitivity	▪ Sensitive to small changes in well being	▪ Not sensitive to small changes in well being	▪ Sensitive to small changes in well being (8,16,22). However, may be oversensitive to small changes in well being (19,23,24) ▪ Insensitive to size of the programme (14).

1. Shelling 1968; 2. Mishan 1971; 3. Klarman 1967; 4. Weisbrod 1968, 5. Drummond *et al.*, 1997; 6. Viscusi 1992; 7. Olsen et al., 2001; 8. Birch et al., 1999; 9. Bala et al., 1998; 10. O'Brien and Viramontes, 1994; 11. O'Brien and Gafni, 1996; 12. Johannesson and Weinstein, 1996; 13. Klose, 1999; 14. NOAA, 1993; 15. O'Connor and Pennie, 1995;16. Kartman et al., 1996; 17. Zillich et al., 2002; 18. Stavem, 2002; 19. Clarke, 2002; 20. Boyle et al., 1985; 21. Stalhammar, 1996, 22. Smith, 2001; 23. Seip and Strand, 1992; 24. Duffield and Patterson; 1991.

Table 1.3. Questions and Considerations for a Contingent Valuation Study

Question	Consideration
What question do we want to answer?	Problem Definition: 1. Pricing and demand studies 2. Project appraisal for resource allocation Current Status of Program: 1. Program currently exists 2. Program does not currently exist (Dis)Utility of program to respondent: 1. Gain in utility from program 2. Loss of utility from program
What type of measure is used?	Monetary measure of utility change: 1. Compensating Variation: Use money to adjust consumers' utilities to their pre-programme level. 2. Equivalent Variation: Use money to adjust consumers' utilities to their post-programme level. "Direction" of measurement: 1. Willingness to pay (WTP) 2. Willingness to accept (WTA)
What is asked of whom?	Externality and option value: 1. Currently Diseased 2. Currently Non-diseased: At future risk 3. Currently Non diseased: Not at future risk Framing of program consumption and payment: 1. Ex-post user-based question: Respondent is asked to assume he or she is at the point of consuming some unit of the programme being evaluated. 2. Ex-ante insurance-based question: Respondent is asked to assume they are at risk, in the future, of a disease and consuming some unit of the programme being evaluated.
What characteristics of the program are important for determining how it is valued?	Program outcome description: 1. Certain outcomes 2. Uncertain outcomes Nature of "market" for valuation scenario: 1. Public good market 2. Political market
What question formats minimise bias and increase precision?	Valuation scenario: 1. Holistic versus decomposed 2. Degree of Realism Value elicitation method: 1. Open-ended questions: Respondent asked directly for maximum WTP (minimum WTA) 2. Bidding Games: A first bid is made to the respondent, who accepts or rejects, and then the bid is raised or lowered. 3. Payment Card: Range of WTP (WTA) values from which the respondent may choose. 4. Take it or leave it: Respondent is asked if he is WTP (WTA) a random chosen value (out of a large number of determined prices). 5. Take it or leave it (with follow-up): Take it or leave it method with a follow-up bid question given to the respondent. Questionnaire type (Added from O'Brien and Gafni (1996): 1. Face to Face interview: 2. Telephone Interview 3. Mail Questionnaire 4. Interactive Computerised Questionnaire:

Adapted from O'Brien and Gafni (1996).

Table 1.2 shows the strengths and weaknesses of the CV method. The main arguments for the superiority of WTP as a measure for health intervention are that it: 1) is theoretically correct, because of its base in Welfare economic theory, 2) values benefits in the same unit as the costs and therefore allows direct comparison and, 3) provides a method of valuation that is familiar to individuals (Olsen and Smith, 2001; O'Brien and Gafni, 1996; Klose, 1999; Diener et al., 1998; Johannesson, 1993) although the extent to which this is true in health care systems that are largely free at the point of service is debatable. Other aspects/qualities of CV may make it particularly appropriate for evaluating vaccination (Birch *et al.*, 1999). It is sensitive to small changes in well-being at the individual level (Birch *et al.*, 1999; Kartman *et al.*, 1996; Smith, 2001) and many vaccines that are now available prevent self-limiting, acute and/or mild diseases (e.g. varicella and influenza). This may also be a disadvantage if CV is oversensitive to small changes in well-being making the results unstable (see below). Second, it imposes no restrictions on which dimensions of a vaccine programme individuals are allowed to express a value for (Olsen *et al.*, 2001; Birch *et al.*, 1999; Bala *et al.*, 1998; O'Brien and Gafni, 1996). WTP should thus be able to measure the different "Current use" non-health attributes and "Non current use" attributes of vaccination described above (caring externalities, security).

On the other hand, the principal disadvantage of the CV techniques is that the hypothetical WTP is usually found to be higher than the actual WTP and may be oversensitive to small changes in health or programme benefits (Seip & Strand, 1992; Duffield and Patterson; 1991; Clarke, 2002). Individuals may be limited by their ability to pay. Finally, there is little evidence of empirical validity (Klose *et al*, 1999; National Oceanic and Atmospheric Administration, 1993).

1.3.2.2 Natural Units

In cost-effectiveness analysis, costs are compared to a single one-dimensional natural unit of health, which may differ in magnitude between the alternative programmes. Examples of natural units are cases, hospitalisations and deaths averted. The most commonly used natural unit is life-years gained (Tsuchiya and Williams, 2001).

Table 1.4. Natural Units in the context of vaccination

	Natural Units
Definition	▪ Single one-dimensional unit of health change.
Theoretical basis	▪ Not based on welfare economic theory or on the concept of choice and opportunity cost.
Practicality	▪ Easy to estimate outcomes based on literature review or results from clinical trials.
Validity	
Content	▪ Cannot capture more than one health attribute. ▪ Cannot measure non-health attributes.
Empirical	▪ Dependent on the studies the outcome is based upon. Easier to assess than Contingent Valuation or Quality of Life Measures. Can measure *Criterion Validity*.
Sensitivity	▪ Dependent on the outcome that is chosen.

The main advantage of Natural Units are that they are easier to estimate, have greater validity and are less subjective than Monetary Values or Quality of Life outcomes as they can be found in a review of medical literature or taken directly from clinical data on effectiveness (Table 1.4). On the other hand, Natural Units are one-dimensional and therefore cannot capture simultaneously the benefit of an intervention on all attributes of health and therefore, it is difficult to make comparison across a broad range of effects (Table 1.4). This is a major disadvantage when estimating the desirability of vaccination under scarcity. For example, currently many developed countries are choosing between vaccinating children against varicella (which is prevalent but mild) and/or meningogoccal disease (which has low prevalence but a high case-fatality) and/or pneumococcal

disease (which has low prevalence but high morbidity). In this situation, only by using measures that incorporate multiple dimensions of Health (Monetary Values or Quality of Life measures) can the different vaccination programmes be appropriately compared. Alternatively, an array of different Natural outcomes can be presented to decision-makers who then must make their own trade-off between effects (Drummond *et al.*, 1997).

1.3.2.3 Health-Related Quality-of-Life Outcomes

The main advantage of using Health-Related Quality-of-Life (HR-QOL) values is that it allows a broad range of health attributes to be included into a single measure, which allows comparisons across a wide variety of health intervention programmes (Olsen and Smith., 2001, Birch *et al.*, 1999, Bala *et al.*, 1998; O'Brien and Viramontes, 1994; O'Brien and Gafni, 1996; Klose, 1999). On the other hand, its major critique is that it is incapable of capturing non-health benefits (Olsen and Smith, 2001; Donaldson *et al.*, 1997).

Quality-Adjusted Life-Years (QALYs) are the most used method for measuring outcomes (Elixhauser *et al.*, 1998), mainly because of the reluctance of policymakers in the healthcare sector to evaluate interventions in monetary terms (Drummond *et al.*, 1997; Johannesson, 1996; Brouwer and Koopmanschap, 2000). The concept of QALY was developed to capture simultaneously gains from reduced morbidity and reduced mortality, and to combine these into a single measure. The measure assigns a Quality of life-weight, ranging from 0 to 1, where a weight of 1 corresponds to optimal health and 0 corresponds to a health state judged equivalent to death (some states may be considered worse than death and would thus have a negative QALY). This weight is then multiplied by the years of life spent in the health state. The QALY gained is the difference, over time, between

the QALY weight with and without the intervention. Several alternatives to the QALY have been suggested: Healthy-Year Equivalents (HYE), Saved-Young-Life Equivalents (SAVE), Disability-Adjusted Life-Years (DALY). Discussion of alternatives to QALY is beyond the scope of the thesis for more information please consult Drummond *et al.* (1997), Mehrez and Gafni (1989, 1991, 1992), Nord, (1992a) and World Bank (1993).

As discussed earlier, in this thesis we do not debate which theoretical foundation economic analysis should be based on, or whether QALYs are measures of utility, rather, we examine from an empirical perspective the different valuation techniques. In this section we describe and discuss the properties of the different methods that are used to value health interventions in terms of QALYs. These instruments are the 1) Visual Analogue Scale (VAS), 2) Standard Gamble (SG), 3) Time-Trade-Off (TTO), and 4) Multi-Attribute Utility Scales (MAUS). See Brazier et al. (1999) for an in-depth review of these techniques.

Visual Analogue Scale. VAS is used here interchangeably with the category rating scale (CR). The VAS consists of asking the respondent to reveal their preferences on a scale with well defined end points, which can be numbers, categories, or consist of a line on a page (Green *et al.*, 2000; Drummond *et al.*, 1997). Some empirical studies suggest that VAS can be transformed into SG or TTO by using power curves (Torrance, 1976; 1996).

The main advantages of the VAS is its practicality (i.e. ease of use and high completion rates) and its sensitivity to changes in health (Juniper *et al.*, 2002; Salaffi *et al.*, 2002) (Table 1.5). The main disadvantages of the VAS are that: 1) it is not a choice-based technique and therefore has no foundation in economic

theory (Brazier et al., 2000) and, 2) there is evidence of poor to moderate correlation with choice-based techniques (SG and TTO) (Froberg et al., 1989; Bakker et al., 1994; Clarke *et al.*, 1997; Read *et al.*, 1984; Nord, 1992; Rutten-van Molken *et al.*, 1995;). Furthermore, it has shown to produce End-of scale bias in which individuals tend to refrain from using the upper and lower end of the scales.

Standard Gamble. SG is the standard technique of measuring preferences under uncertainty. It is based on the Expected Utility Theory of decision-making under uncertainty, first presented by von Neumann and Morgenstern (1944). Similarly to CV it uses the economic concept of opportunity costs under uncertainty. SG asks individuals the probability (p) of immediate death (or some other outcome worse than the one being valued) they are prepared to accept to avoid the certainty of the health-state being valued (HS_i - see Figure 1.2).

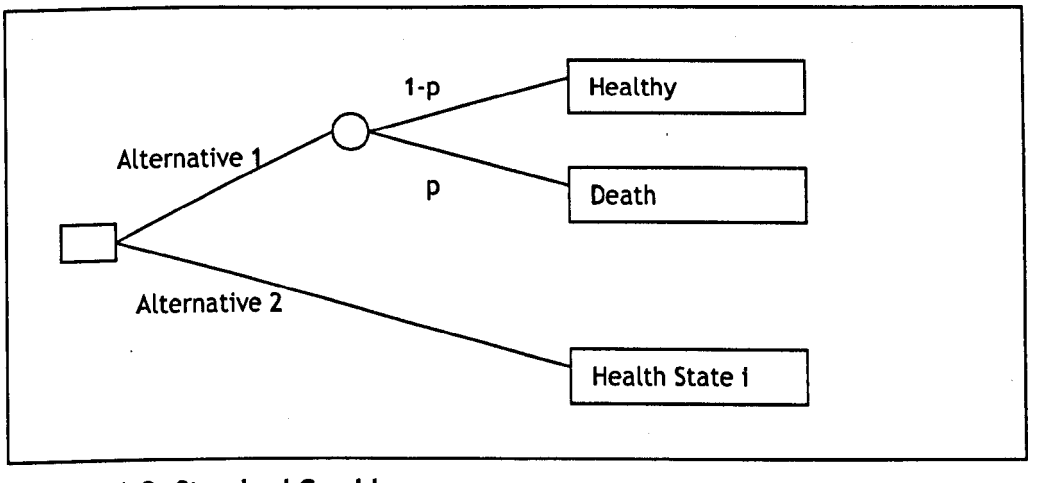


Figure 1.2. Standard Gamble

For a temporary Health State (HS_i) a QALY-weight can be estimated from the SG as follows. The standard gamble questionnaire elicits the probability p that makes the respondent indifferent between the current condition ($HS_i * t + 1 * (L - t)$) and the expected benefit of treatment ($(1-p) * L + p * 0$) (based on Figure 1.2).

Where, HS_i is the QALY-weight of health state i, QALY-weight for death is 0, QALY-weight for Healthy is 1, t is duration of disease, L is the current life expectancy and p is the probability of instant painless death following the intervention. From these equations we have:

$$HS_i = \{(L*(1-p))- (L - t)\} /t$$

If the disease is chronic (t = L), then $HS_i = 1-p$. We do not use discounting, here, because it is inconsistent with the QALY utility model (Mehrez and Gafni, 1989; Johannesson et al., 1994). Furthermore, these equations assume constant-proportional trade-off (Pliskin et al., 1980). Preferences for temporary health states can also be measured relative to each other using the SG and Chained methods. With the Chained methods, the health state to be evaluated is not weighed directly against death as it is in conventional SG measurement, but in a multi-step procedure using intermediate anchor health states, which are worse than the health state being valued. See Drummond *et al.*, 1997 for more details and Jansen *et al.*, 1998 for a published example of the method.

Researchers have suggested that the SG is too complex and not intuitive to most respondents (Froberg, 1989). The main reported problems with SG are refusals due to conflicts with personal beliefs or straightforward difficulties in understanding the tasks or dealing with small probabilities (Green *et al.*, 2000). Completion rates have, however, been reported to be acceptable in many studies across different populations (Green *et al.*, 2000). The main advantage of SG is that it has a basis in economic theory. That is, it is choice-based and is based on the Expected Utility Theory of decision-making under uncertainty (Table 1.5). The main disadvantage of using SG for vaccine preventable disease is that many are acute and non-life threatening. The use of SG (and TTO) to value morbidity for acute diseases has

well documented measurement and evaluation problems (Bala, and Zardin, 2000; Bala *et al.*, 1999; Stalmeier *et al.*, 1996; Gafni, 1994; Dolan and Gudex, 1995; Stiggelbolt, 1995; Bleichrodt and Johannesson; 1997). Furthermore, SG has been shown to be insensitive to small changes in health status (De Wit *et al.*, 2000). Finally, there is limited evidence of empirical validity of SG.

Time Trade-Off. TTO was developed by Torrance et al. (1986) as a simple alternative to the SG (i.e. to overcome problems of presenting probabilities of death). The TTO consists of asking the respondent to choose between two alternatives both with certain outcomes: health state i for time t_1 followed by death or Perfect health (or a better Health State) for time $t_2<t_1$. Time t_2 is varied until the respondent is indifferent between the two alternatives. The preference score (HS_i) for health state i is: $HS_i = 1-t_2/t_1$. As with the SG technique, Chained methods can be used within the TTO framework to measure preferences for temporary health states relative to each other. See Drummond *et al.*, 1997 for more details and Jansen *et al.*, 1998 for a published example of the method.

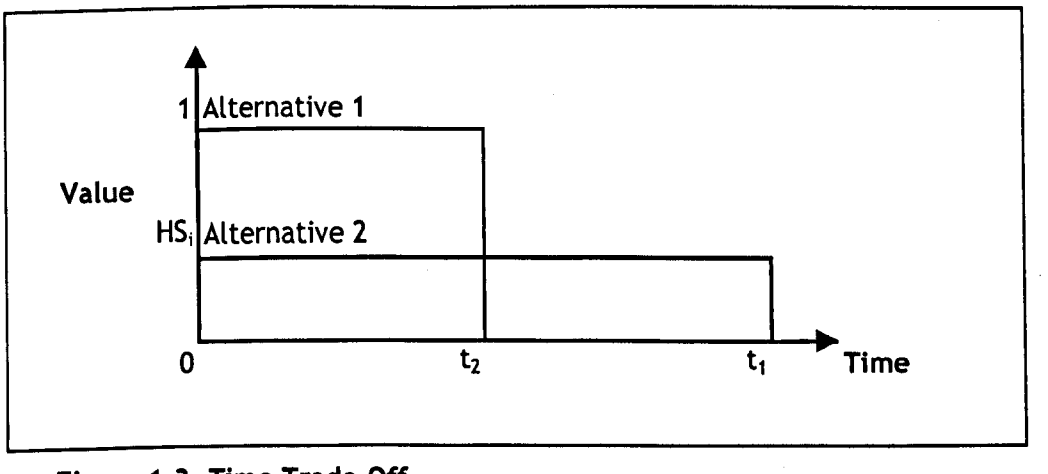


Figure 1.3. Time Trade-Off.

TTO has been found to be easier to use and has shown better completion and response rates than the SG (Lenert *et al.*, 2001; Dolan *et al.*, 1996). Furthermore, although the literature available is sparse, TTO seems to have slightly higher empirical validly than SG (Green *et al.*, 2000; Brazier *et al.*, 1999). On the other hand, SG has greater foundation in economic theory (Table 1.5).

The main disadvantages of using TTO for vaccine preventable disease are similar to SG. That is, similarly to SG, TTO seems to be insensitive to small changes in health (Muirhead *et al.*, 1994; Tsevat *et al.*, 1993; Bala, and Zardin, 2000; Bala *et al.*, 1999; Stalmeier *et al.*, 1996; Gafni, 1994; Dolan and Gudex, 1995; Stiggelbolt, 1995).

Multi-Attribute Utility Scales (MAUS). Pre-scored Multi-attribute health status indices or Multi-Attribute Utility Scales (MAUS) are a simple alternative to the complex task of measuring preference through the techniques described above. These Multi-Attribute Health Status Classification systems can be transformed into utilities (QALYs) by adding one additional assumption to the three axioms of utility theory. The assumption is that utility independence among the attributes of health can be represented by at least first-order utility independence, and perhaps stronger utility independence (i.e additive utility independence)(Keeney and Raiffa, 1976). Here, we briefly describe three of the main systems available: 1) EuroQol (EQ-5D), 2) Short-Form 6D (SF-6D) and 3) Health Utilities Index Mark II(HUI2). For further information please refer to Brazier et al. (1999).

EQ-5D. The EQ-5D was developed by the EuroQol Group (a multidisciplinary, European research network) as a generic, single index measure of health status for the use in the evaluation of health care interventions (EuroQol Group, 1990). It

has widely been adopted in clinical studies and is in use in more than 30 countries world-wide. The EQ-5D includes five attributes: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each attribute has three levels thus producing 243 healthy states exclusive of unconscious and dead. The preference scores were originally measured using the TTO technique in the UK (Dolan et al., 1996)

HUI2: The HUI2 was developed as a generic, single index measure of health status for the use in the evaluation of health care interventions (Torrance, 1996). Preferences for the HUI2 scoring function were measured on a random sample of parents of schoolchildren in the City of Hamilton (Canada) and surrounding districts using both the SG and a VAS. The HUI2 is comprised of 7 attributes: Sensation, Mobility, Emotion, Cognition, Self-care, Pain and Fertility (Fertility can be excluded if not required (Torrance, 1996)). The HUI2 is of particular interest for valuation of child vaccination as it was developed for chronic childhood diseases using parents as proxies.

SF-6D. The SF-6D was developed as a possible alternative to the EQ-5D (O'Brien *et al.*, In press). It is based on 6 of the 8 dimensions of the SF-36: Physical functioning, Role limitations, Social functioning, Pain, Mental health, Vitality. The General Health dimension was omitted from the SF-36 and Emotional and Physical Role limitation were combined into one dimension (Brazier *et al.*, 2002). The combination of levels and attributes produce a universe of 18000 health states (Brazier *et al.*, 2002). SG was used to elicit preferences among the UK general public (Brazier *et al.*, 2002)

The major advantages of MAUS, described in this section (i.e. HUI, EQ-5D, SF-6D), are that: 1) it is easy-to-use and briefly self-completed (compared to SG and TTO) (Brazier *et al.*, 1999), 2) it has basis in economic theory (Keeney and Raiffa, 1976), and 3) it can capture small changes in heath status (De Wit et al., 2000; de Vries et al., 1998) (Table 1.5). A further advantage for the HUI2, is that it is validated for childhood diseases (Torrance, 1996).

The major disadvantages of MAUS is that it cannot measure the potential non-health attributes of vaccination and evidence of empirical validity is limited. A further concern is the recent empirical evidence, which casts doubt on whether QALYs estimated from the EQ-5D, HUI3 and SF-6D are comparable (O'Brien et al. (In press), Longworth and Bryan (In press)).

It should be pointed out that although we compare MAUS with VAS, SG and TTO in Table 1.5 we are not comparing like with like. This is because MAUS are not a method for collecting valuations but rather a method of calculating them. Hence, as shown in Table 1.5 MAUS inherit all of the theoretical problems of the valuation methods underlying them (SG, TTO or VAS) and incorporate assumptions about an underlying valuation model. Moreover, they use valuations from a sample other than the people in the study, unlike the other methods. Therefore, it should be born in mind that there are more differences between the techniques than are included in the Table 1.5. The goal of Table 1.5 is to show the advantages and disadvantages of different techniques that are used to estimate QALY values, which will be different between VAS, SD, TTO and SG.

Other HR-QoL instruments. Ratio Scaling or Magnitude Scaling (ME), developed in pychometrics, consists of asking respondents to provide a ratio of undesirability of pairs of health states (Green *et al.*, 2000; Drummond *et al.*, 1997). That is, a

patients will state that health state A is 10 times worse than health state B. By asking a series of questions the disutility can then all be linked together and converted into an interval scale of preference. The Person Trade-Off (PTO), for example, asks respondents to state how many patients in a certain health state should have their lives extended by one year in order to be equivalent to extending the lives of 100 healthy patients by one year (Nord *et al.*, 1993). We do not discuss these techniques as they are seldom used and their feasibility, practicality and theoretical validity are relatively unknown (Green *et al.*, 2000).

Table 1.5. HR-QoL techniques to value QALYs in the context of vaccination (Based on Green et al., 2000)

	VAS	Standard Gamble	Time Trade-Off	MAUS (HUI, EQ-5D, SF-6D)
Theoretical basis	▪ Not based on welfare economics. ▪ Does not involve choice or opportunity cost (1,2,3,4).	▪ Not based on welfare economics. ▪ Based on Utility theory. ▪ Involves choice and opportunity costs under uncertainty (1,5,6).	▪ Not based on welfare economics or utility theory. ▪ Involves choice and opportunity costs (1).	▪ Valued from SG (HUI, SF-6D) and TTO (EQ-5).
Practicality	▪ Easy to use and quick. ▪ High completion and response rates (6-12).	▪ Complex and non-intuitive (6). ▪ Acceptable completion and response rates (21-24). Lower than VAS and TTO (7,21).	▪ Good completion and response rates (21,23, 28-30).	▪ Easy to use and quick. ▪ High completion and response rates (32).
Validity				
Content	▪ Cannot measure non-health attributes (13).	▪ Cannot measure non-health attributes (13).	▪ Cannot measure non-health attributes (13).	▪ Cannot measure non-health attributes (13). ▪ Restrictive in the health dimensions being valued (32).
Empirical	▪ *Criterion Validity*: Absence of a reference unit (1). ▪ *Construct Validity*: Correlation with health gain (14,15). ▪ *Convergent Validity*: Moderate correlation/agreement with SG, TTO (6,11,16-19). ▪ *Bias*: End of Scale Bias (2,9,20).	▪ *Criterion Validity*: Absence of a reference unit (1). ▪ *Construct Validity*: Correlation with health gain (21,25). ▪ *Convergent Validity*: ▪ Reasonable (1,5,21,26) and poor (25,27) correlation/agreement between SG and TTO. ▪ SG elicit greater utilities than TTO (1,3,25). ▪ *Bias*: Possibility of starting point bias.	▪ *Criterion Validity*: Absence of a reference unit (1). ▪ *Construct Validity*: Correlation with health gain (21,25,29, 31) ▪ *Convergent Validity*: ▪ Reasonable (1,5,21,26) and poor (25,27) correlation/agreement between SG and TTO. ▪ TTO elicit lower utilities than SG (1,3,25). ▪ *Bias*: Possibility of starting point bias.	▪ *Criterion Validity*: Absence of a reference unit. ▪ *Construct Validity*: Correlation with health gain (32,33). ▪ *Convergent Validity*: Reasonable correlation between SG and TTO (32). Differences in correlation between MAUS instruments (34-36).
Sensitivity	▪ Sensitive to small changes in well being (14,15).	▪ Not sensitive to small changes in well being (15, 40-45).	▪ Not sensitive to small changes in well being (14,38-45)	▪ Sensitive to small changes in well being (37).

1. Green *et al.*, 2000; 2. Nord, 1991; 3. Drummond *et al.*, 1997; 4. Richardson, 1994; 5. Torrance, 1986; 6. Froberg et al., 1989; 7. Lenert *et al.*, 2001; 8. Torrance, 1987; 9. Kaplan *et al.*, 1993; 10. Busschbach *et al.*, 1994; 11. Bakker *et al.*, 1994; 12. Gudex *et al.*, 1999; 13. Olsen *et al.*, 2001; 14. Salaffi *et al.*, 2002; 15. Juniper *et al.*, 2002; 16. Clarke et al., 1997; 17. Read *et al.*, 1984; 18. Nord, 1992; 19. Rutten-van Molken *et al.*, 1995; 20. Bleichrodt and Johannesson, 1997; 21. Dolan *et al.*, 1996; 22. Rabin *et al.*, 1993; 23. Patrick *et al.*, 1994; 24. Lenert *et al.*, 1997; 25. de Wit, 2000; ; 26. Krabbe et al., 1997; 27. Hornberger et al., 1992; 28. Johnson *et al.*, 1996; 29. Ashby *et al.*, 1994; 30. Fryback et al., 1993; 31. Gage *et al.*, 1996; 32. Brazier *et al.*, 1999; 33. Barr et al., 1993; 34. Stavem K, 1999; 35. O'Brien *et al.*(in press); 36. Longworth *et al.* (in press); 37. de Vries et al., 1998; 38. Muirhead et al., 1994; 39. Tsevat et al., 1993. 40. Bala, and Zardin, 2000; 41. Bala *et al.*, 1999; 42. Stalmeier *et al.*, 1996; 43. Gafni, 1994; 44. Dolan and Gudex, 1995; 45. Stiggelbolt, 1995.

1.3.2.4 Discussion

In this section we provide a framework for the evaluation of the different valuation techniques used to measure the benefit of vaccination (Table 1.1b). A review of the literature suggests that CV is the most appropriate technique to evaluate benefits in terms of Monetary values because of its greater theoretical basis, practicality, content validity and sensitivity (Table 1.2). For HR-QoL, the most appropriate techniques seem to be SG, TTO and MAUS (EQ-5D, HUI and SF-6D) because they are choice-based (or based on choice-based techniques) (Brazier et al., 1999).

The main empirical advantage of the CV method over the HR-QoL techniques is that it imposes no restrictions on which attributes of vaccination people are allowed to express a value for (Table 1.2 and 1.5). Furthermore, contrary to SG and TTO, CV is sensitive to small changes in well-being (Table 1.2 and 1.5). Evidence of empirical validity is scarce for all techniques (CV, SG, TTO and MAUS) due to the absence of a "Gold-Standard". However, there exists more evidence against the criterion and convergent validity of CV than SG, TTO and MAUS (NOAA, 1993).

The main difference between Cost-Benefit and Cost-Utility analysis is the way in which the benefits of health care programmes are valued. Only very few studies have directly compared WTP (from CV) and QALY's (from SG, TTO or MAUS) (Bala *et al.*, 1998; O'Brien and Viramontes, 1994; Stavem K, 2002). The results raised questions as to whether the use of QALY's or WTP in economic evaluation would lead to similar allocation of health resources.

In Chapter 4, we compare CV, SG and HUI2 in the context of varicella vaccination. In so doing we investigate whether attributes of vaccination, such as security and caring, are measurable and, if so, assess their relative importance compared to direct health effects. Furthermore, we assess whether HR-QoL techniques (SG and HUI2) are truly incapable of measuring small changes in well-being individuals and non-health benefits. Finally, we investigate the construct and convergent validity of CV and HR-QoL instruments. In Chapter 4 we also examine how individual preferences can be aggregated to estimate the overall population's value of the benefit of vaccination taking into account herd-immunity externalities and non-health effects using mathematical models.

1.4 DISCUSSION: FRAMEWORK FOR THE ECONOMIC EVALUATION OF VACCINATION PROGRAMMES

Many guidelines have been published to ensure the quality of economic evaluation and standardisation/comparability of methods/results, (Drummond *et al.*, 1996; Commonwealth of Australia, 1995; Torrance *et al.*, 1996; Lovatt, 1996)). It has been suggested that, due to its unique characteristics, additional specific guidelines may be needed for the economic evaluation of vaccination programmes (Beutels *et al.*, 2002; Edmunds *et al.*, 1999). In this chapter, we give brief background information necessary to understand the different methodological issues that are specific to the economic evaluation of vaccination programmes. In subsequent chapters, we will use varicella vaccination to illustrate and investigate the different methodological issues in order to provide evidence from which specific guidelines for economic evaluation of vaccination programmes can be built.

We separate methodological issues into 4 categories: 1) Mathematical Model (Chapter 3), 2) Intervention outcome and valuation technique (Chapter 4), 3) Study Design (Chapter 5), and 4) Sensitivity Analysis (Chapter 5).

The specific questions that will be addressed are:

1. Mathematical Model:
   - What model should be used in economic evaluation of vaccine programmes?
   - What is the impact of including herd-immunity externalities?
2. Intervention outcome and valuation technique:
   - What valuation technique and intervention outcome (i.e. type of economic analysis) should be used in the economic evaluation of vaccine programmes?
   - What are the important attributes of vaccination?
   - How can outcome measures be aggregated from an individual to a population level?
3. Study Design:
   - What is the impact of the study design on the results of economic analyses?
4. Sensitivity Analysis:
   - What type of sensitivity analysis should be used?
   - What should be varied in the sensitivity analysis? What is the relative importance of the choice of model, methodological assumption and parameter estimates on results of economic analysis?

Chapter 2
Epidemiology of Varicella-Zoster virus

2.0 INTRODUCTION

The aims of chapter 2 are twofold, to:

1) Provide base-line epidemiological data for the economic evaluation of varicella vaccination, and
2) Study the dynamics and natural history of varicella-zoster virus to help in the design and parameterisation of a realistic model of VZV transmission, which will be used to evaluate the economic and public health impact of varicella vaccination.

First, in this chapter, we analyze general practitioner surveillance, hospitalisation and mortality data from England and Wales to investigate the following age-specific epidemiological characteristics of varicella and zoster: 1) incidence, 2) GP consultations, 3) hospitalisation and 4) mortality. These results will provide base-line data for our economic analysis.

Secondly, in this chapter, we investigate the relationship between varicella and zoster incidence, which will provide insight into the dynamics of the varicella-zoster virus. This will allow us to develop a realistic model of VZV transmission,

which will be used to predict the overall benefit of varicella vaccination (including externalities such as herd-immunity and exogenous boosting).

2.1 BACKGROUND

Varicella zoster virus (VZV) produces two distinct clinical syndromes: varicella and zoster (Hope-Simpson, 1965). Varicella or chickenpox is the primary manifestation of VZV infection. Following primary infection the virus becomes latent in dorsal root ganglia and may reactivate years or decades later to cause zoster, also known as shingles, in a significant proportion of the population (Hope-Simpson, 1965). The events leading to reactivation are not clearly understood although decreased cell-mediated immunity is thought to play a major role (Hope-Simpson, 1965). The precise relationship between varicella and zoster incidence is still unclear. It has been established that zoster is infectious and can transmit varicella (Hope-Simpson, 1965). By doing so zoster appears to stabilise the variability in varicella epidemics permitting VZV to persist in small populations (Garnett and Grenfell, 1992a; Garnett and Grenfell, 1992b; Ferguson *et al.*, 1996). Although zoster is thought to be less infectious than varicella, the contribution zoster makes to the overall force of varicella infection remains uncertain. The role of varicella on zoster incidence is more ambiguous primarily because of the lack of understanding of the mechanism of reactivation. It has been suggested that varicella can decrease the risk of zoster by boosting specific immunity to VZV (Hope-Simpson, 1965; Palmer *et al.*, 1985; Brisson *et al.*, 2002; Thomas *et al.*, 2002; Gershon *et al.*, 1996). Economic analysis relies greatly on epidemiology for valid base-line data (such as incidence of disease, hospitalisation and mortality) and for insight on the natural history of infection and disease, which is essential to build valid mathematical models for prediction of the benefits of intervention.

2.2 DATA SOURCES

General Practitioner Surveillance Data. Information on the age-specific consultation rate for varicella and zoster is available through the Royal College of General practitioners (RCGP), which instituted a sentinel surveillance program in 1967 using a representative sample of the practitioners throughout England and Wales (Fleming, 1999). The clinical diagnosis, age and sex of each patient with a new illness are reported weekly by around 70 GP practices in England and Wales (this currently covers a population of about 570,000 although variations in the number of practices reporting occur). Additional age-specific consultation rates for varicella and zoster are available from the National Survey of Morbidity in General Practice (MSGP4) database, which was derived from a survey of English and Welsh general practices in 1991-1992 (McCormick *et al.*, 1995). The study covered approximately a 1% sample of the population of England and Wales (502,493 patients, 468,042 person-years at risk). Details of all consultations were recorded during the study year, along with socio-economic and socio-demographic information on the patients.

Hospitalisation Data. Hospitalisation data for England is available from Hospitalisation Episode Statistics (HES database), which covers every inpatient National Health Service admission in England (approximately 49 million person-years at risk per year). However, HES does not provide details of the drugs used in hospitals, or information concerning out-patients.

HES currently collects 12 million records per year, and each record contains over 50 items of information. This includes the dates of admission and discharge, discharge method and seven discharge diagnosis fields coded by International Classification of Disease code (ICD-10, ICD-9 before 1995/96) as well as details

relating to the patient (for a full description of all data fields in HES see http://tap.ccta.gov.uk/doh/hes_dd.nsf). A recent systematic review of studies comparing routine discharge hospital episode statistics in the UK with the original medical records found that the median coding accuracy was 77% for ICD-9 (Campbell *et al.*, 2001). Hence, the level of inaccuracy should be born in mind when interpreting these statistics and should be taken into account in the sensitivity analysis of economic evaluations that use this data.

Mortality Data. The annual number of deaths attributed to varicella and zoster in England and Wales is available from the Office for National Statistics (Office for National Statistics, 2000). The ONS mortality database includes information on the underlying cause of all deaths in England and Wales. Underlying cause of death is coded into ICD-9, from death certificates, using an automated computerised system (Rooney and Devis, 1996).

2.3 EPIDEMIOLOGY OF VARICELLA AND ZOSTER

2.3.1 METHODS - DATA ANALYSIS

Incidence. The force of infection, λ, is the instantaneous incidence rate of infection amongst susceptibles. The force of varicella infection was estimated, here, from physician consultation data (MSGP4 data). To estimate the force of infection from physician consultation data, consultation rates were adjusted given that physicians do not see all children with chickenpox (see Brisson *et al.*, 2001 for age-specific rates). The proportions of varicella cases seeking physician consultation were derived from a review of the literature (Lieu *et al.*, 1994; Sulivan-Bolyai *et al.*, 1987; Saddier *et al.*, 1998; Law *et al.*, 1999a; Brisson *et al.*, 2001) and assuming that all individuals contract varicella during their lifetime. The estimated percent of individuals with varicella seen by a GP for 0 to 4, 5 to

14, 15 to 44, 45 to 64, 65 + age groups respectfully were 43, 33, 52, 53, and 86%. The adjusted MSGP4 rates were validated using 1996 serologic data from England and Wales (Figure 2.1).

The force of infection was calculated by using Farrington *et al.* (1990)'s functional form to generate an expected proportion of individuals of age t who would have been exposed to the virus:

$$F(t) = 1 - \exp\{(a/b)te^{-bt} + (1/b)(a/b - c)(e^{-bt}-1)-ct\} \quad (1)$$

where a, b and c $\geq$ 0. The function is fitted to the observed age-specific proportion of individuals with history of infection using maximum likelihood methods. The model log likelihood, l(t), stratified by age group (t), was obtained from the binomial likelihood:

$$l(t)=(1-x(t))\ln[1-F(t)]+ x(t)\ln[F(t)] \quad (2)$$

where, x(t) is the observed age-specific proportion of individuals with history of infection calculated from MSGP4 adjusted rates and F(t) is the proportion of individuals with history of infection as predicted by the model (equation 1).

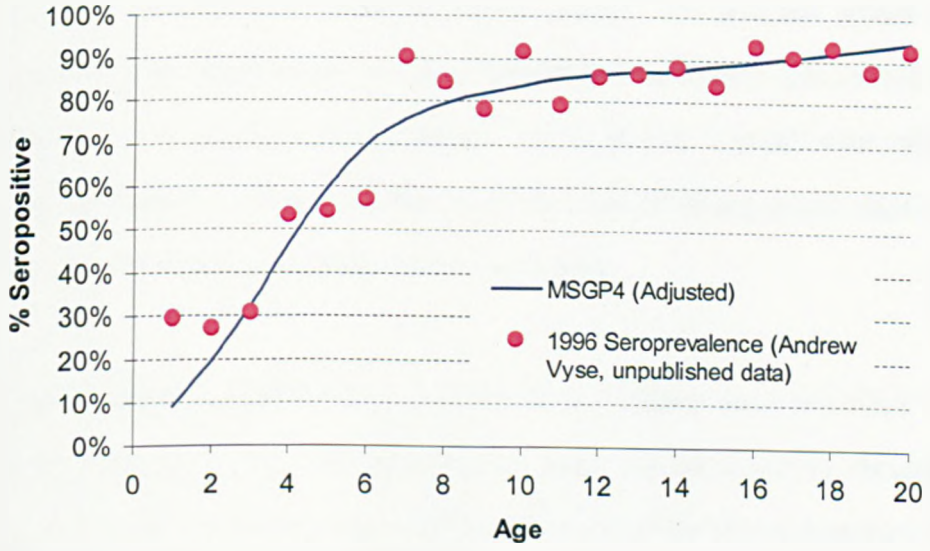


Figure 2.1. Varicella seroprevalence.

The age-specific varicella incidence rate was calculated using the force of infection estimates and the average age-specific population of England and Wales between 1991-2000 (Office for National Statistics, 2000). The estimated proportion of positives by age shows good agreement to the age-specific serological data (Figure 2.1).

Because of its high severity individuals with zoster are likely to consult a general practitioner. Zoster consultation rates were thus assumed to be reasonable estimates of incidence rates. The age-dependent proportion of zoster cases which result in Post-Herpetic Neuralgia (PHN - defined as pain lasting more than 1 month after the onset of zoster) was taken from a prospective study of PHN in general practice (Hope-Simpson, 1975) and from the MSGP4 database, by comparing the reported incidence of PHN (ICD-9 0531) with the total number of zoster episodes. The average time to complete cessation of PHN was estimated from two population-based studies (Hope-Simpson, 1975; de Morgas and Kierland, 1975) and from 3 large datasets compiled from controlled randomised clinical trials of antiviral therapy for the treatment of acute herpes zoster (Dworkin *et al.*, 1998; Wood *et al.*, 1996; Wood *et al.*, 1998). Time to complete cessation of pain was measured for each of the six groups: two placebo groups and two aciclovir, one famciclovir and one valaciclovir treatment groups (we took an average of those receiving valaciclovir within 48 and 72 hours after rash onset). Only individuals in pain after one month of onset of herpes zoster were included, as this is the definition of PHN used in the study.

Hospitalisation. Hospitalisation statistics for England were extracted from the HES database for the 1995/96 financial year. We extracted all records with a varicella (ICD-10 B01) or zoster (B02) code in any of the seven diagnostic fields.

In HES, a patient's period of care under a consultant is called an *episode* and the overall stay in the hospital is termed a *spell*. If responsibility for a patient is transferred from one consultant to another during a *spell* a new HES record is completed with possibility of additional diagnosis. Hence, for a particular *spell* in hospital, there are as many HES records as *episodes*. To aid in the analysis of *spells*, episodes are given an order number in HES (*epiorder*). Since we are mostly interested in the number and length of hospital admission for varicella and zoster, multiple records of the same *spell* must be de-duplicated. Records were de-duplicated by identifying and deleting records, which had identical admission and discharge dates and personal identifiers (birth date, postal code and gender). In our analysis, we kept the record with the highest *episode* number.

All hospital separations with a varicella (ICD-10 B01) or zoster (B02) diagnostic code in the first position were considered to be admissions due to VZV. Furthermore, a person was considered to have an underlying condition (condition associated with greater risk of zoster) if there was a discharge diagnosis code for at least one of the following conditions: Human immunodeficiency virus (ICD-10 B20-4), all malignant neoplasms (C00-97), all in situ neoplasms (D00-09), neoplasms of uncertain or unknown behaviour (D37-48), agranulocytosis (D70), certain disorders involving the immune mechanism (D80-89) and cystic fibrosis (E84).

Hospitalisation rates were estimated by dividing the number of hospitalisations in 1995/1996, as derived from HES, by the estimated mid-1995 population of England (Office for National Statistics, 2000).

Mortality. The annual number of deaths for which the underlying cause was

recorded as varicella and zoster in England and Wales during 1993-2000 were extracted from the Office for National Statistics (Office for National Statistics, 2000). In 1993 computerised cause of death coding was introduced in England and Wales to increase the consistency and international comparability (Rooney and Devis, 1996). This created discontinuities in time trends between 1992 and 1993 (Rooney and Devis, 1996). Mortality data before 1993 were therefore excluded from the analysis.

The varicella and zoster death rates were calculated using the average number of deaths in England and Wales during 1993-2000 as the numerator and the average population of England and Wales during this time period as the denominator.

2.3.2 EPIDEMIOLOGY OF VARICELLA

Incidence. The estimated values for the force of infection of varicella in England and Wales are shown in Table 2.1. The force of infection was used to estimate the age-specific annual number of cases and incidence rate of varicella in England and Wales (Table 2.2). The overall incidence of varicella is estimated to be 1,291 cases per 100,000 person-years, the highest rate occurs in children less than 5 years of age (10,331 cases per 100,000 person-years). These rates suggest that a total of 670,000 cases of varicella occur in England and Wales every year. Children under 15 years are estimated to account for 84% of these cases. The bulk of remaining cases (14%) are estimated to occur in adults of childbearing age (15-44 years).

The age-specific number of varicella cases reported by general practitioners is determined by patient consultation patterns, which may be age and time dependant. The consultation patterns also depend on the type of primary health

care available, which can vary by country. Therefore, consultation rates should not be interpreted as varicella incidence rates. They are, however, useful to examine trends in disease incidence. During the 1990's, there have been changes in the age-specific varicella consultation rates in England and Wales (Figure 2.2). Although the consultation rates have remained relatively stable in children under 5 years, the rate in older children (5-14 years) and adults (15+) have roughly halved between 1990 and 2000 (Figure 2.2). Table 2.2 shows the average consultation rates for varicella in England and Wales between 1991-2000.

Table 2.1. Maximum likelihood estimates of the varicella force of infection (infections per susceptible-year) by age group.

Age Group	England and Wales[a]
0-1	0.11
2-4	0.18
5-11	0.15
12-18	0.09
19-24	0.09
25-44	0.08
45-64	0.07
65+	0.07

a. MSGP4 data, 1991-1992.
Deviance = 11.8, degrees of freedom = 15

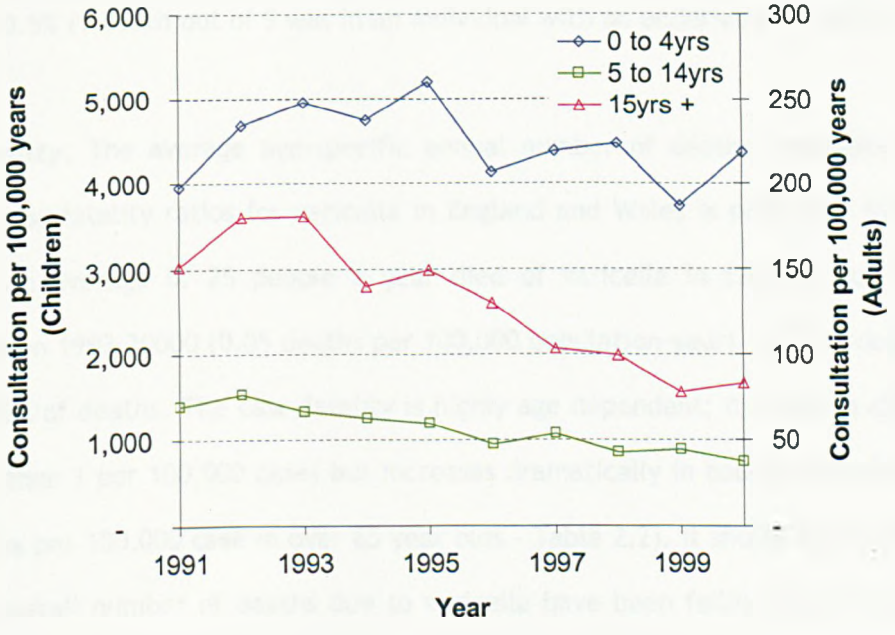


Figure 2.2. Annual age-specific varicella consultation rate in England and Wales from 1991-2000.

Hospitalisation. The age-specific number of hospitalisations, hospitalisation rate, risk of hospitalisation per varicella case and mean length of stay are presented in Table 2.2. In 1995/96, the overall hospitalisation rate for varicella was 4.5 per 100,000 person-years. Seventy percent of hospitalisations were in children under 15 years. However, the risk of hospitalisation per case of varicella and the average length of stay increases steeply with age (Table 2.2). The risk of hospitalisation and mean length of stay are 8 and 5-times greater in adults over 65 years than children under 5 years, respectively.

Among all hospitalised patients, 5% had a least one reported underlying condition (Table 2.3). The percent of hospitalisations with an underlying condition increased with age from 4% in individuals younger than 45 years to 21% in adults older than 65 years. The most common condition was malignant neoplasm (70%, half of which was leukaemia), followed by cystic fibrosis (9%), agranulocytosis (9%), certain disorders involving the immune mechanism (8%) and human immunodeficiency virus (4%). The risk of death during hospitalisation was less than 0.5% (1 death out of 9 was in an individual with an underlying condition).

Mortality. The average age-specific annual number of deaths, mortality rates and case-fatality ratios for varicella in England and Wales is presented in Table 2.2. An average of 25 people a year died of varicella in England and Wales between 1993-20000 (0.05 deaths per 100,000 population-year). Adults accounted for 85% of deaths. The case-fatality is highly age dependant; it is low in children (less than 1 per 100,000 case) but increases dramatically in adults (from 9 to 689 deaths per 100,000 case in over 65 year olds - Table 2.2). It should be noted that the overall number of deaths due to varicella have been falling over the past 5 years from 32 in 1996 to 18 in 2000.

Table 2.2. Age-specific epidemiology of varicella in England and Wales.

	Incidence			Consultation			Hospitalisation					Mortality			
	N[a]	%	Rate[b]	N[c]	%	Rate[b]	N[d]	%	Rate[b]	Hospitalisation[e] (per 100 case)	Length of Stay	N[f]	%	Rate[b]	Case-Fatality[g] (per 100,000 case)
0to4	344,662	51	10331	148,754	54	4,459	1,240	57	38.7	0.4	2.2	3	10	0.08	1
5to14	224,242	33	3384	73,482	27	1,109	287	13	4.6	0.1	3.0	1	5	0.02	1
15to44	95,730	14	435	49,306	18	224	560	26	2.7	0.6	4.0	9	35	0.04	9
45to64	4,945	1	42	2,642	1	22	64	3	0.6	1.4	5.8	4	14	0.03	73
65+	1,289	0	16	1,103	0	13	38	2	0.5	3.1	10.6	9	35	0.11	689
Overall	670,868	100	1291	275,286	100	522	2,189	100	4.5	0.3	3.0	25	100	0.05	4

a. Estimated average annual number of cases of varicella in England and Wales 1991-2000.
b. Rate per 100,000 person years.
c. Estimated average annual number of varicella cases seeking medical advice in England and Wales 1991-2000.
d. Observed number of varicella hospitalisations in England, HES 1995/96.
e. Hospitalisation rate divided by the estimated incidence rate.
f. Observed average number of varicella deaths in England and Wales, ONS 1991-2000.
g. Mortality rate divided by the estimated incidence rate.

Table 2.3. Underlying Conditions and outcome among individuals hospitalised with varicella and zoster, England 1995/96.

Underlying condition/outcome	Varicella		Zoster	
	N	Percent of Hospitalisations	N	Percent of Hospitalisations
Human immunodeficiency virus	5	0.2	11	0.5
All malignant neoplasms	81	3.7	154	7.2
All in situ neoplasms	0	0.0	0	0.0
Neoplasms of uncertain or unknown behaviour	0	0.0	0	0.0
Agranulocytosis	11	0.5	3	0.1
Certain disorders involving the immune mechanism	9	0.4	4	0.2
Cystic Fybrosis	10	0.5	5	0.2
Total	116		177	
At least one underlying condition	106	4.8	164	7.6
Death	9	0.4	52	2.4

2.3.3 EPIDEMIOLOGY OF ZOSTER

Incidence. The average annual incidence of zoster in England and Wales (1991-2000) by age group is shown in Table 2.4. The overall rate of zoster is 373 cases per 100,000 population year. The incidence increases with age from 200 cases per 100,000 in children (5-14 years) and young adults (15-44 years) to over 900 cases per 100,000 person-years in those aged 65 years or greater. These rates suggest that there are approximately 225,000 cases of zoster every year in England and Wales. Adults over 45 years account for over 70% of these cases. During the 1990's, the overall zoster consultation rate has been slowly increasing in England and Wales (Brisson *et al.*, 2001) due, in large part, to the ageing of the population.

Post Herpatic Neuralgia. The proportion of zoster cases which result in chronic pain (PHN) increases from close to zero in the under 30s to greater than 30% in those over the age of 80 years (Figure 2.3a). There is reasonably good agreement between estimates derived from the MSGP4 survey and Hope-Simpson's survey in general practice (Hope-Simpson, 1975), the somewhat higher rates observed in the MSGP4 survey probably being due to the code ICD-9 0531 including other neurological complications of zoster, not just PHN (for this reason Hope-Simpson's estimates were used in the economic analysis (Chapter 5)). Figure 2.3b shows the proportion of individuals (over the age of 50 years) reporting pain more than one month after rash onset. It appears that antiviral therapy during acute shingles hastens initial pain resolution in some individuals (Figure 2.3b) but has little impact on the rate at which individuals resolve pain if they have had PHN for a number of months, as noted previously (Dworkin and Portenoy, 1996). Most of the studies presented in Figure 2.3b do not have sufficiently long periods of follow-up to accurately estimate the mean duration of PHN. Applying the clearance rate in

individuals who have had pain for at least 6 months from Hope-Simpson's study to the others, it is possible to estimate the mean duration of pain from each of the groups of patients. This ranges from 0.93 years for patient groups receiving aciclovir therapy to 2.14 years for patients in the placebo arm of the famciclovir trial. In the economic analysis a base-case value of 1.40 years was taken, derived from Hope-Simpson's study (Hope-Simpson, 1975). This value was chosen as Hope-Simpson's study was the only one of sufficient duration to accurately quantify the mean length of PHN, and the rate of resolution of PHN in this study is similar to the placebo groups in the aciclovir trials and is intermediate between the other studies (Figure 2.3b). Furthermore, it is likely that a significant proportion of individuals with herpes zoster will not consult a physician early enough to receive antiviral therapy (i.e. within 3 days of rash onset)

Hospitalisation. Zoster hospitalisation statistics are presented in Table 2.4. The overall zoster hospitalisation rate was 4.4 per 100,000 person-years in England during 1995/96. Sixty-nine percent of hospitalisations were in adults older than 65 years. The proportion admitted to hospital per case of zoster is low in children under 4 years of age (1%) falls to 0.6% in 5 to 64 year olds then increases to more than 2% in those over 65 years (Table 2.4). The average number of inpatient days per zoster admission also increases with age from approximately 4 days in 0 to 4 year olds to 14 days in the elderly (over 65 years) (Table 2.4).

Of the 2148 hospitalisations due to zoster in England in 1995/96, 8% had at least one underlying condition (Table 2.3). The percent of hospitalisations with an underlying condition for 0-14, 15-64 and 65+ groups was 20%, 13% and 5% respectively. The most common condition was malignant neoplasm (87%), followed by HIV infection (6%). Overall, 2% of all admissions due to zoster resulted in death

in hospital (Table 2.3), 4% of which were in patients with an underlying condition.

Mortality. An average of 49 deaths a year were recorded with zoster as the underlying cause in England and Wales between 1993-2000 (0.09 deaths per 100,000 population-year-Table 2.4). Zoster is rarely recorded as the underlying cause of death in those under the age of 65 (Table 2.4). The estimated mortality rate of zoster in this age group is less than 0.014 deaths per 100,000 person-years. In the older age group (65+ years), the estimated mortality rate increases to 0.566 deaths per 100,000 person-years. The case-fatality ratio is also highly age dependant increasing from less than 1 death per 100,000 cases in children to more than 61 deaths per 100,000 cases in adults older than 65 years. The number of deaths due to zoster have been falling, from 64 deaths in 1993-1994 to 40 deaths in 1999-2000. The number of deaths attributed to zoster (49 deaths per year - Table 2.4) by the ONS is similar to the annual number of deaths in individuals hospitalised for zoster (52 deaths per year - Table 2.3).

Table 2.4. Age specific epidemiology of zoster in England and Wales.

	Incidence			Hospitalisation					Mortality			
	N[a]	%	Rate[b]	N[c]	%	Rate[b]	Hospitalisation[d] (per case)	Length of Stay	N[e]	%	Rate[b]	Case-Fatality[f] (per 100,000 case)
0to4	3081	1	92	40	2	1.2	1.1	3.5	0	0	0.000	0
5to14	14537	6	219	86	4	1.4	0.7	3.4	0	0	0.002	1
15to44	46760	21	212	222	10	1.1	0.5	4.6	1	2	0.003	2
45to64	83674	37	712	327	15	3.0	0.6	5.2	2	3	0.014	2
65+	76766	34	932	1473	69	19.1	2.3	13.5	47	95	0.566	61
Overall	224818	100	373	2148	100	4.4	1.2	10.8	49	100	0.094	25

a. Estimated average annual number of zoster cases in England and Wales 1991-2000.
b. Rate per 100,000 person years.
c. Observed number of varicella hospitalisations in England, HES 1995/96.
d. Hospitalisation rate divided by the estimated incidence rate.
e. Observed average number of zoster deaths in England and Wales, ONS 1993-2000.
f. Mortality rate divided by the estimated incidence rate.

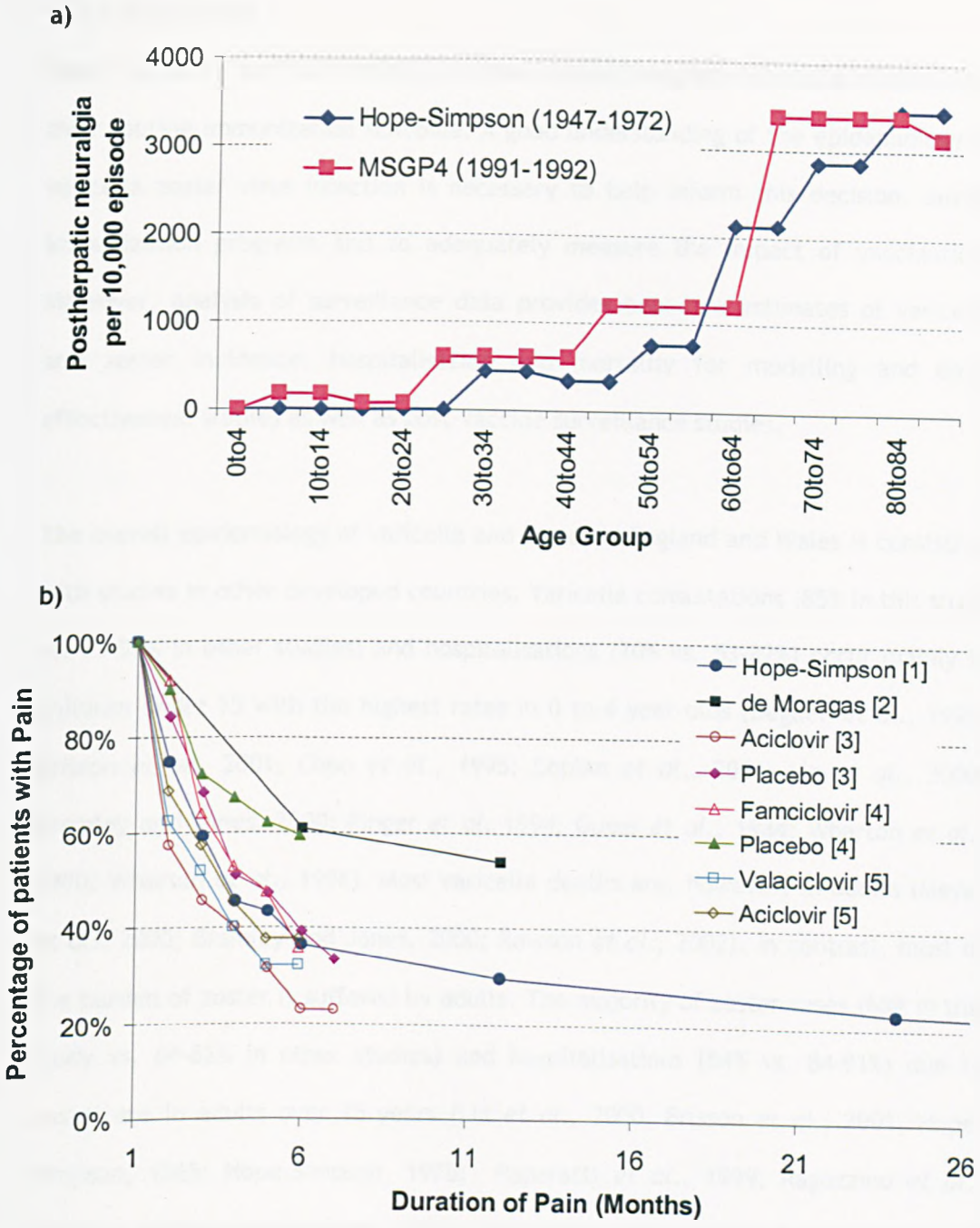


Figure 2.3. PHN: (a) the proportion of acute zoster episodes resulting in PHN and (b) the proportion of individuals who report being in pain following acute zoster. The studies from which the data were taken are given in the legend. Note that those patient groups that did not receive antiviral therapy have solid markers, in contrast to those who received treatment. [1] Hope-Simpson, 1975; [2] de Moragas and Kierland, 1975; [3] Wood *et al.*, 1996; [4] Dworkin *et al.*, 1998; [5] Wood *et al.*, 1998.

2.3.4 DISCUSSION

Many countries are now deciding if they should integrate varicella vaccine into their routine immunization schedule. A good understanding of the epidemiology of varicella zoster virus infection is necessary to help inform this decision, design immunization programs and to adequately measure the impact of vaccination. Moreover, analysis of surveillance data provides base-line estimates of varicella and zoster incidence, hospitalisation and mortality for modelling and cost-effectiveness studies as well as post-vaccine surveillance studies.

The overall epidemiology of varicella and zoster in England and Wales is consistent with studies in other developed countries. Varicella consultations (85% in this study vs. 79-92% in other studies) and hospitalisations (70% vs. 53-82%) occur mainly in children under 15 with the highest rates in 0 to 4 year olds (Deguen *et al.*, 1998; Brisson *et al.*, 2001; Choo *et al.*, 1995; Coplan *et al.*, 2001; Lin *et al.*, 2000; Bramley and Jones, 2000; Finger *et al.* 1994; Guess *et al.*, 1984; Wharton *et al.*, 1990; Wharton *et al.*, 1996). Most varicella deaths are, however, in adults (Meyer *et al.*, 2000; Bramley and Jones, 2000; Rawson *et al.*, 2002). In contrast, most of the burden of zoster is suffered by adults. The majority of zoster cases (68% in this study vs. 64-82% in other studies) and hospitalisations (84% vs. 84-91%) due to zoster are in adults over 45 years (Lin *et al.*, 2000, Brisson *et al.*, 2001, Hope-Simpson, 1965; Hope-Simpson, 1975; Paparatti *et al.*, 1999; Ragozzino *et al.*, 1982; de Moragas and Kierland, 1957). The highest rate of zoster is in 65+ year olds (Wharton *et al.*, 1996; Ragozzino *et al.*, 1982; Brisson *et al.*, 2001; Hope-Simpson, 1965; Hope-Simpson, 1975) and seems to be increasing in the elderly population (Brisson *et al.*, 2001). Although the age-specific distribution is similar, the consultation and hospitalisation rates presented here are lower than France but higher than Canada and the United States (Brisson *et al.*, 2001; Deguen *et al.*, 1998; Choo *et al.*, 1995; Lin *et al.*, 2000; Coplan *et al.*, 2001, Wharton *et al.*, 1990;

Wharton *et al.*, 1996; Guess *et al.*, 1984). These dissimilarities are likely to be mainly due to the differences in the structure of the various health systems

The shape of the force of infection estimated England and Wales (increasing in the pre-school years, peaking during primary school and declining thereafter) is consistent with other countries (Brisson *et al.*, 2001; Halloran *et al.*, 1994) and with that of other childhood infections such as measles, mumps and rubella (Edmunds *et al.*, 2001). This suggests that preschool and school-age mixing is an important determinant of varicella transmission as with other childhood infections such as measles and rubella.

The proportion of varicella and zoster hospitalisation with at least one underlying cause is different in England than studies in other countries. Lin *et al.* (2000) report that, in the US, 17% and 31% of hospitalisations due to varicella and zoster respectively have an underlying cause compared to 5% and 8% for England. Gil *et al.* (2001) report that, in Spain, 8% of varicella hospitalisations have underlying conditions. The higher prevalence of HIV in the United-States and Spain may account for much of these differences. Excluding HIV, the proportion of varicella hospitalisation with an underlying condition is 5%, 8% and 5% in England, the United States and Spain. However, HIV does not explain discrepancies in the proportion of zoster hospitalisations with an underlying condition between the US and England. Results suggest that the majority of varicella hospitalisations (95%) and deaths (approximately 85%) are among otherwise healthy individuals and thus could be prevented by mass vaccination.

The epidemiology of varicella and zoster has been changing in England and Wales over the past two decades (Fairley and Miller, 1996; Brisson *et al.*, 2001; Ross and Fleming, 2000). During the 1980's, there was a dramatic increase in varicella

consultation rates in children less than 5 years and in adults. Because varicella mortality and morbidity increases steeply with age, the rise in adult cases was a source of concern (Fairley and Miller, 1996). However, during the 1990's, varicella consultations have halved in adults (Figure 2.2). The fall in adult varicella cases is broadly reflected in the gradual decrease in varicella deaths in adults during the past decade. The epidemiology of zoster is also changing with the steady increase in overall incidence and the fall in mortality over the 1990s. Furthermore, hospitalisation results are sensitive to the algorithm used to identify admissions due to varicella and zoster. If mention of varicella or zoster in any of the 7 diagnostic positions is used instead of the first position then hospitalisation rates are increased by approximately 30% and 100% for varicella and zoster respectively. The average length of stay is also increased by approximately 30% for both varicella and zoster. The proportion of hospitalisation with an underlying condition increases from 5% to 6% for varicella and 8% to 13% for zoster. Therefore, the figures presented in Tables 2.2-2.4 should be used with caution as base-line estimates.

Hospital admission and mortality data from England show a steep rise in varicella and zoster hospitalisations per case, average number of inpatient days and mortality with age. Since, currently, varicella occurs mainly in children the increase in severity with age does not lead to a high number of varicella related deaths or hospital days. However, mass immunization results in an increase in the average age at infection in those who are not immunized. Therefore, there is a danger that mass immunization can lead to an increase in hospitalisation and death. Such perverse outcomes from mass infant vaccination has been observed for rubella in Greece (Panagiotopoulos *et al.*, 1999).

Zoster is considered to be much more severe than varicella (Miller *et al.*, 1993). However, the age-specific severity, as measured by the age-specific proportion

hospitalised per case and inpatient days, are relatively similar between the two diseases (Tables 2.2 and 2.4), this statement ignores QALYs, which we measure in Chapter 4. However, the overall burden of disease is considerably higher for zoster because over 85% of cases occur in adults (less than 15% for varicella). The total annual number of inpatient days and deaths were 4 (23,000 vs. 6,500 days) and 2 (49 vs. 24 deaths) times higher for zoster than varicella respectively. Zoster may occur more frequently in adults who have not been boosted by varicella contacts (exogenous boosting) (Hope-Simpson, 1965). A reduction of varicella incidence after mass immunization could lead to an increase in the incidence of zoster. This could have a major impact on the overall effectiveness and cost-effectiveness of varicella vaccination. In the next section we investigate whether exposure to VZV reduces the rate of reactivation (zoster incidence).

2.4 RELATIONSHIP BETWEEN VARICELLA AND ZOSTER INCIDENCE

2.4.1 METHODS

2.4.1.1 Data

Data were taken from the MSGP4 dataset. Details of all consultations were recorded during the study year, along with socio-economic information on the patients (McCormick *et al.*, 1995). For children under 16 years, all first episodes of varicella and zoster were included in the analysis. For adults, first episodes of varicella and zoster were included in the analysis if data were available on whether the case currently lived with a child <16 years of age or not (82% of cases). To estimate the incidence of varicella, consultation rates were adjusted (using previously estimated age-specific rates (see earlier)) because not all children with varicella consult a general practitioner. All zoster cases are assumed to visit a general practitioner.

2.4.1.2 Statistical Analysis

We analysed data stratified by 1-year age groups, sex, ethnicity, social class and presence of a child in the household using a Poisson regression model with an adjustment for person-years observed to test whether the incidence of disease was different in adults living with children. The model was used to estimate the overall incidence ratio and to test whether this was age dependent.

The poisson regression can be described as follows. Let y_i represent the number of cases of zoster. We assume that y_i is represented by the following function:

$$y=x\beta + \varepsilon \qquad (3)$$

where, **x** is the vector of variables, β is the vector of regression coefficients and ε is the error term. The model assumes that ε ~ Poisson (λ). The model log likelihood, $l_{a,g,e,s,i}$, stratified by 1-year age groups (a), sex (g), ethnicity (e), social class (s) and presence of a child in the household (i) was obtained from the following function:

$$l_{a,g,e,s,i} = n_{a,g,e,s,i} log(\lambda_{a,g,e,s,i}) - \lambda_{a,g,e,s,i} \qquad (4)$$

where, n is the observed number of cases of zoster and λ is the expected incidence predicted by the model (equation 3). The analysis was performed in GLIM (Francis et al., 1994). The command function was **glm** where the y-variable was the count for a cell ($yvar count) with poisson error ($error p) and log-link ($link l) with an offset based on the logarithm of person-ears at risk ($offset log(pyears)).

2.4.1.3 Model Structure

The model represents the natural history of varicella and zoster in a population stratified according to age (a) and presence of at least one child in the household (i=C (children), N (no children)) (see Figure 2.4 for flow diagram). The population is divided into 4 mutually exclusive epidemiological groups: the proportion susceptible to varicella, denoted $S_i(a,t)$; immune to varicella and temporarily immune to zoster, $R_i(a,t)$; susceptible to zoster, $Y_i(a,t)$; and recovered from zoster, $Z_i(a,t)$. For simplicity repeat cases of zoster were not modelled since recurrence is thought to be low and is not well characterized in the literature. The rates, with respect to time and age, at which individuals flow between epidemiological states, are described by the following set of partial differential equations:

$$\left.\begin{aligned}
\frac{\partial S_i(a,t)}{\partial t}+\frac{\partial S_i(a,t)}{\partial a} &= \rho_{i'}(a)S_{i'}(a,t)-\left(\lambda_i(a,t)+\rho_i(a)+\mu(a)\right)S_i(a,t)\\
\frac{\partial R_i(a,t)}{\partial t}+\frac{\partial R_i(a,t)}{\partial a} &= \lambda_i(a,t)\left(S_i(a,t)+Y_i(a,t)\right)+\rho_{i'}(a)R_{i'}(a,t)-\left(\sigma+\rho_i(a)+\mu(a)\right)R_i(a,t)\\
\frac{\partial Y_i(a,t)}{\partial t}+\frac{\partial Y_i(a,t)}{\partial a} &= \sigma R_i(a,t)+\rho_{i'}(a)Y_{i'}(a,t)-\left(\delta(a)+\lambda_i(a,t)+\rho_i(a)+\mu(a)\right)Y_i(a,t)\\
\frac{\partial Z_i(a,t)}{\partial t}+\frac{\partial Z_i(a,t)}{\partial a} &= \delta(a)Y_i(a,t)+\rho_{i'}(a)Z_{i'}(a,t)-\left(\rho_{i'}+\mu(a)\right)Z_i(a,t)
\end{aligned}\right\} \quad (5)$$

Here, subscripts i and i' represent opposite classes (i.e. if i=C then i'=N), $\mu(a)$ is the death rate (Office for National Statistics, 2000), $\rho_i(a)$ are the rates at which individuals move between living with and without children, $\lambda_i(a,t)$ is the force of infection (per capita rate at which susceptibles to varicella are infected and susceptibles to zoster are boosted), σ is the rate of loss of immunity to zoster, $\delta(a)$ is the rate of reactivation of VZV in those who are susceptible to zoster.

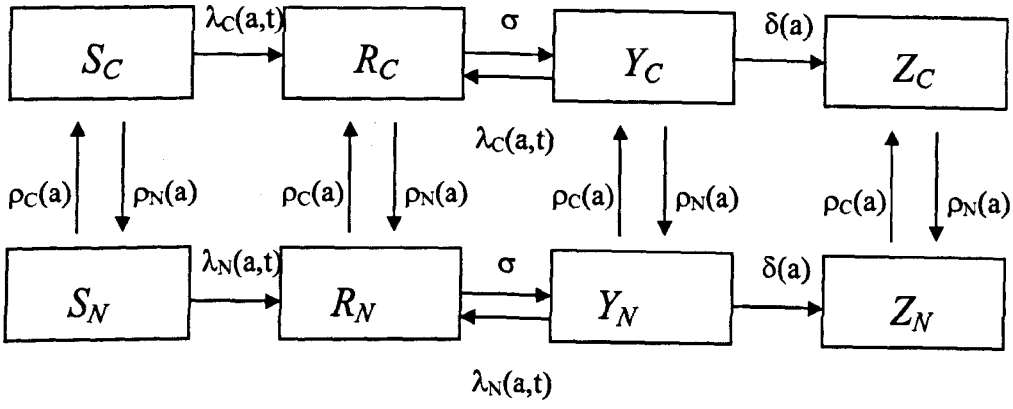


Figure 2.4. Flow diagram of varicella and zoster. See text for parameter definitions.

2.4.1.4 Parameter Estimation

We estimated the rate at which individuals flow between living with and without children, $\rho_i(a)$, by modelling the age-specific proportion of adults with at least one child in their household. The population can be broadly represented by 6 mutually exclusive groups: the proportion who live with "siblings" aged less than 16 years, denoted *B(a)*; who have left home and are not living with children, *M(a)*; who are living with "their" children, *K(a)*; whose children have left home, *L(a)*; who are living with "their" grand-children, *G(a)* and; who have stopped living with their "grand-children", *H(a)* (Figure 2.5). Hence groups *B*, *K* and *G* live with children, and groups *M*, *L* and *H* do not.

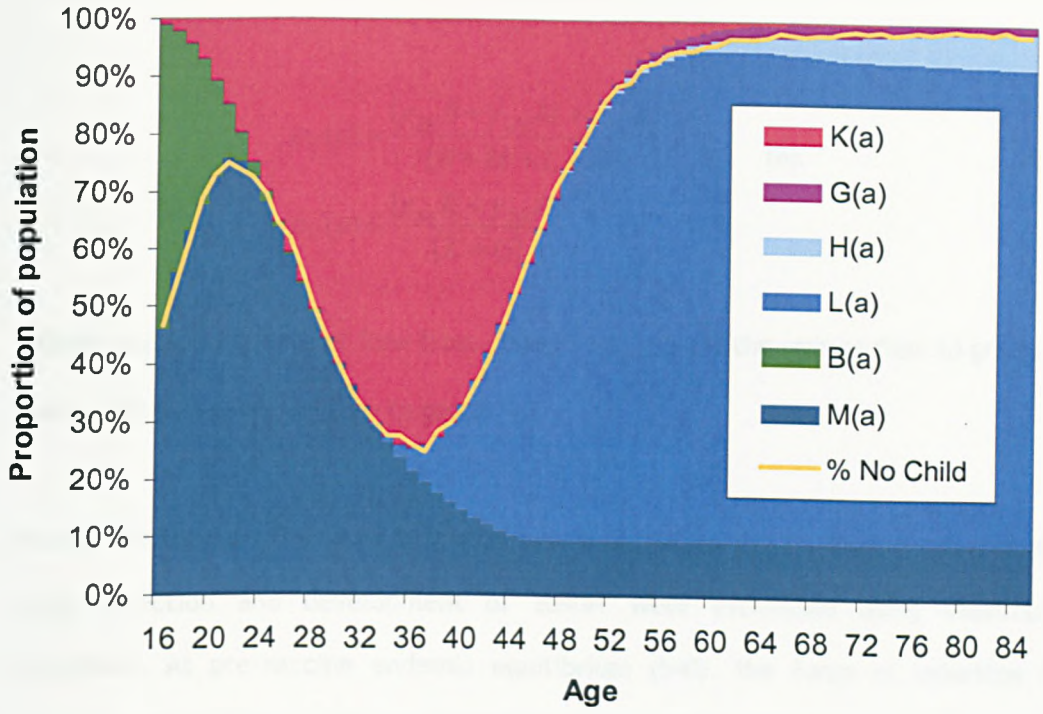


Figure 2.5. Proportion of adults who live with and without children. The solid line (%No Child) represents the observed age-specific proportion of adults not living with children. The width of each colour band represents the estimated age-specific proportion of adults in the 6 groups described by the model.

The rate of flow from *B(a)* and *M(a)* to *K(a)* was estimated from observed data on the age that adults have their first child . Remaining rates were estimated by fitting the model to the age-specific proportion of adults living with children in England and Wales as reported in MSGP4 survey (Figure 2.5). The population was split into 2 exposure groups, high exposure C (*K+G*) and low exposure N (*B+M+L+H*). We included adults who live with siblings (*B*) into exposure group N because their exposure is likely to be to previously infected older children. The overall age-specific rates at which individuals flow between the two groups are given by:

$$\rho_C(a)=\frac{(\gamma_{BK}B+\gamma_{MK}M+\gamma_{LG}L)}{(B+M+L+H)} \qquad (6)$$
$$\rho_N(a)=\frac{(\gamma_{KL}K+\gamma_{GH}G)}{(K+G)}$$

Where, $\gamma_{IJ}(a)$ is the rate of flow from class I to J, $\rho_C(a)$ is the rate of flow to group C and, $\rho_N(a)$ is the rate of flow to group N.

Having determined the flows between exposure groups the parameters describing rates infection and development of zoster were estimated using maximum likelihood. At pre-vaccine endemic equilibrium (t=0), the force of infection in children less than 16 years, $\lambda_i(a<16,0)$, is assumed to have a Gamma functional form:

$$\lambda_i(a,0)=\theta[(a+\kappa)^{\alpha-1}e^{-a/\beta}/\Gamma(\alpha)\beta^{\alpha}]. \qquad (7)$$

The force of infection in adults, $\lambda_i(a\geq16,0)$, was assumed to depend only on whether they live with or without children (i). The age-specific rate of reactivation of VZV, $\delta(a)$, was assumed to possess the following functional form: $\omega e^{-\varphi a}+\pi a^{\eta}$.

The model log likelihood, $l_{i,d}(a)$, stratified by presence of at least one child in the household (i), disease (d=varicella or zoster) and age (a), was obtained from the binomial likelihood:

$$l_{i,d}(a)=x_{i,d}(a)\ln[m_{i,d}(a)]+(n_i(a)-x_{i,d}(a))\ln[1-m_{i,d}(a)] \qquad (8)$$

where, $n_i(a)$ is the number of person-years in the study, $x_{i,d}(a)$ is the observed number of cases of disease (d) in the MSGP4 database and $m_{i,d}(a)$ is the incidence predicted by the model (equation 5). The predicted incidence in adults living with

children includes a contribution from group *B* as well as the higher exposure groups *K* and *G*. The full-model likelihood is the sum, over a, i and d, of the specific model log likelihoods. Estimates for parameters θ, κ, α and β (which are parameters of the gamma functional form describing $\lambda_I(a<16,0)$ (equation 7)), $\lambda_C(a\geq16,0)$, $\lambda_N(a\geq16,0)$, ω, φ, π and η (which describe the functional form of $\delta(a)$) and σ, were obtained by maximizing the full-model log likelihood. In total these 11 parameters were estimated from 364 data points.

2.4.2 ROLE OF ZOSTER ON VARICELLA

The force of varicella infection due to zoster has been estimated to be 1% of the total force of varicella infection. This estimate was based on data collected by the Immunization Monitoring Program - Active (IMPACT), a Canadian paediatric hospital-based surveillance network. Of 1119 children admitted for chickenpox or a related complication, a source of infection was identified for 576 and of these only 5 followed exposure to Herpes Zoster whereas the rest followed exposure to chickenpox (unpublished data from Dr. Barbara Law). An additional study by Ferguson *et al.* (1996) estimated zoster to contribute to 7% of varicella cases.

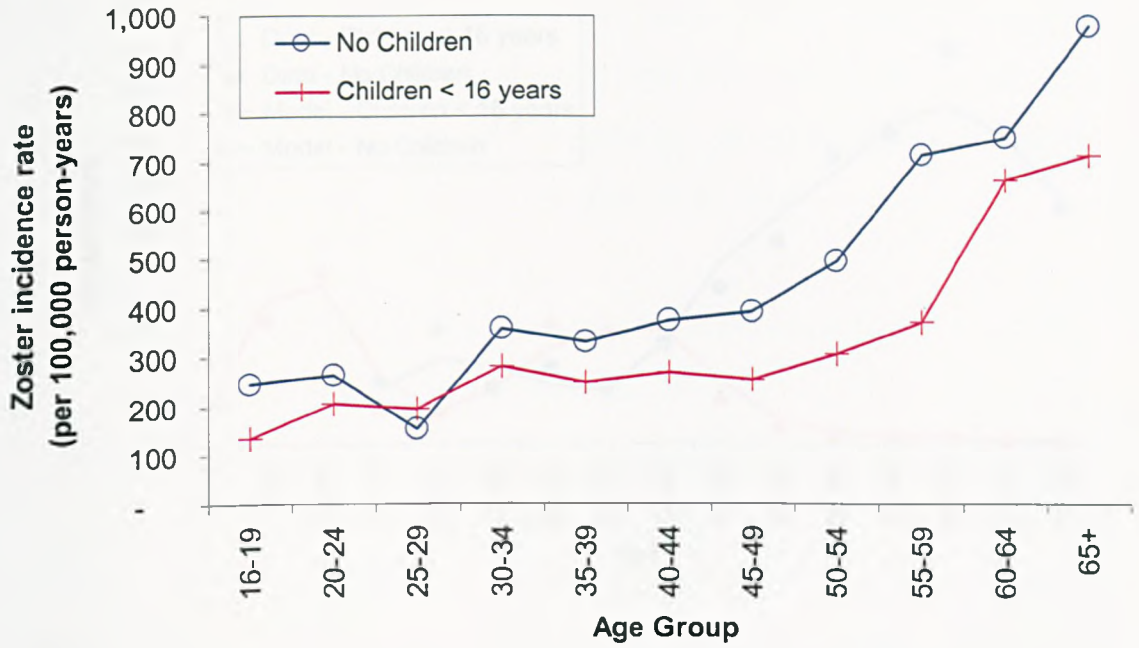
2.4.3 ROLE OF VARICELLA ON ZOSTER

In Figure 2.6a we present the age-specific annual incidence rate of zoster in England and Wales by household exposure to children (Figure 2.6a). Living with children was found to be significantly protective against zoster ($P < 0.001$) with an incidence ratio of 0.75 (95% CI 0.63-0.89). There was no evidence of confounding by sex, ethnicity or socio-economic class. Furthermore, the protective effect of living with children did not differ significantly by age (P for interaction 0.79). It is worth noting that although the protective effect of living with children is highly significant it is likely to be underestimated by this incidence ratio, as many adults not currently living with children may have done so in the recent past.

To examine the mechanisms which lead to VZV reactivation, we first examined whether adults living with children were significantly more exposed to varicella. Young adults living with children have a higher crude varicella incidence rate than those who do not (Age Range=20 to 40 years, Incidence Ratio=1.29, 95% CI 1.08-1.55, $P < 0.005$), but this difference is not evident in older adults (Figure 2.6b). This is the pattern expected if all adults who live with children have greater exposure to varicella, because, at older ages, the proportion of adults susceptible to infection is lower among those who live with children than those who do not, due to their history of higher exposure to infection.

To further investigate this relationship we developed an age-structured mathematical model of the natural history of VZV that allows exposure to varicella to boost against the development of Herpes-zoster (see earlier). The quality of fit of the model to the data was good (Figure 2.7). Under the 'best fit' model, the force of infection (per capita rate at which susceptibles become infected) in adults with and without children in the household is 0.15 and 0.07 per year respectively. Exposure to varicella is thus estimated to be twice as high in adults living with children compared with those who do not. Furthermore, exposure to varicella is estimated to boost cell-mediated immunity for an average of 20 years (95% CI 7-41 years). The maximum likelihood estimates of the other parameters are: for $a<16$ years, $\lambda_i(a,0)=\theta[(a+\kappa)^{\alpha-1}e^{-\alpha/\beta}/\Gamma(\alpha)\beta^{\alpha}]$, where κ=2.86, θ=2.00, α=6.80, β=1.38; and; $\delta(a)=\omega e^{-\varphi a}+\pi a^{\eta}$, where ω=0.11, φ=0.17, π=1.06E-05, η=1.91.

a)



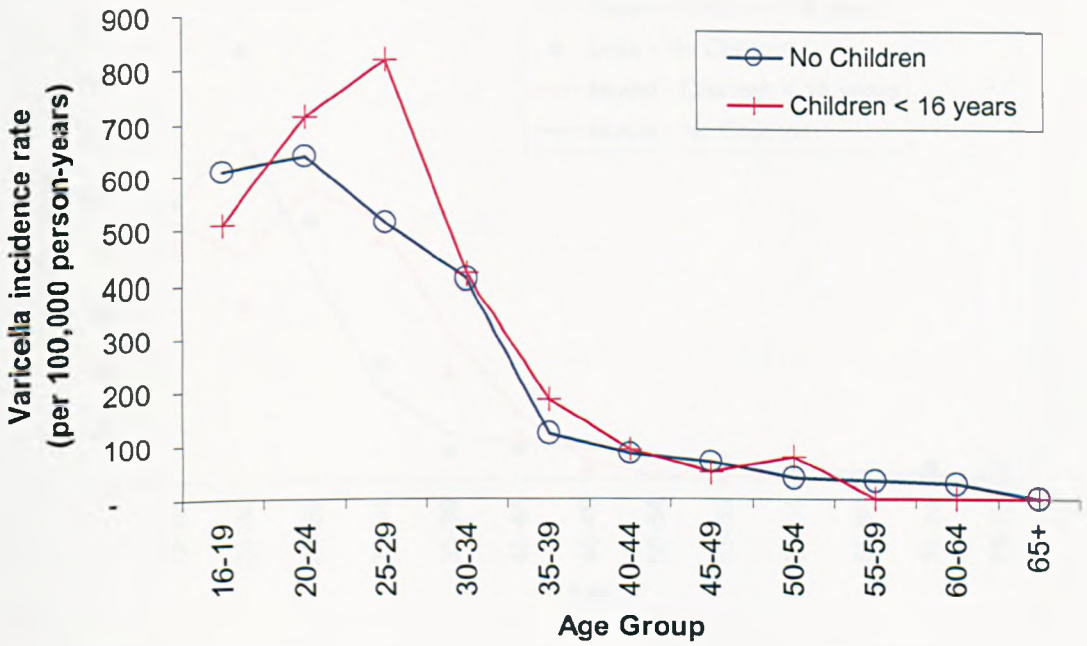
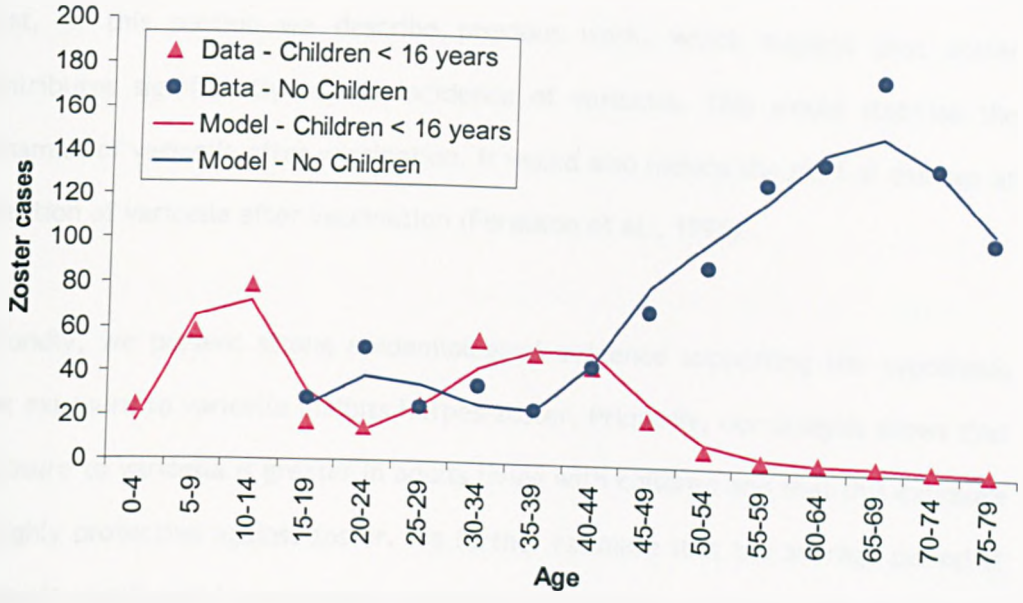


Figure 2.6. Varicella and zoster incidence rate. Age-specific incidence of (a) zoster and (b) varicella per 100,000 person-years in England and Wales (1991/92) for adults with and without children in their household.

a)



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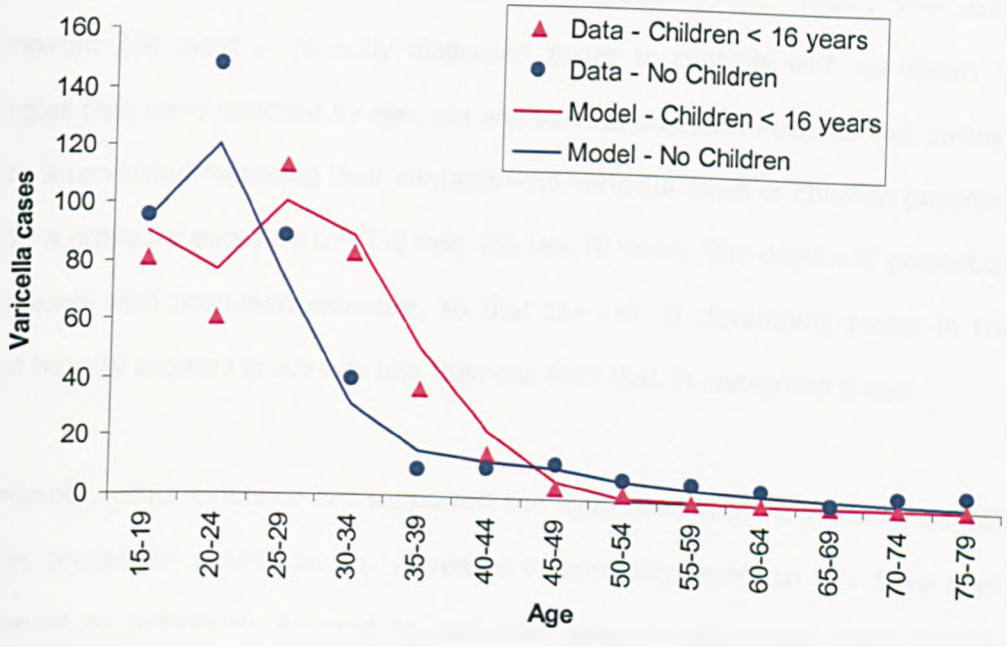


Figure 2.7: Best-Fit model. The number of cases of (a) zoster and (b) varicella observed in MSGP4 and predicted by the best-fit model stratified by 5-year age group and household exposure to children (one year age groups were actually used in the analysis).

2.4.4 DISCUSSION

First, in this section we describe previous work, which suggest that zoster contributes significantly to the incidence of varicella. This would stabilise the dynamics of varicella after vaccination. It would also reduce the shift of the age at infection of varicella after vaccination (Ferguson et al., 1996).

Secondly, we present strong epidemiological evidence supporting the hypothesis that exposure to varicella inhibits Herpes-zoster. Primarily, our analysis shows that exposure to varicella is greater in adults living with children and that this exposure is highly protective against zoster. We further estimate that the average period of immunity conferred by exposure to varicella is 20 years. A recent study by Thomas *et al.* (2002) produced similar conclusion (Edmunds *et al.*, 2002). The study compared 244 cases of recently diagnosed zoster to controls with no history of shingles that were matched by age, sex and general practice. Patients and controls were interviewed regarding their contacts with varicella cases or children (assumed to be a proxy for exposure to VZV) over the last 10 years. The degree of protection increased with presumed exposure, so that the risk of developing zoster in the most heavily exposed group was less than one fifth that in unexposed group.

Previously, other evidence has supported the hypothesis that re-exposure to VZV offers protection against zoster. Increases in immunity levels to VZV have been observed in individuals exposed to varicella cases or vaccinated with the live attenuated vaccine (Arvin *et al.*, 1983; Sperber *et al.*, 1992; Levin *et al.*, 1998). A study conducted in Japan found that the incidence rate of zoster in pediatricians and family practitioners was half to 1/8 that of the general population (Terada *et al.*, 1995). Further studies have reported a negative correlation, although not statistically significant, between varicella and zoster incidence (Hope Simpson, 1965; Brisson *et al.* 2001; Ikada et al. 1973). Finally, a small study among

vaccinated leukemic children showed that both household exposure to varicella and receipt of more than 1 dose of vaccine were highly protective against zoster ($P < 0.01$) (Gershon *et al.*, 1996). Currently, a large clinical trial is underway to determine whether varicella vaccination can protect against zoster in the elderly through boosting cell-mediated immunity to VZV (Oxman, 1995). If vaccination does prevent or inhibit zoster in this clinical trial, then it is likely that exposure to the wild virus would perform a similar function.

Our findings have major implications for varicella vaccination: by reducing varicella cases (and thus the opportunity of exposure to VZV), mass infant immunization could increase the incidence of zoster in individuals who have not been vaccinated (Gershon *et al.*, 1996, Plotkin, 1994).

2.5 SUMMARY

In this chapter we provide a comprehensive picture of the pre-vaccine epidemiology of VZV, which will provide base-line data for the economic analysis of varicella vaccination and aid in the design of a realistic model of VZV transmission. Two results are of importance for varicella vaccination:

1. Varicella related morbidity and mortality increases significantly with age. Mass immunization results in an increase in the average age at infection in those who are not immunized. The worry is that enough adults with severe varicella will be infected to counterbalance the benefit in reduction in children. Because severity of varicella increases steeply with age, this danger is a legitimate one.
2. Exposure to varicella protects against zoster & the overall burden of disease is significantly higher for zoster. We show that exposure to varicella reduces the risk of zoster by boosting specific immunity to the virus (exogenous boosting). These findings could have major implications for varicella vaccination: by

reducing varicella cases (and thus the opportunity of exposure to VZV), mass immunisation could increase the incidence of zoster. Due to the higher severity of zoster, a small increase in zoster incidence could counterbalance the reduction in varicella morbidity compromising the effectiveness and cost-effectiveness of varicella vaccination.

Both dangers of varicella vaccination are classic examples of externalities, which must be taken into account when assessing the overall benefit (detriment) of mass varicella vaccination. To adequately measure these externalities mathematical modelling is necessary. In Chapter 3 we investigate these concerns.

The research in this chapter has been published in full (or in part) in the following peer reviewed articles:

- **Brisson M**, Edmunds WJ. Epidemiology of Varicella-Zoster virus in England and Wales. J Med Virol 2003;70 Suppl 1:S9-14.
- **Brisson M**, Gay NJ, Edmunds WJ, Andrews NJ. Exposure to Varicella Boosts Immunity to Herpes-zoster: Implications for mass vaccination against chickenpox. Vaccine 2002; 20: 2500-2507.
- **Brisson M**, Edmunds WJ, Law B, et al. Epidemiology of varicella and zoster in Canada and the United-Kingdom. Epidemiol Infect 2001; 127:305-314.
- Edmunds WJ, **Brisson M**, Rose JD. The epidemiology of herpes zoster and potential cost-effectiveness of vaccination in England and Wales. Vaccine 2001;19: 3076-90.

Chapter 3
Modelling the Impact of Vaccination Programmes

3.0 INTRODUCTION

The aims of Chapter 3 are to:

1) Predict the impact of varicella vaccination from the individual and population perspectives,
2) Illustrate the effect of herd-immunity on the dynamics of infectious disease using varicella vaccination as an example, and
3) Assess the importance of herd-immunity externalities when estimating the overall of benefit vaccination.

First, in this chapter, we model varicella vaccine efficacy. That is, we estimate the direct effect of varicella vaccination on the vaccinee, which we call the individual perspective. Second, we estimate the overall impact of varicella vaccination using a dynamic mathematical model taking into account herd-immunity externalities, which we call the population perspective. We investigate the dangers of varicella vaccination: 1) upward shift the age at infection and 2) increase in zoster incidence. In doing so, we illustrate the different dynamical effects of vaccination and present which parameters are most influential on model results. Thirdly, we compare results from the dynamic model with those of a static

model, which is the most common model used in economic evaluations of infectious disease. This will illustrate how herd-immunity externalities influence the benefit of vaccination.

3.1 MODELLING VACCINE EFFICACY

3.1.0 BACKGROUND

In clinical trials vaccine efficacy is measured as the relative risk of infection in the vaccinated group compared with unvaccinated individuals (Halloran *et al.*, 1997). In general, vaccine efficacy is comprised of three components (McLean and Blower, 1993): the proportion of individuals who acquire protection; the degree to which they are protected; and the duration of that protection. It can be difficult to estimate the contribution of each effect to the overall vaccine efficacy measured in controlled trials, because these often have a short time span relative to the period over which the vaccine is intended to offer protection (often life-time). Clearly, however, it is critical to have good estimates of these parameters to allow accurate long-term predictions of the impact of vaccination programs to be made.

Halloran *et al.* (1994) attempted to estimate vaccine efficacy parameters for varicella zoster (VZV) vaccine by reviewing the literature available at the time and employing a Delphi process. These parameter values have been used in subsequent studies (Coudeville *et al.*, 1999; Lieu *et al.*, 1994). Since many countries are in the process of evaluating the cost-effectiveness of varicella vaccination it is now timely to re-examine these estimates and amend them if necessary.

In this section, we re-evaluate Halloran *et al.*'s (1994) estimates in the light of new data. Additionally, Halloran *et al.* (1994) used the standard approach of

estimating each parameter separately. This approach can result in a poor fit to the data when all the parameters are combined even though each individual estimate seems plausible. Our approach differs in that we estimate the parameters simultaneously from the observed breakthrough rates (varicella infection in seroconverted vaccinees (Halloran *et al.*, 1994) over time.

3.1.1 METHODS

3.1.1.1 Selection of studies

Most of the published studies of vaccine immunogenicity and efficacy have specifically involved the Oka/Merck product (Varivax®, Merck Research Laboratories). Published data using the other manufacturer's vaccines were too few to include in the analysis.

The pre-licensure studies of Varivax® involved four different lots prepared in 1982, 1984, 1987 and 1991 (Arbeter *et al.*, 1982; Arbeter *et al.*, 1984; Weibel *et al.*, 1984; Weibel *et al.*, 1985; Arbeter *et al.*, 1986; Johnson *et al.*, 1989; White *et al.*, 1991; Kuter *et al.*, 1991; Clements *et al.*, 1995; Johnson *et al.*, 1997). These lots differed in the relative amounts of both live virus and non-viable viral antigen as well as method of preparation. To avoid bias only studies in which active surveillance was carried out over time were used to analyse the base-case and worst-case scenarios. These included studies done with the 1987 and 1991 lots. For the base-case scenario efficacy data for the 1991 lot were chosen since this study vaccine most closely resembles the currently licensed product. Based on previously unpublished data provided by Merck Research Laboratories, a total of 1164 children were randomised to receive one of 5 vaccine preparations containing from 2900 to 9000 pfus. The mean age at vaccination of these children was 4.4 years and 65% of vaccinees were followed for five years post vaccination. For the worst-case scenario data from studies using the 1987 lot (Krause and

Klinman, 1995) were selected since this vaccine had much higher breakthrough rates (modified varicella infection in vaccinees) than that observed in any other published clinical trial using the Oka/Merck vaccine. These studies included a total of 4142 children who were randomised to receive one of five vaccine preparations varying in potency from 1000 to 1625 pfu's per dose. The mean age of vaccinees was 4.0 years.

For the best-case scenario, data from the randomised placebo-controlled clinical trial of the 1982 lot (Krause and Klinman, 1995) containing 17,430 pfu/dose were used. Unfortunately only a single year of active follow-up data was available for this study and thus it was necessary to include data gathered by a combination of active and passive follow-up. The likely underestimation of the number of varicella-like infections occurring after immunisation due to passive reporting was considered acceptable for the best-case analysis since the objective was to estimate the parameters of the best possible vaccine.

3.1.1.2 Model

A mathematical model, similar to Halloran *et al.*'s (1994), was used to simulate the expected number of breakthrough cases through time in a vaccine efficacy trial (Figure 3.1, see Appendix 1 for formal mathematical structure). Since studies did not include individuals who did not seroconvert, we consider only individuals who responded to vaccination (Krause and Klinman, 1995). There are three distinct classes that represent the different states of protection, which we term "vaccinated protected", "vaccinated susceptible" and "immune" (Halloran *et al.*, 1994). Of vaccine responders a proportion T pass into the "vaccinated protected" class, and $1-T$ into the "vaccinated susceptible" class. These two classes differ in their response to exposure to infection, which occurs at a rate λ (the force of varicella infection, assumed to be 0.2 per year, which is the rounded average

value of Halloran et al's estimation for age groups 5 to 9 and 10 to 14 (Halloran *et al.*, 1994)). Those in the vaccinated protected class do not develop disease however a proportion *k* are boosted into the immune class. A proportion *b* of those in the vaccinated susceptible class develop immunity after a breakthrough infection (*b* represents their susceptibility relative to unvaccinated susceptible individuals). There is assumed to be no sub-clinical boosting of vaccinated susceptibles to the vaccinated immune class (the only substantial difference between our model and that of Halloran et al. (1994)). We suppose that individuals who are vaccinated susceptible have lost their immune protection to a degree that effective contact with wild type virus results in breakthrough infection instead of sub-clinical boosting. Such an assumption has no significant effect on the value of the other parameter estimates. Individuals in the vaccinated protected class pass into the vaccinated susceptible class at the waning rate *W*; individuals in the immune class have permanent immunity.

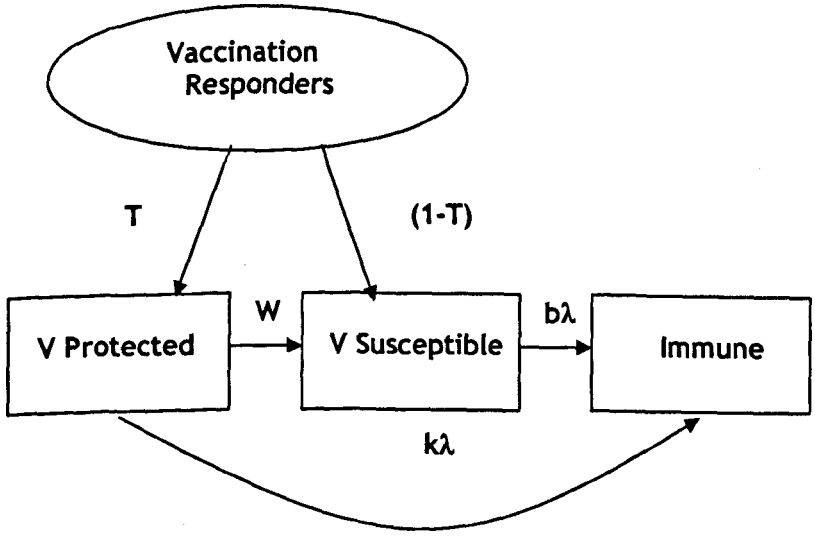


Figure 3.1. Flow diagram of the natural history of varicella among vaccinated individuals.

The efficacy parameters were estimated by comparing the expected annual incidence of breakthrough infections with that observed in the vaccinated arm of clinical trials. The parameter values, which minimised the weighted least square,

were chosen (weights were proportional to the number of individuals in the study at each time point (t)):

$$\frac{\sum_t n_t (y_t - \hat{y}_t)^2}{\sum_t n_t} \qquad (1)$$

where, t is time, n_t is number of individuals at time t, y_t and $\hat{y}_t$ are the observed and modelled number of breakthrough cases respectively.

To reduce the number of parameters to be estimated *k* was set to 50% for the worst-case scenario and 100% for the best-case; for the base-case *k* was allowed to vary between these values. The only constraints on the remaining parameters were that *T* and *b* were allowed to vary between 0% and 100% and that *W* was positive.

3.1.2 VACCINE EFFICACY

Figure 3.2 shows the data and the best fit model for the best, worst and base-cases (best fit parameter values are given in Table 3.1). For comparative purposes the annual proportion of the cohort with breakthrough infections as predicted using Halloran *et al.*'s (1994) base-case and worst-case ("low-efficacy") parameter combinations (see Table 3.1) are also shown in Figure 3.2. It is clear that none of Halloran *et al.*'s (1994) parameter sets fit the data: even the least optimistic vaccine assumptions give far fewer breakthrough cases than are observed. In order to fit the observed data it was necessary to adopt high values for *W*, *T*, *k* and *b* (Table 3.1). That is, although a number of parameter sets gave similar overall fits they all share the same features: vaccination seems to result in a high proportion of individuals who are initially totally protected, but these individuals lose this protection relatively rapidly (approximately 3% in the base-case lose this

protection each year) passing into a class in which if they are exposed they have a high probability of developing a breakthrough infection. Furthermore, a high proportion of individuals who are vaccinated protected seem to become immune through contact with varicella (91% in the base-case) without developing a breakthrough infection.

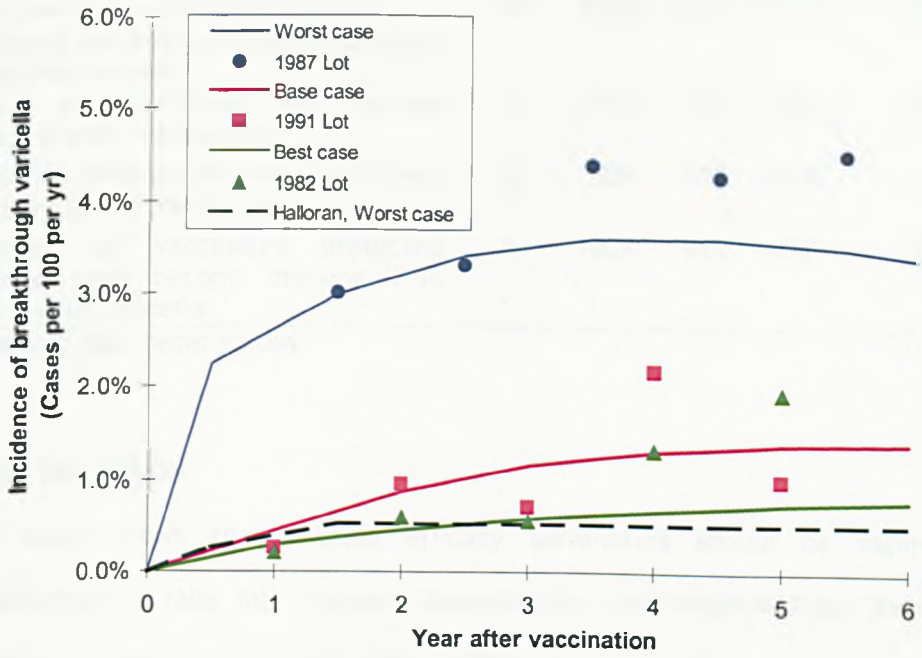


Figure 3.2. Estimated vs observed annual breakthrough percentage as a function of time after vaccination. The number of children in the study for each time point is: 1151, 1148, 974, 835 and 796 for Lot 1991 (In house data provided by Merck Research Laboratories); 2994, 2415, 911, 538, 376 for Lot 1987 (Krause and Klinman, 1995) and; 487 (401 active), 543, 534, 528 and 518 for Lot 1982 (Krause and Klinman, 1995).

Better fits can be produced by stratifying the model to take into account changes in force of infection with age. If the force of infection was assumed to be a step function (increasing from 0.16 to 0.2 yr^{-1} at 2 years) the fit was improved without significantly changing current parameter estimates (results not shown).

Note that the vaccine efficacy parameters (as estimated here) are independent of herd immunity. Herd immunity influences the post-immunisation value of λ, not the characteristics of the vaccine.

Table 3.1. Vaccine efficacy parameters

Parameters	Symbol	Brisson *et al.*			Halloran *et al.*
		Best	Base	Worst	Worst
Rate at which vaccinated protected individuals become partially susceptible to varicella (1/year)	W	0.021	0.031	0.072	0.0057
Percent of individuals who become protected after vaccination	T	97%	97%	88%	83%
Rate of varicella acquisition of vaccinees compared to non vaccinees	b	50%	73%	100%	16%
Proportion of vaccinated protected individuals who become immune if in contact with varicella	k	100%[&]	91%	50%[&]	0%

[&] Assumed parameter values

3.1.3 DISCUSSION

This study shows that vaccine efficacy parameters should be estimated concurrently to take into account dependencies (inter-relationships) between parameters and that simple mathematical models can be useful for such enterprises.

We also have updated Halloran *et al.*'s (1994) vaccine efficacy parameters in the light of new data and the weak methodological approach that was used (Delphi process). Our approach differs in that we estimate the parameters simultaneously from the observed breakthrough rates over time. Our estimates yield higher breakthrough rates, which give a better fit to the observed data. Indeed, the annual number of breakthrough cases with Halloran *et al.*'s (1994) worst-case scenario is lower than that of the lowest observed breakthrough data (Iot 1982,

with passive reporting). Thus studies using Halloran *et al.*'s (1994) parameter sets may be overestimating the predicted effectiveness of varicella immunisation.

In the next section we use the vaccine parameter values estimated here to predict the impact of vaccination on the epidemiology of VZV at the population level (taking into account herd-immunity externalities).

3.2 MODELLING VACCINE EFFECTIVENESS

3.2.0 BACKGROUND

Some important questions remain which limit the widespread acceptability and implementation of the vaccine in developed countries.

- Vaccination could increase the overall morbidity due to varicella. Vaccination can lead to a shift in the average age at infection from children to adults where risk of complication is greater. Hence, by increasing incidence in adults varicella vaccination programs could lead to an overall reduction in public health (Halloran *et al.* (1994), Health Canada (1999), Brisson et al. (2000a)). Such a phenomenon has been observed with rubella vaccination in Greece (Panagiotopoulos *et al.*, 1999).
- High number of varicella cases in vaccinees. A high number of breakthrough cases of varicella have been reported in some vaccine efficacy studies (Krause and Klinman, 1995). Clinical trials have shown that 0.2% to 4.5% of vaccinees a year develop mild breakthrough varicella (modified varicella) in the first years following vaccination (Krause and Klinman, 1995; Section 3.1).
- Vaccination could increase the incidence of zoster (Gershon *et al.* (1996), Garnett and Grenfell (1992), Plotkin (1994)). In section 2.4.3 we show strong epidemiological evidence that exposure to varicella reduces the risk of reactivation (zoster). If this is so, mass vaccination of varicella could increase

the incidence of zoster by reducing the opportunity of exposure to VZV (by reducing chickenpox cases).

- The vaccine can establish latency (Levin *et al.*, 1994). The likelihood and severity of reactivation (zoster) in vaccinees is an additional concern (Krause and Klinman, 2000).

Previous modelling work on the impact of VZV vaccination has focused mainly on the change in incidence and morbidity of varicella due to shifts in the age at infection (Halloran *et al.*, 1994; Schuette *et al.*, 1999) and the possible impact on zoster (Schuette *et al.*, 1999; Garnett and Grenfell, 1992a; Garnett and Grenfell, 1992b). The summary of epidemiological features included in published transmission dynamic models is presented in Table 3.2.

Impact of vaccination on varicella: Halloran *et al.*, (1994) and Schuette and Hethcote (1999) predicted that vaccination of 12-month-old children would reduce both varicella incidence and hospitalisation in the US.

Table 3.2. Summary of epidemiological features included in previous published dynamic models of varicella zoster virus transmission

Reference	Age structure	Breakthrough infection	Zoster
Garnett and Grenfell (1992a,b)	Yes	No	Yes
Halloran et al. (1994)	Yes	Yes	No
Ferguson et al. (1996)	Yes	No	No[A]
Garnett and Ferguson (1996)	Yes	No	Yes
Shuette and Hethcote (1999)	Yes	Yes	Yes

A. Assessed the impact of zoster on varicella dynamics but did not assess the impact of varicella on the incidence of zoster

Impact of vaccination on zoster. Garnett and Grenfell (Garnett and Grenfell, 1992a; Garnett and Grenfell, 1992b) were the first to explore the relationship between varicella and zoster using mathematical models. They examined the

impact of vaccination on the long-term equilibrium incidence of these diseases (Garnett and Grenfell, 1992b). Furthermore, they modelled the impact of mass vaccination on zoster assuming varicella is eliminated at the start of vaccination. Thus, they did not investigate the impact of the post vaccination dynamics of varicella on the incidence of zoster. Ferguson *et al.* (1996), on the other hand, examined the possible influence of zoster on the transmission dynamics of varicella, but did not investigate the impact of vaccination on the incidence of zoster (their model assumes a constant background force of infection from zoster which remains unchanged through time). Finally, Schuette and Hethcote (1999) were the first to model the short to medium-term impact of varicella vaccination on the incidence of zoster using a dynamic framework. In the simulations, zoster incidence increased in the first 30 years after initiation of infant vaccination (Schuette and Hethcote, 1999).

However, within these studies a small number of vaccine coverages and strategies were investigated, vaccine efficacy parameters were optimistic (see section 3.1) and no sensitivity analysis was performed on the Who-Acquires-Infection-From-Whom matrix (WAIFW). Furthermore, parameters used to model zoster were based on assumptions.

In this section we use a mathematical model based on new data on vaccine efficacy (section 3.1) and zoster (section 2.4) to simulate transmission of varicella and zoster in developed countries before and after vaccination using England and Wales as an example. The four main questions addressed are: 1) the effect of vaccination in healthy children on the overall varicella morbidity; 2) the role of vaccine efficacy on varicella incidence and morbidity; 3) the effect of vaccination strategies in minimising incidence and morbidity; and 4) the impact of vaccination on zoster.

3.2.1 METHODS

3.2.1.1 Population

The population of England and Wales is assumed to be stable - i.e. birth is set to equal death. Birth rates are assumed constant through each year. Mortality is assumed to be zero until 65 years and constant thereafter producing an average life expectancy of 75 years. The population is stratified into 66 age cohorts (0,1,2,3,..,65+). This type of simplified age structure is widely used and is a reasonable approximation of the demography of England and Wales (Office for National Statistics, 2000).

3.2.1.2 Model Structure

Two models were used in this study. Model 1 (Figure 3.3a) was built to assess the impact of varicella transmission before and after vaccination in England and Wales whereas Model 2 (Figure 3.3b) was built to investigate the potential impact of varicella vaccination on zoster. Both transmission models are realistic age-structured deterministic models (RAS) based on a set of ordinary differential equations. Similar types of models have been used in other work to study childhood infections such as measles and varicella (Halloran *et al.*, 1994; Schenzle D, 1984; Babad *et al.*, 1995; Bolker and Grenfell, 1993). Models 1 and 2 possess 8 epidemiological age groups (0 to 1, 2 to 4, 5 to 11, 12 to 18, 19 to 24, 25 to 44, 45 to 64 and 65+ years). The younger age groups represent the school structure of England and Wales (i.e. infant, pre-school, primary school, secondary school, college and university) while older age groups are stratified to better capture differences in varicella and zoster incidence and morbidity with age. The models start at the mean varicella epidemic cycle.

Model 1 is illustrated by the flow diagram in Figure 3.3a, which characterises the natural history of varicella with and without vaccination (the mathematical structure is presented in Appendix 2). The mutually exclusive compartments represent the different epidemiological states of the disease and the arrows represent the flow of individuals between them. At 6 months of age, once maternal antibodies to varicella have waned, children enter the susceptible class (*Susceptible*) and if infected pass through the latent (*Latent* - i.e. infected but not infectious) and infectious (*Infectious*) periods before acquiring lifelong immunity (*Immune*). Following vaccination, individuals either remain in the fully susceptible class (*Susceptible*) because of complete vaccine failure (primary failure) or pass into one of two mutually exclusive classes: 1) a temporary protection class (*V Protected*) in which individuals are immune from infection but may lose protection over time; and 2) a modified susceptible class (*V Susceptible*) in which individuals retain some degree of partial protection (1-*b*) and if infected are likely to experience a less severe infection (Bernstein *et al.*, 1993). Vaccinated protected individuals can also become permanently immune (*V Immune*) by having an effective contact with an infectious individual (contact which would otherwise lead to infection).

The age-specific varicella force of infection $\lambda(a,t)$ (the per susceptible rate of infection) is composed of the force of infection caused by varicella ($\lambda_V(a,t)$) and by zoster (λ_Z) (see Appendix 2). The force of infection caused by varicella ($\lambda_V(a,t)$) is a function of the age-specific number of infectious individuals and the effective contact rate between age groups. It is allowed to take different values in each of 8 age groups (< 2, 2 to 4, 5 to 11, 12 to 18, 19 to 24, 25 to 44, 45 to 64 and > 65 years). In model 1, the force of infection due to zoster is constant through time (λ_Z) - i.e. independent of the prevalence of zoster.

Model 2, illustrated by Figure 3.3b, adds a complexity to model 1 by attempting to incorporate the natural history of zoster (solid bold boxes & lines) (see Appendix 3 for mathematical structure). Following varicella infection individuals acquire lifelong immunity to varicella and a temporary immunity to zoster (*Immune*). Once immunity to zoster has waned individuals become susceptible to zoster (*Sus Boosting*). Unless they die in the meantime, two events can then occur: 1) individuals have a reactivation episode (*Zoster*) and then become permanently immune (*Zoster Immune*); or 2) individuals are boosted by contacts with varicella and return to the temporarily immune class (*Immune*). Repeat cases of zoster were not modelled since reoccurrence is low (Levin *et al.*, 1994). Furthermore, zoster was assumed not to occur in vaccinees even though studies in immunocompromised children have shown VZV to reactivate after vaccination. However, after vaccination zoster is reduced by 6 fold and cases are less severe (Gershon *et al.*, 1999).

In Model 2 the force of varicella infection caused by zoster ($\lambda_Z(a,t)$) is a function of the overall number of zoster infectives (see Appendix 3). The rate of VZV reactivation ($\rho(a)$) is assumed to be dependant on age (see Chapter 2 and Appendix 3).

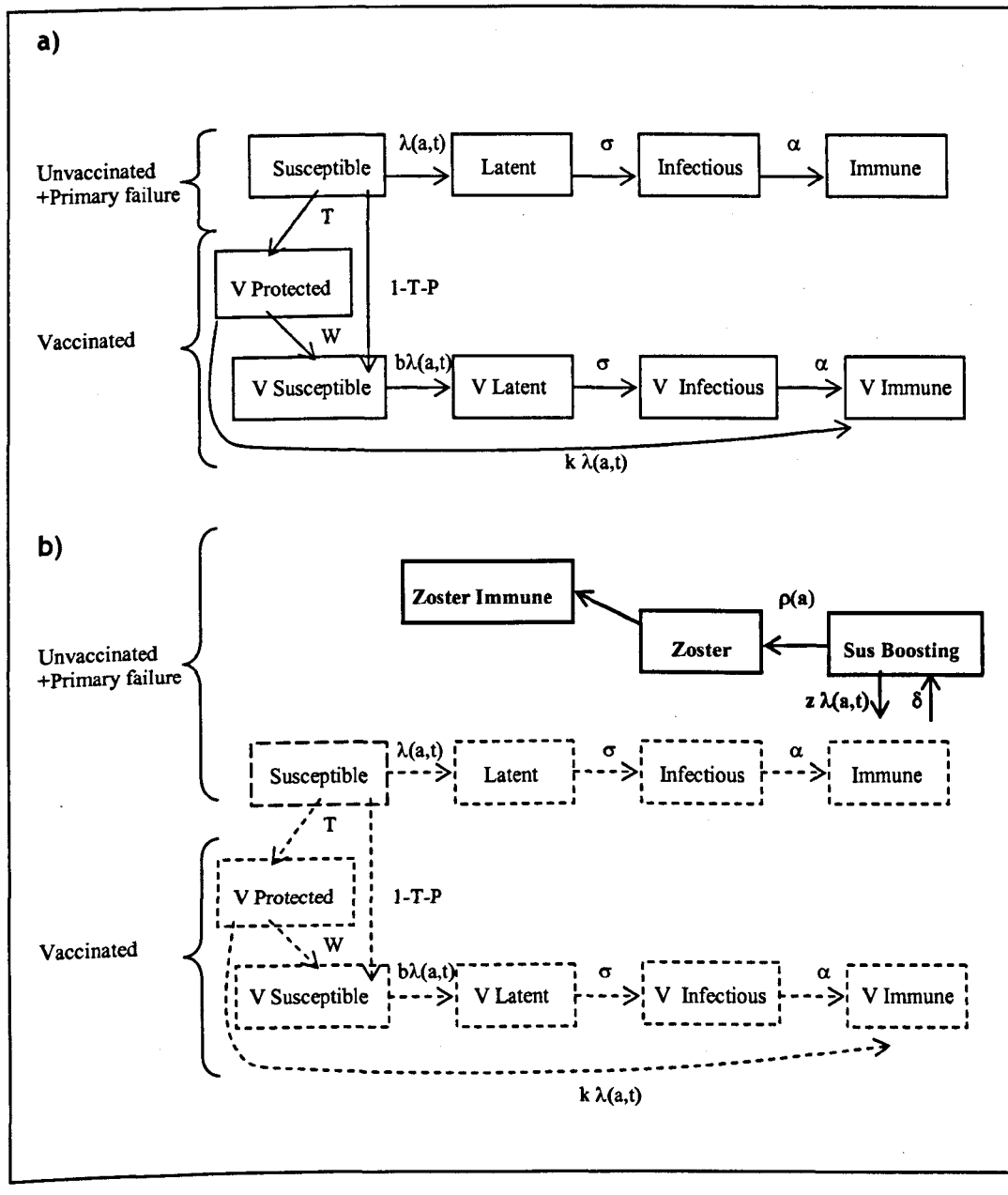


Figure 3.3. Flow diagram of varicella and zoster before and after vaccination. The mutually exclusive compartments represent the different varicella and zoster epidemiological states. Arrows represent the flow between theses states. a) Model 1, represents the transmission dynamics of varicella. b) Model 2, represents the transmission dynamics of both varicella and zoster. See text and table 3.3 for details.

3.2.1.3 Mixing patterns - The Who-Acquired-Infection-From-Whom matrix

The standard technique to take account of age-dependant mixing patterns of the population is to use a Who-Acquired-Infection-From-Whom (WAIFW) matrix (Anderson and May, 1991). The WAIFW matrix represents the effective contact

rate between age groups - i.e. the rate at which an infective of age X will infect a susceptible of age Y. Since the elements of the matrix cannot be observed directly in populations they must be estimated from the pre-vaccination force of infection. With such a technique a large number of possible matrix structures can be assumed from the same observed data. It is therefore necessary to perform a sensitivity analysis to assess how changes in the matrix structures influence results. In this study we explore the effect of five WAIFW matrices on the results. The chosen matrix structures are; our base matrix (*base matrix*); two variations on the base matrix (*matrix 1* & *matrix 2*); a purely proportional (*proportional matrix*); and a highly assortative mixing matrix (*assortative matrix*) (see Appendix 4 for the matrix structures).

The structure of the *base matrix* was chosen to reflect the importance of school and parent-child transmission of varicella. Contact rates within pre-school (2 to 4 years old), primary school (5 to 11 years), secondary school (12 to 18 years), university (19 to 24 years) are allowed to be large. The highest contact rates are observed within the 19 to 24 age group, which may reflect higher contact patterns amongst University students (Edmunds *et al.*, 1997). Infants (0 and 1) are assumed to come into contact with all other children at a similar rate and with adults at different rates (the highest estimated rates were with the 19 to 24 and 25 to 44 year groups, which probably represents parent-infant contacts). Adults (45 to 64 and 65+) are assumed to mix with themselves and with children at similar rates. School-aged children (2 to 4, 5 to 11 and 12 to 18) mix with other children not of their own age at a unique rate.

Matrix 1 is different to the *base matrix* in that specific rates are added for ''grand parent''-child contact (0 to 1, 2 to 4, 5 to 11 with 45 to 64 and 65+) and work related contacts (19 to 24, 25 to 44 and 45 to 64). *Matrix 2* has a similar structure

to the *base matrix* but with contact rates in the 19 to 24 age group set to be 2/3 of the *base matrix*. The purely *proportional matrix* assumes that each age group has a unique contact rate and the rate of effective contact between two age groups is dependent on the product of their respective contact rates. This matrix structure puts the least emphasis on mixing within age groups. Finally, the *assortative matrix* (like-with-like) implies a strong amount of within age group mixing. The *assortative matrix* has unique coefficients along the leading diagonal for all but the 65+ age group. It is important to note that this structure is not purely like-with-like since it allows a low contact rate between different age groups.

3.2.1.4 Model Output

Following mass immunisation, varicella cases are classified into two groups characterised by their degree of severity; 1) Natural (NV) and 2) Breakthrough varicella (BV). Natural or full-blown varicella occurs in unvaccinated individuals and primary failures. Breakthrough varicella, which occurs in seroconverted vaccinated individuals, is clinically modified and significantly less severe than natural varicella (Bernstein *et al.*, 1993). Since breakthrough cases are very mild and are assumed to require no medical care we primarily investigate the influence of vaccination on natural varicella cases.

Varicella morbidity is represented by the total number of inpatient days due to varicella. The frequency of varicella and zoster hospitalisation and length of stay per admission were determined using the Hospital Episode Statistics for England (see Tables 2.2 and 2.4 in Chapter 2). We applied the age-specific length of stay per varicella case to the predicted number of natural cases of varicella. Breakthrough cases were assumed not to require hospitalisation. Using the hospital separation data might overestimate the severity of illness among older

individuals since the validity of diagnostic codes for varicella decreases markedly after age 50 years (Choo *et al.*, 1995). Furthermore, the incidence of co-morbid disease increases with age making it difficult to be sure that all days in hospital are attributable to varicella. On the other hand, our results assume that breakthrough varicella never requires hospital admission, which might be an underestimation of morbidity among older adults.

3.2.1.5 Biological parameters

The parameter definitions, values and data sources are described in table 3.3. The average duration of latency ($1/\sigma$) and infectiousness ($1/\alpha$) for varicella is respectively 14 and 7 days (Beneson, 1995). Natural immunity to varicella is assumed to be life-long. Duration of immunity to zoster after boosting (Model 2) is set at 20 years (see Section 2.4 for details) but is varied in the sensitivity analysis. The average length of zoster infectiousness ($1/\alpha_z$) is 7 days (Beneson, 1995).

3.2.1.6 Vaccine efficacy parameters and estimates

The waning rate (W), proportion of individuals who become temporarily protected after vaccination (T), residual susceptibility (b) and boosting (k) were estimated concurrently to take into account dependencies (inter-relationships) between parameters (see Section 3.1 for more details). The rate of primary vaccine failure (P) observed in clinical trials has ranged from 0% to 6% (Weibel *et al.*, 1985; White *et al.*, 1991; Clements *et al.*, 1995). For the model P was set to 1% for the *best vaccine*, 4% for the *base vaccine* and 6% for *the worst vaccine* scenario. Relative residual infectiousness (m) is defined as the relative rate of varicella transmission to susceptible non-vaccinated contacts (NV) from infected vaccinees (i.e. those with breakthrough infection) versus that from infected non-vaccinees. M can be estimated epidemiologically by dividing the household secondary attack rate (SAR) from vaccinated to unvaccinated individuals ($SAR_{V\text{-}NV}$) with the secondary attack

rate from unvaccinated to unvaccinated individuals ($SAR_{NV\text{-}NV}$) (Halloran *et al.*, 1997). The observed rate for $SAR_{NV\text{-}NV}$ is 86% (Ross, 1962). There are no published estimates for $SAR_{V\text{-}NV}$ however the rate can be estimated from $SAR_{V\text{-}V}$, which has been reported as 5% (Weibel *et al.*, 1985), 8.6% (Johnson *et al.*, 1989) and 12% (Watson *et al.*, 1993) in three different vaccine trials. If we set $SAR_{V\text{-}V}$ to equal 8.6% and we suppose that 10% of vaccinees are susceptible to varicella infection then the relative residual infectiousness is close to 100% ($m = [SAR_{V\text{-}NV} / SAR_{NV\text{-}NV}] = [(8.6\%/10\%) / 86\%] = 100\%$). A second method of estimating relative residual infectiousness is through the ratio of lesion numbers observed in vaccinees with breakthrough varicella compared to unvaccinated individuals with natural varicella. Published reports suggest this ratio is 17% (Bernstein *et al.*, 1993). Taking both methods into account, relative residual infectiousness (m) is varied between 20% and 100% (i.e. 20% best vaccine, 50% base vaccine and 100% worst vaccine).

3.2.1.7 Vaccination policies

The different vaccination strategies investigated were:

Infant: Routine vaccination at 1 year of age.

Catch-up: Infant + vaccination of 1 to 11 year old children in first year of program.

Adolescent: Routine vaccination at 12 years.

Table 3.3. Model Parameters

Model Parameters	Mean value			Source Data
Demographic Parameters				
England and Wales Population	50,000,000			(ONS, 2000)
Birth rate (births/year)	667,000			
Mortality rates by age group (1/year):				
0-64	0.0			
>65	0.1			
Biologic Parameters				
Force of varicella infection by age group ($\lambda_v(a,t)$) (1/year):				(See Section 2.3)
Force of varicella infection due to zoster (λ_z) (1/year):				
Model 1	0.001			(Appendix 2)
Model 2	5.4^{e-7}*Zoster Prevalence			(Appendix 3)
Duration of varicella (days):				(Beneson, 1995)
Duration of latent period ($1/\sigma$)	14			
Duration of infectious period($1/\alpha$)	7			
Proportion of effective varicella contacts that boost against zoster (z)	100%			
Duration of immunity to zoster after varicella infection ($1/\delta$) (years)	20 (95%CI 7-41)			(Section 2.4)
Rate of reactivation by age group ($\rho(a)$) (1/year) for different durations of immunity ($1/\delta$):	$1/\delta$=7	$1/\delta$=20	$1/\delta$=41	(Appendix 3)
0-1	8.08e-02	2.0	4.0	
2-4	7.45e-04	7.9e-02	4.51e-03	
5-11	6.94e-03	2.0e-02	3.41e-02	
12-19	5.06e-03	1.1e-02	2.10e-02	
20-24	3.02e-03	6.0e-03	1.10e-02	
25-44	4.61e-03	8.3e-03	1.44e-02	
45-64	5.93e-03	8.9e-03	1.76e-02	
>65	1.73e-02	2.3e-02	5.68e-02	

3.2.2 IMPACT OF VACCINATION ON VARICELLA

3.2.2.1 Age Distribution & Coverage.

Incidence (Infant vaccination; base matrix; base vaccine). Model 1 produces a yearly epidemic of varicella before vaccination (see Figure 3.4) with an average predicted incidence rate of 13029 cases/1,000,000 population-year and 87% of cases occurring in children under 15. Considering reporting rates (<50% in children and >90% in adults), these results are consistent with sentinel surveillance and medical billings data from the England and Wales (5220 per 1,000,000 year; and 80% in under 15s respectively (section 2.3)), Canada (5110 per 1,000,000 year; and 85% (Brisson *et al.*, 2001; Law *et al.*, 1998), France (9855 per 1,000,000 year; and

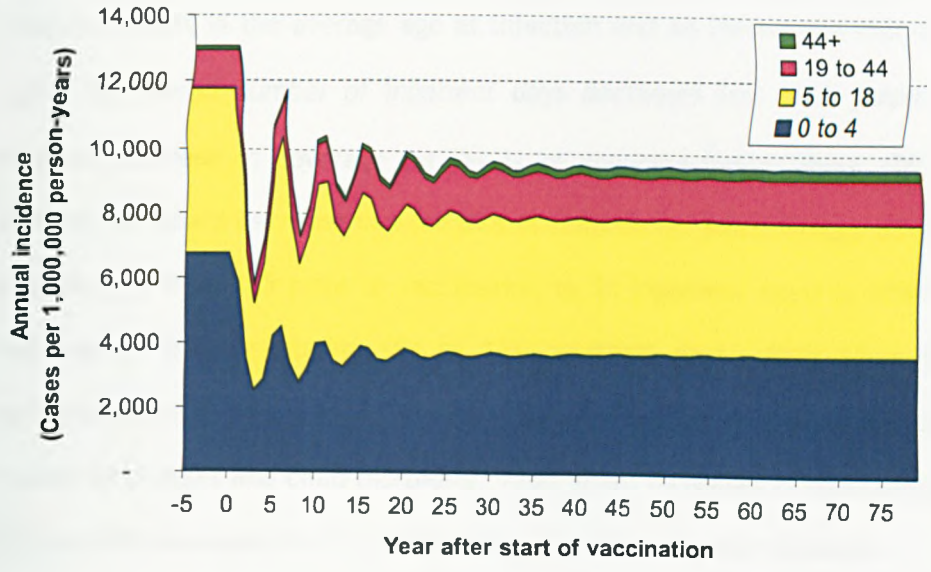
92% (*Deguen et al.*, 1998)) and Scotland (6205 per 1,000,000 year; and 79% (Fairley and Miller, 1996)).

At 30% coverage (Figure 3.4a), the number of annual cases is rapidly reduced then oscillates between high and low epidemic years before reaching a new equilibrium. A slight shift in the age distribution is predicted but the bulk (73% compared to 83%) of infection remains in children under 12 years of age. Such dynamic patterns are observed with the base-case model for levels of coverage under 60%. As coverage increases (between 30% and 60%) oscillations in the number of cases before equilibrium become more pronounced, the number of cases at equilibrium decrease and a greater shift in the age at infection occurs (results not shown).

If high coverage is achieved, as should be expected in England and Wales (and other developed countries), more complex dynamics are produced. As shown in Figure 3.4b, 90% vaccine coverage produces an immediate decline in cases, which lasts for more than 10 years (honeymoon period). During this time susceptibles (unvaccinated, primary failures and partially susceptibles) slowly accumulate. Once a threshold of susceptibles is surpassed an epidemic occurs (post-honeymoon epidemic). Thereafter, the infection settles into a new epidemic cycle and equilibrium. The post-honeymoon epidemic would occur primarily in individuals who were in age groups immediately above those who were vaccinated when vaccination began. The epidemic occurs mostly in the 19 to 44 year cohorts. Finally, at equilibrium proportionately there are more cases in adults (48% occur in those over 18 years of age), but the absolute number is lower than the pre-vaccination state. The transmission dynamics shown in Figure 3.4b are similar for vaccine coverage between about 70% and 95%. As coverage increases the honeymoon period is longer, the post-honeymoon epidemic is shorter but more

intense and the shift in the age at infection (proportion of cases in adults) is more pronounced (results not shown).

a)



b)

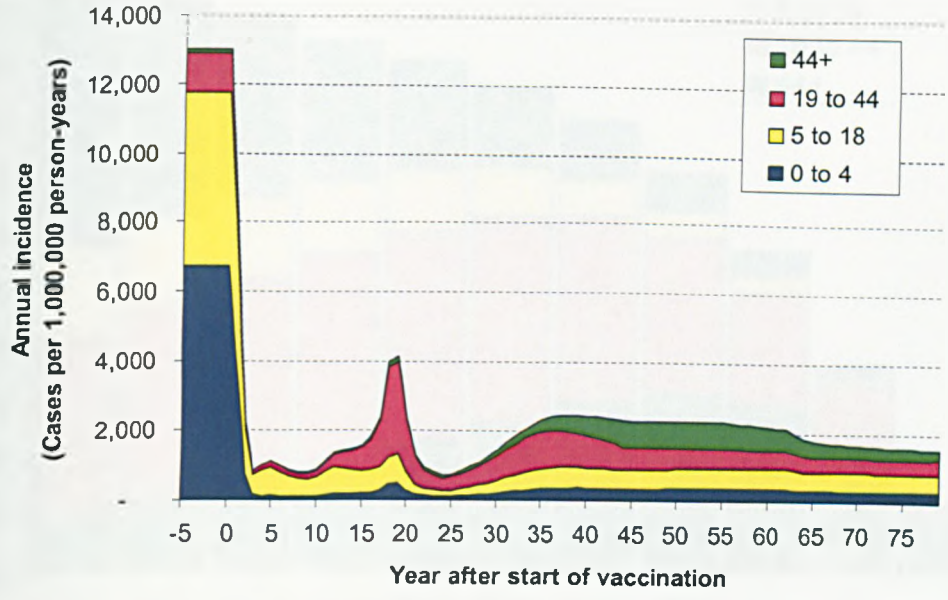


Figure 3.4. Age Distribution & Coverage. a) Age-specific number of natural varicella cases for low vaccine coverage (30% coverage, *base vaccine*), b) Age-specific number of natural varicella cases for high vaccine coverage (90% coverage, *base vaccine*). The width of each colour band represents the age-specific varicella incidence rate.

Morbidity (Infant vaccination; base matrix; base vaccine). Figure 3.5 represents the estimated yearly age-specific number of inpatient days expected in a population of 1,000,000 at equilibrium after mass vaccination, for the *base case*. Mass vaccination seems to reduce the overall morbidity as coverage increases despite a shift in the average age at infection and an increase in morbidity with age. The overall number of inpatient days decreases less than proportionately with an increase in coverage for levels of coverage below about 60%. This is because the sharp decrease in morbidity in children (at 60% coverage an estimated decrease of from 125 prior to vaccination to 35 inpatient days) is offset by the increase in adult morbidity (84 to 126 inpatient days). Only when coverage exceeds 80% does vaccination seem to reduce varicella transmission sufficiently to reduce both adult and child morbidity. Thus, small increases in coverage between 70% and 90% are expected to significantly reduce the overall morbidity.

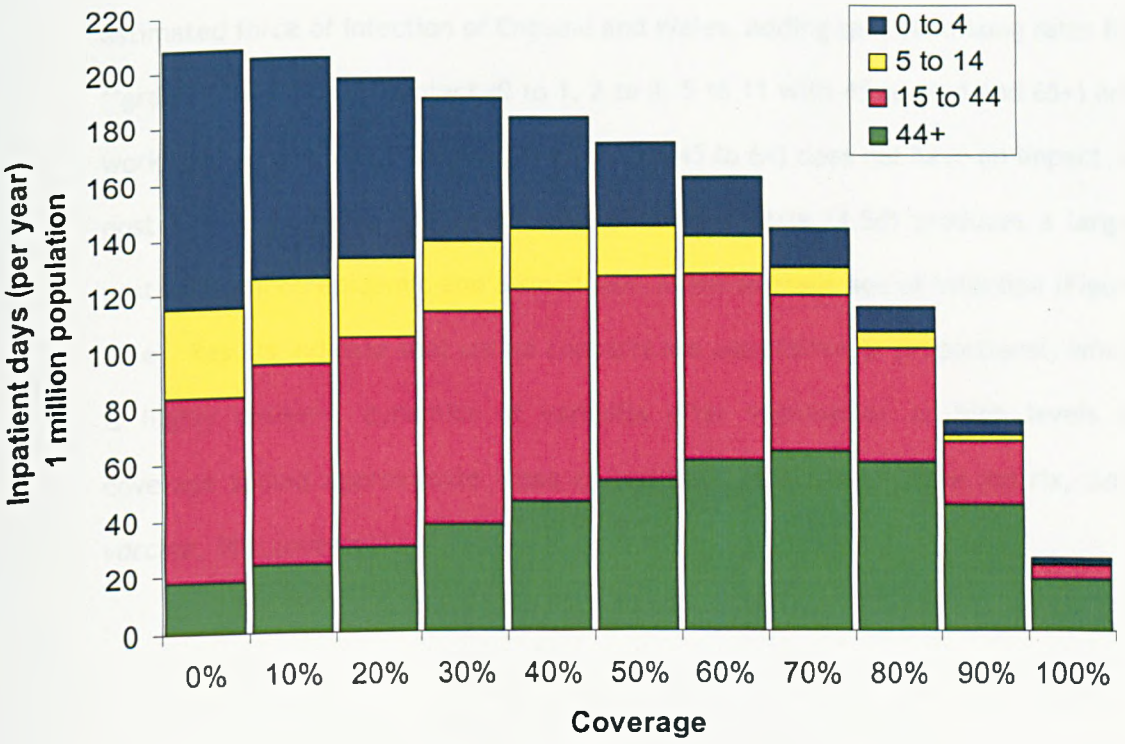


Figure 3.5. Age distribution & coverage. Predicted age distribution of varicella associated inpatient days (morbidity measure) at equilibrium by vaccine coverage (*base case* vaccine used).

3.2.2.2 WAIFW matrices

Incidence (Infant vaccination; 90% coverage; base vaccine). The transmission dynamics shown in Figure 3.4 are dependant on the age-specific mixing patterns. Figure 3.6 shows the age-specific number of natural varicella cases for the different WAIFW matrices.

The more proportional matrices (*proportional matrix* and *matrix 2* - Figure 3.6c, d) do not produce a post-honeymoon epidemic. On the other hand, they induce a larger shift in the age at infection due to a higher degree of contact between children and adults (Figure 3.6e). The remaining WAIFW structures (*Matrix 1* and the *assortative matrix*) produce a post-honeymoon epidemic (Figure 3.6a,b). *Matrix 1* (Figure 3.6b) produces almost identical short-term dynamics as the *base matrix* and a similar shift in the age at infection (Figure 3.5e). Thus, with the estimated force of infection of England and Wales, adding specific mixing rates for ''grand parent''-child contact (0 to 1, 2 to 4, 5 to 11 with 45 to 6g 4 and 65+) and work related contacts (19 to 24, 25 to 44 and 45 to 64) does not have an impact on post-vaccine dynamics. Finally, the *assortative matrix* (3.5d) produces a larger post-honeymoon epidemic and a small shift in the average age of infection (Figure 3.5e). Results indicate that unless contacts are assortative or proportional, which is highly unlikely, dynamics of varicella after vaccination at high levels of coverage should approximate those of our base case model (*base matrix, base vaccine, 90% coverage*).

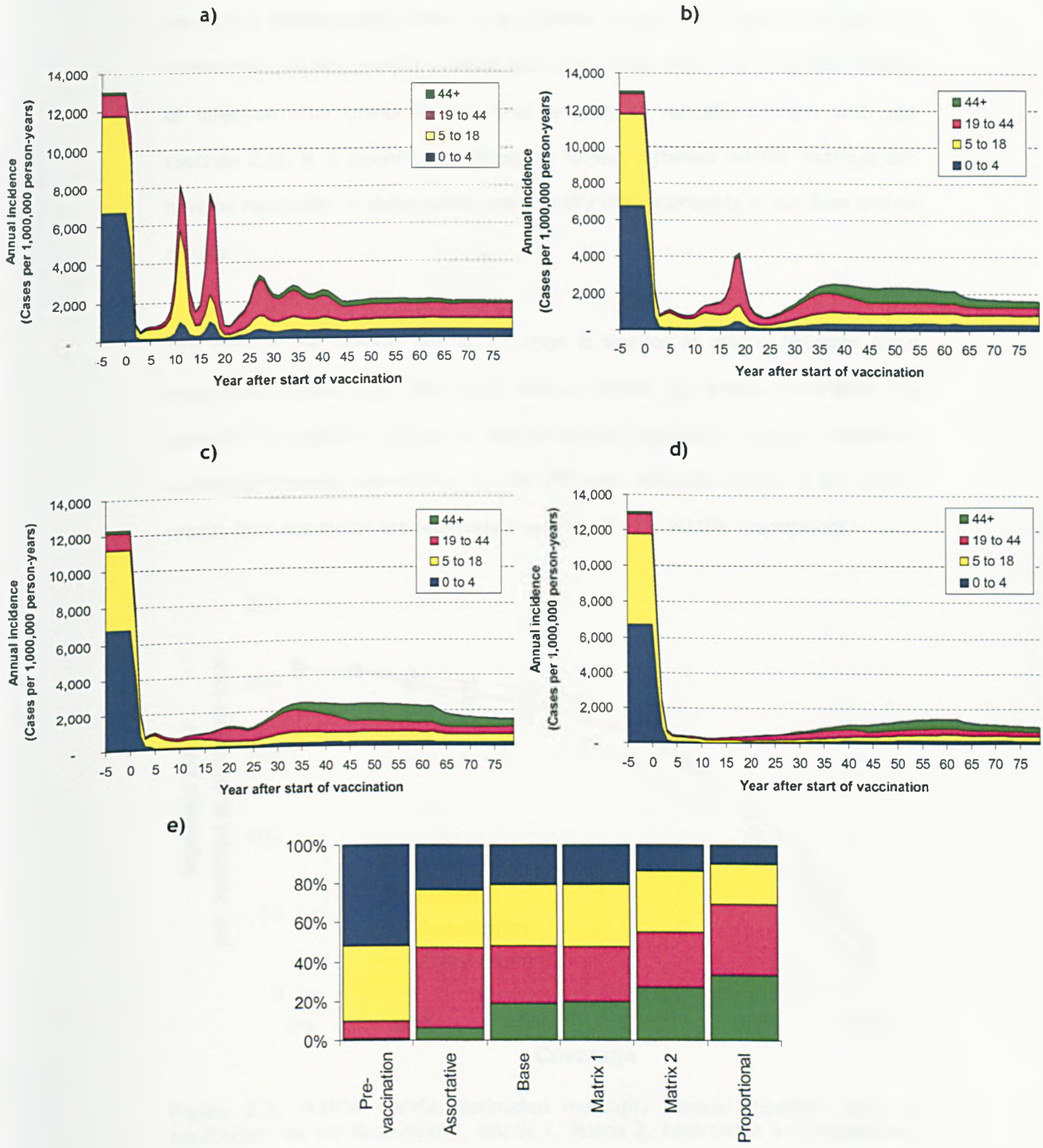


Figure 3.6. WAIFW Matrix. Estimated incidence of natural varicella cases for a) *Assortative mixing*, b) *Matrix 1*, c) *Matrix 2*, d) *Proportional mixing*, and e) the age distribution of infection at equilibrium by WAIFW matrix structure. All simulations assume the *base vaccine* and 90% coverage.

Morbidity (Infant vaccination; base vaccine). As shown by Figure 3.4a and 3.6, mixing patterns influence the nature and scale of the shift in the age distribution of infection after immunisation. Since severity of varicella changes with age (Section 2.3), it is essential to assess the impact different WAIFW matrices can have on morbidity. In doing so we can quantify the uncertainty of our *base matrix* results.

The shift in the average age at infection is smaller as mixing becomes more assortative (Figure 3.6). The more contact across age groups the higher the potential for adverse effects of vaccination on varicella morbidity. However, equilibrium results are similar for the different Matrices (Figure 3.7). Hence, results from our model are relatively insensitive to the WAIFW assumptions.

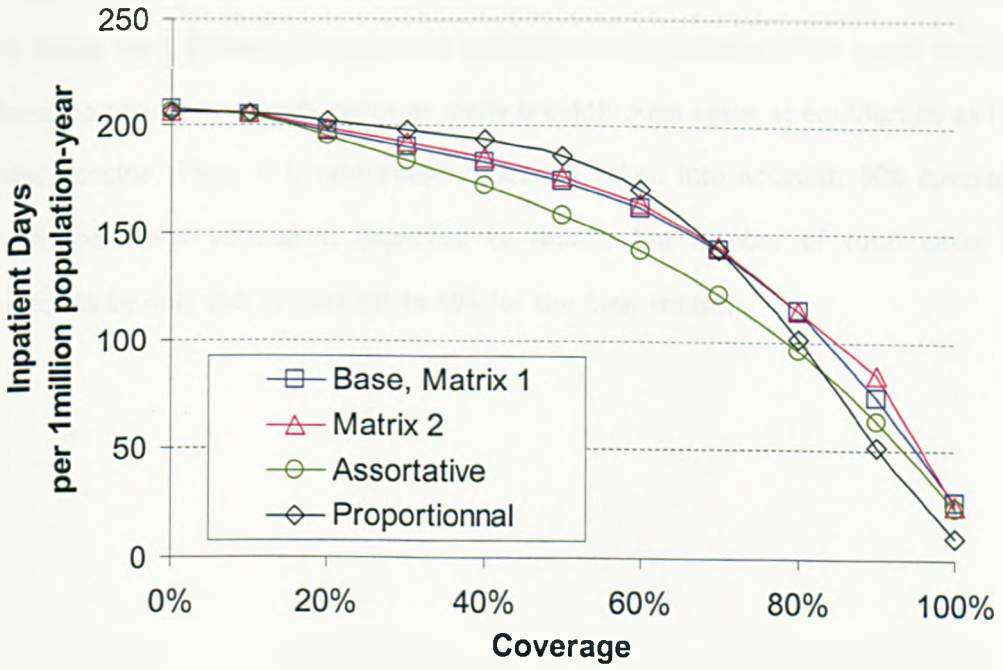


Figure 3.7. WAIFW Matrix. Estimated morbidity (annual inpatient days) at equilibrium for the *Base matrix*, *Matrix 1*, *Matrix 2*, *Assortative* and *Proportional matrix*.

3.2.2.3 Vaccine efficacy

Incidence (Infant vaccination; 90% coverage; base matrix). Figure 3.8 shows the predicted impact of the various vaccine efficacy scenarios on the number of natural and breakthrough cases of varicella for high vaccine coverage. Before attaining post-immunisation equilibrium, the *worst vaccine* (Figure 3.8c) produces several epidemic peaks whereas the *best* and *base vaccines* produce one small epidemic (Figures 3.8a, b). The continuing transmission of varicella following vaccination with the *worst vaccine* produces 80% more natural cases than the *base vaccine* over the first 30 years.

At equilibrium the *base* and *worst vaccines* are expected to produce similar numbers of natural varicella cases (10% and 16% of pre-vaccination state respectively). However, the *worst*, *base* and *best vaccine* scenarios are predicted to cause very different numbers of breakthrough infections. The *worst vaccine* scenario results in roughly twice as many breakthrough cases at equilibrium as the *base vaccine*. Thus, if breakthrough cases are taken into account, 90% coverage with the *worst vaccine* is expected to reduce the number of total cases of varicella by only 25% in contrast to 60% for the *base vaccine*.

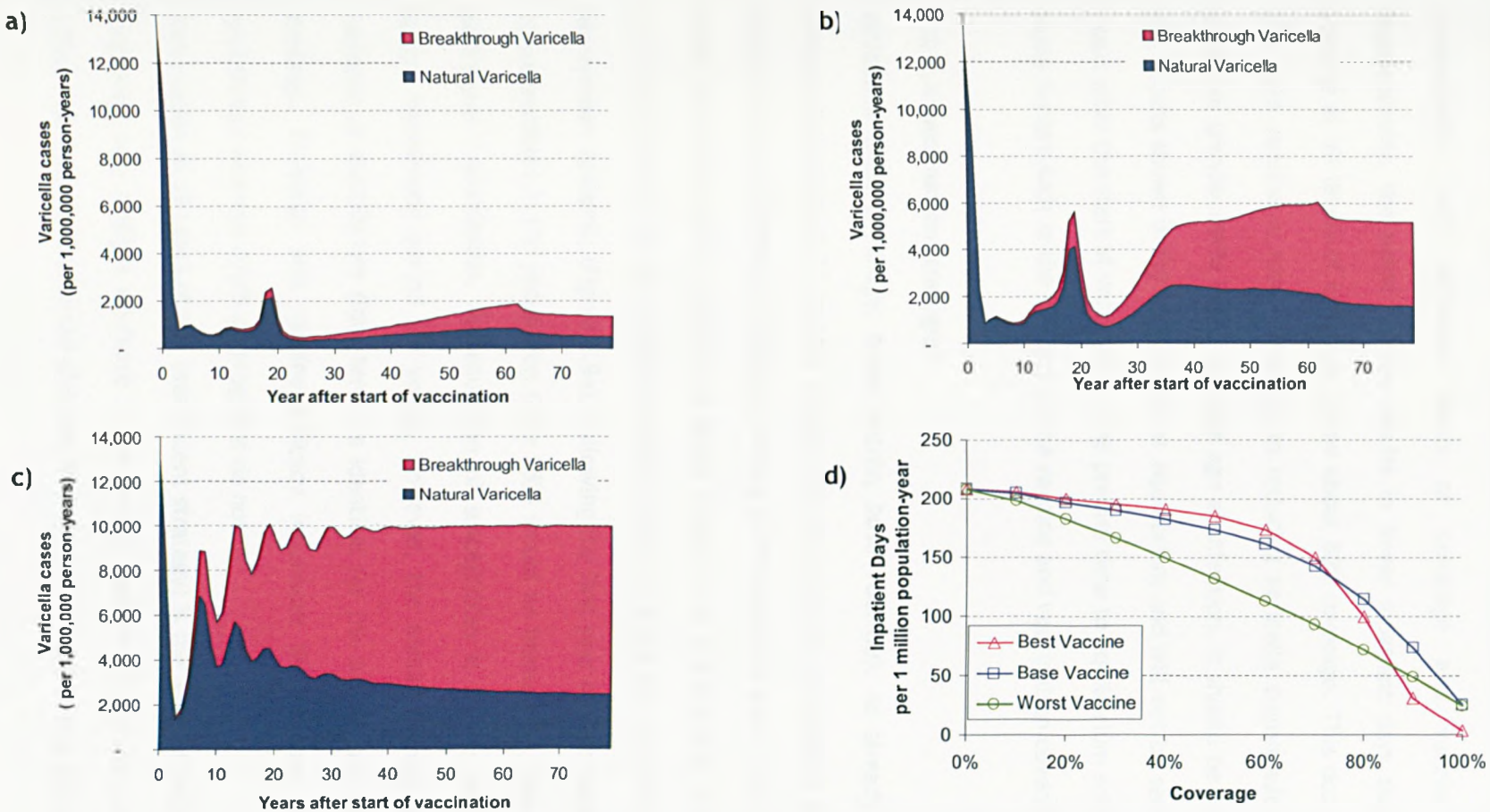


Figure 3.8. Vaccine efficacy. Predicted incidence of natural & breakthrough varicella cases over time (90% infant coverage) with a) best case vaccine, b) base case vaccine, c) worst case vaccine; and d) estimated morbidity (annual inpatient days) at equilibrium for the base, worst, and best vaccine.

Morbidity (Infant vaccination; base matrix). Figure 3.8d represents the estimated yearly number of inpatient days at equilibrium after routine mass immunisation with different levels of coverage and vaccine efficacy. Paradoxically, the *worst vaccine* results in fewer inpatient days than the *best vaccine* at all levels of coverage below about 80% coverage. This occurs because the *best vaccine* is more effective in reducing varicella transmission and thus produces greater shifts in the average age at infection. It should be stressed that the results shown in Figure 3.8d are at equilibrium and will not be seen for many years after the start of vaccination (the precise time to equilibrium will depend on many factors such as the efficacy of the vaccine and vaccination coverage).

3.2.2.4 Vaccination strategies

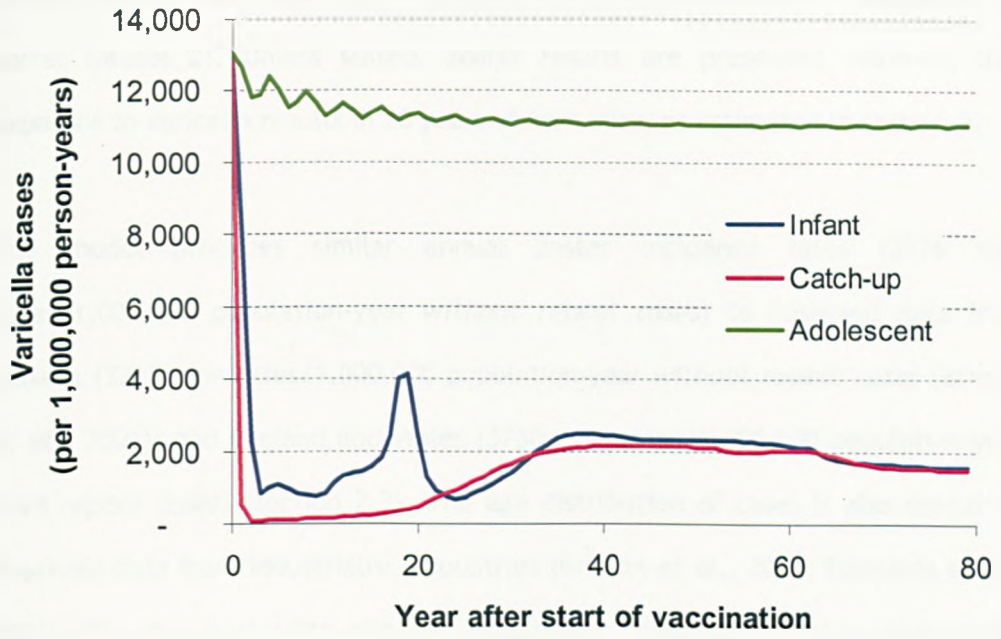
Incidence (90% coverage; base matrix; base vaccine). As already presented above vaccination at 12 months of age with no catch-up campaign is expected to produce a post-honeymoon epidemic among individuals who were 1 to 11 years old when the immunisation programme began (Figures 3.4, 3.6 and 3.8). Introducing a *catch-up strategy* for all children between 1 and 11 years can eliminate the post-honeymoon epidemic (Figure 3.9a). Following the first year of vaccination the bulk of susceptibles in the population (over 85%) would be immunised. This practically eliminates transmission. Accumulation of susceptibles is slower and creates a longer honeymoon period (20 years). However, the annual number of cases of varicella at equilibrium (long-term) is identical for the *infant* and any catch-up strategy. Coverage and vaccine efficacy influences the number of cases at equilibrium whereas catch-up programs do not.

Vaccination at 12 years of age (adolescent strategy) is the least effective strategy producing only a slight decrease in the annual number of natural cases (Figure 3.9a). Vaccinating 12-year-old children with the base vaccine and 90% coverage is

predicted to reduce the total number of natural varicella by only 13% at post-immunisation equilibrium. This is because by age 12 more than 85% of children have developed varicella. However, this strategy is expected to prevent 93% of adult cases at equilibrium.

Morbidity (90% coverage; base matrix; base vaccine). Figure 3.9b represents the estimated yearly age-specific number of inpatient days expected in a population of 1m following mass vaccination with 90% coverage and the base vaccine. Initially, infant and catch-up strategies are expected to significantly reduce morbidity (Figure 3.9b). However, in the long-term (after 80 years) inpatient days are expected to be reduced by only 50% with 90% vaccine coverage. This is because the sharp decrease in morbidity in children (234 to 16 inpatient days per 1m population-year) is partially offset by the increase in adult morbidity (86 to 150 inpatient days per 1m population-year).

a)



b)

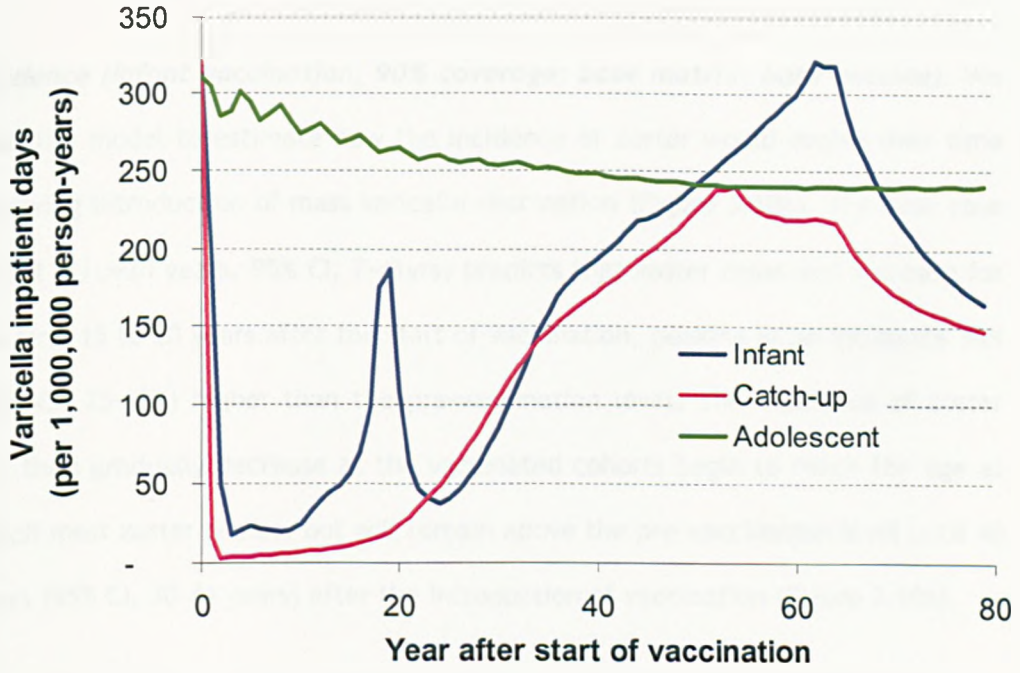


Figure 3.9. Vaccine strategy. Estimated a) varicella incidence and b) inpatient days due to varicella over time by vaccine strategy (90% coverage, base vaccine).

3.2.3 IMPACT OF VACCINATION ON ZOSTER

In this section, we examine the potential impact of childhood vaccination on zoster (Model 2). Unless stated, zoster results are presented assuming that exposure to varicella results in 20 years of immunity, as estimated in section 2.4.

The model produces similar annual zoster incidence rates (3176 new cases/1,000,000 population-year *without repeat cases*) to observed data from Canada (3212 new cases/1,000,000 population-year *without repeat cases* (Brisson *et al.*, 2001)) and England and Wales (3730 new cases/1,000,000 population-year *with repeat cases*) (section 2.3). The age distribution of cases is also similar to observed data from industrialised countries (Brisson *et al.*, 2001, Edmunds *et al.*, 2001). The pre-vaccination and post-vaccination varicella dynamics produced by Model 2 are nearly identical to Model 1.

Incidence (Infant vaccination; 90% coverage; base matrix; base vaccine). We used the model to estimate how the incidence of zoster would evolve over time following introduction of mass varicella vaccination (Figure 3.10a). The base case model ($1/\sigma$=20 years, 95% CI, 7-41yrs) predicts that zoster cases will increase for the first 15 to 20 years after the start of vaccination, peaking at an incidence 39% (95% CI, 25-42%) higher than the pre-vaccination level. The incidence of zoster will then gradually decrease as the vaccinated cohorts begin to reach the age at which most zoster occurs, but will remain above the pre-vaccination level until 40 years (95% CI, 30-44 years) after the introduction of vaccination (Figure 3.10a).

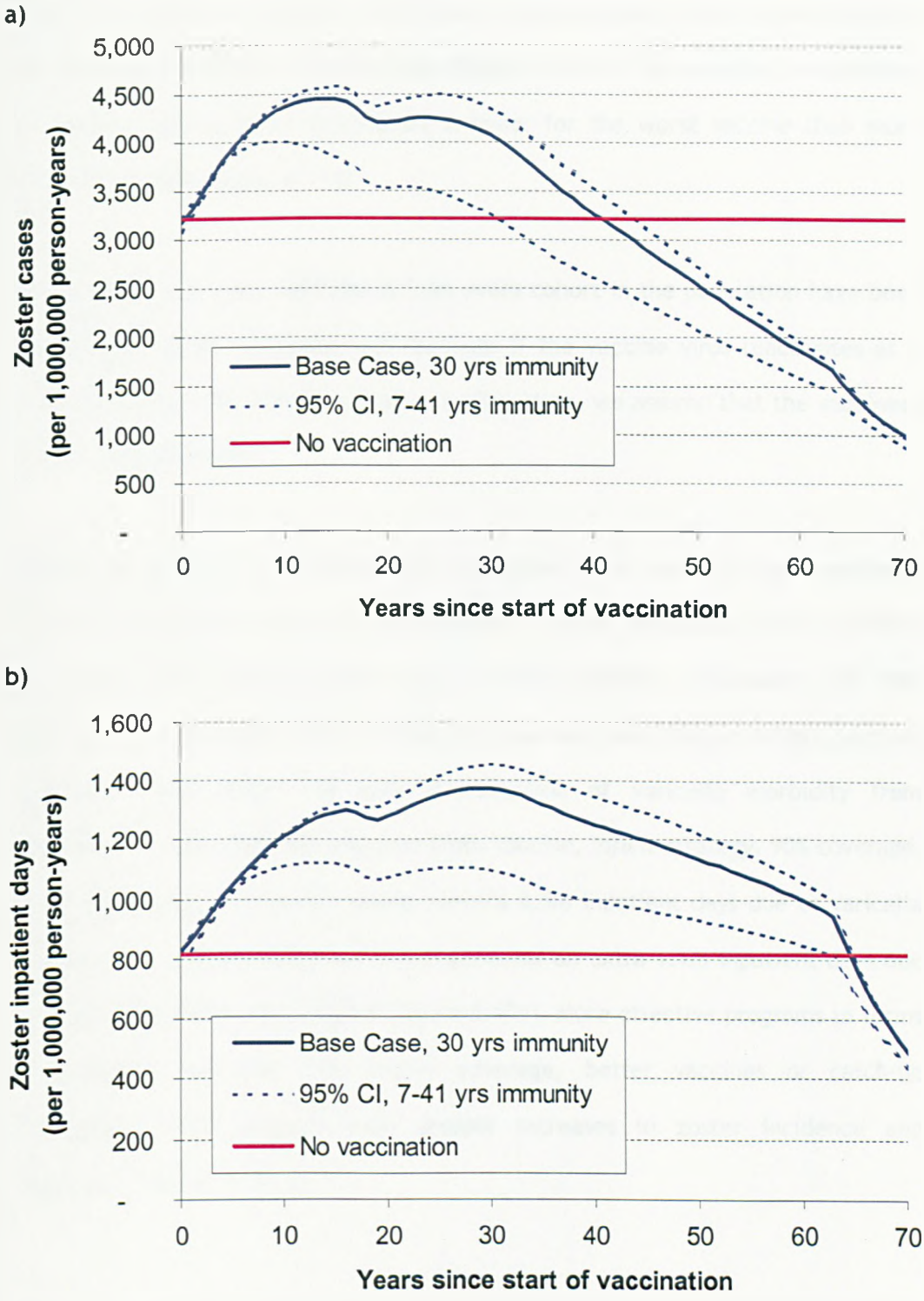


Figure 3.10. Dynamics of zoster. Estimated a) incidence and b) morbidity (annual inpatient days) over time after the introduction of vaccination for the Base case model ($1/\sigma$=20 years) and the 95% confidence bounds of $1/\sigma$ (7 and 41 years). The no vaccination scenario is represented by the red line.

The more effective vaccines or effective programs against varicella will produce the greatest increases in zoster cases (Figure 3.11a,c). For example, the number of cases of zoster after vaccination is lower for the *worst vaccine* than more efficacious ones (Figure 3.11c).

In the long-term, once individuals from every cohort in the population have been vaccinated, zoster incidence will decrease if the vaccine virus reactivates at a lower rate than the wild-type (Figure 3.10a). Here, we assume that the vaccinees do not develop zoster.

Morbidity (Infant vaccination; 90% coverage; base matrix; base vaccine). Figure 3.10b shows the predicted increase in zoster morbidity due to varicella vaccination. The model predicts that, infant varicella vaccination with 90% coverage will increase zoster morbidity for over 60 years (Figure 3.10b). Such an increase would offset the gain in reduction of varicella morbidity from vaccination. Under base assumptions (*base vaccine*, *infant strategy*, 90% coverage, 20yrs immunity), vaccination would prevent 0.5m inpatient days due to varicella over 60 years (Figure 3.9b) but would generate an extra 1.1m inpatient days due to zoster in a population of 50m (Figure 3.10b). More effective programs in terms of varicella reduction (i.e. higher coverage, better vaccines or catch-up strategies) would produce even greater increases in zoster incidence and morbidity (Figure 3.11b,d).

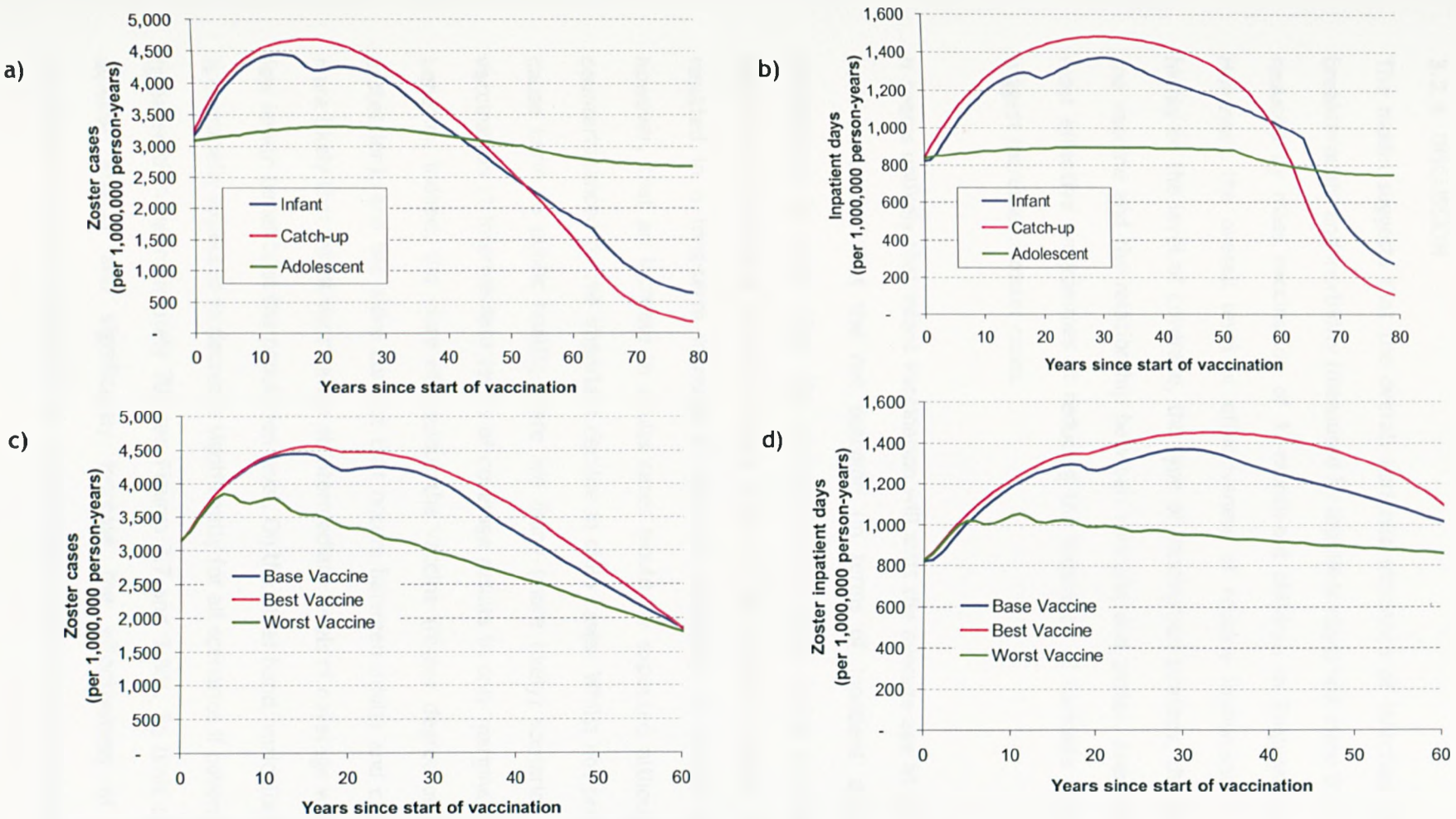


Figure 3.11. Zoster incidence and morbidity. Estimated zoster a) incidence and b) morbidity (annual inpatient days) over time following the introduction of vaccination (at year 0) for different vaccine strategies. Estimated zoster c) incidence and d) morbidity (annual inpatient days) following the introduction of vaccination for different vaccine efficacy.

3.2.4 DISCUSSION

The model suggests that the overall *varicella* incidence of infection (natural & breakthrough) and morbidity (measured by inpatient days) will more than likely be reduced by mass vaccination of 12-month-old children in England and Wales. However, the overall level of effectiveness of routine immunisation depends highly on the level of coverage, the type of vaccination strategy, the efficacy of the vaccine and the relationship between varicella and zoster. Importantly, the most effective programmes at reducing the incidence of varicella result in the biggest increase in zoster cases.

It seems unlikely that infant vaccination will shift the average age at infection to such an extent that the net outcome (in terms of inpatient days due to chickenpox) is worse than the pre-vaccination state. Using our *base case* assumptions regarding vaccine efficacy then, of the scenarios tested, no matrix resulted in a long-term increase in varicella morbidity. It should be noted, however, that an increase in adults cases would be expected although this is counterbalanced by the important decline in child cases. Whilst not predicted to cause harm to public health, there are many (more likely) scenarios in which vaccination at intermediate levels of coverage results in only marginal long-term benefits. Indeed, the more efficacious the vaccine (higher degree of individual protection), and the more contact that occurs between adults and children the more likely that infant vaccination at intermediate levels of coverage will result in few health benefits at the population level. On the other hand, varicella morbidity is eventually expected to decrease significantly for all scenarios if coverage is high (greater than approximately 70%-see Figures 3.7 and 3.8d). To limit the risk of adverse effects and significantly increase the effectiveness of varicella vaccination (at preventing varicella), programmes should aim at achieving a higher

coverage than 70%. Such levels of coverage might be difficult to achieve in some countries. Only 60-70% of mothers say they would definitely, or probably have their children vaccinated against chickenpox in England (Health Education Authority, 1998).

If high levels of coverage (over 70%) are attained post-honeymoon epidemics are expected to occur, unless there is very little within-group mixing, or the vaccine has very low efficacy. Such epidemics have been observed after measles (1989-1990) and mumps (1970-1980) vaccination programmes in the United-States (Atkinson *et al.*, 1992; Cochi *et al.*, 1988) and elsewhere (Chen *et al.*, 1994). The use of catch-up campaigns can reduce these epidemics as well as minimize the overall number of varicella cases after vaccination. It should be stressed, however, that although catch-up programs have a major impact on the short-term dynamics of infection, they do not influence the long-term effectiveness of the program.

As expected, the higher the vaccine efficacy the more mass vaccination reduces the incidence of varicella *infection*. On the other hand, lower vaccine efficacy reduces the shift in the average age at natural infection by allowing a certain number of cases to occur every year. Thus, paradoxically, for intermediate levels of coverage, lower efficacy vaccines could be more effective in reducing morbidity than better vaccines, particularly if exposure to varicella does boost the immune response to zoster. However, less efficacious vaccines are expected to result in a significant number of breakthrough cases even at high levels of coverage. Although breakthrough cases are mild and are assumed, here, to require no medical care, such a high number of cases in vaccinees may have an impact on vaccine acceptance.

Since the number of breakthrough cases of varicella might be significant even at high levels of coverage, elimination is unlikely to be a goal of routine immunisation. Given the mild nature of breakthrough varicella, reduction of morbidity of chickenpox is a more realistic target. If morbidity reduction is the goal of vaccination then using a vaccine with lower efficacy could actually be more effective than the use of higher efficacy vaccines. These results might provide some reassurance to concerns that, in the field, the vaccine would lose potency because it requires freezing.

If vaccination is highly effective against varicella, as it is likely to be with high coverage (Vazquez *et al.*, 2001, Clements *et al.*, 2001, Seward *et al.*, 2001), and exposure to varicella is protective against zoster (section 2.4, Thomas *et al.*, 2001), then an increase in zoster will occur after infant vaccination. Because the burden of zoster is high compared to varicella, such an increase might render infant immunization highly cost-ineffective and could lead to adverse public health consequences. These predictions depend on one main assumption. That exposure to varicella boosts against zoster. The longer the period of immunity after boosting the greater the increase in zoster after vaccination. Therefore, our results may overestimate the impact of vaccination on zoster if the period of immunity conferred by exposure is shorter than 20 years. However, as shown in figure 3.10 the duration of immunity is likely to be long enough to produce a significant increase in zoster after vaccination. It should be noted that, in the long-term a reduction of zoster cases will occur provided vaccine recipients are less likely to develop zoster than individuals who acquire natural infection (Garnett and Grenfell (1992)). However, if zoster can occur in a high proportion of vaccinees and varicella can boost immunity against zoster there is a risk that

incidence of zoster could increase in the long-term (Garnett and Grenfell, 1992). This scenario is unlikely. Studies in immunocompromised children have shown a 6-fold reduction in zoster after vaccination (Gershon *et al.*, 1999). Thus it seems likely that in the long-term the incidence of zoster will decrease following the introduction of childhood vaccination, though a short to medium term increase in incidence of the possible size shown in Figures 3.10 and 3.11 could have a negative effect on public health and confidence in immunisation.

The model presented here differs and extends that of Halloran *et al.* (1994), Schuette and Hethcote (1999) and Garnett and Grenfell (1992) in several ways. First, improved vaccine parameter estimates, based on up-to-date data from clinical trials were used. Secondly, the age-structure of the model more accurately reflects school aged mixing patterns. Thirdly, we assessed the sensitivity of our results to different age-dependent mixing patterns and discussed which of the patterns are more likely given available evidence on observed mixing patterns. Fourthly, Halloran et al. (1994) did not attempt to assess the possible effect of VZV vaccination on the incidence of Herpes zoster. Finally, although previous models have suggested that a rise in zoster incidence may occur following mass infant varicella vaccination (Schuette and Hethcote, 1999; Garnett and Grenfell, 1992), these studies relied on assumptions for key parameters such as the period of boosting. The model presented here is more rigorous and better parameterised since it is based on the analysis of a large, population based survey (see section 2.4), thus its predictions should be more robust.

In conclusion, the overall effectiveness of *infant* varicella vaccination depends on the impact it will have on zoster. Further work is necessary in this area. In the mean time, sensitive surveillance of zoster incidence should be a priority in

countries where immunization is underway. In countries where vaccination has yet to be implemented, pre-adolescent vaccination is a safe alternative to *infant* vaccination, since it carries no risk of increasing the age at infection or the incidence of zoster.

In the next section we illustrate why dynamic models, such as the one presented above, are important in the context of the economic evaluation of vaccination programmes.

3.3 COMPARISON BETWEEN DYNAMIC AND STATIC MODELS: THE IMPACT OF HERD-IMMUNITY

3.3.0 BACKGROUND

As described in Chapter 1, although there are many types of models that are used to predict the impact of vaccination they can be broken down into two main categories: 1) dynamic and 2) static. The major difference between these types of analysis is that in dynamic models the rate at which susceptibles become infected is dependant on the number of infectious individuals in the population (thus the system is inherently non-linear) (Edmunds *et al.*, 1999; Anderson and May, 1991; Nokes and Anderson, 1988), whereas static models treat this rate as a fixed parameter (Edmunds *et al.*, 1999). Since mass vaccination results in fewer infectious individuals in the population, under the dynamic framework the rate at which susceptibles become infected will decline, whereas under a static framework this rate remains unaltered (though there may be fewer susceptibles to act on due to vaccination). Thus dynamic models capture herd-immunity effects, whereas static models omit them.

Currently, because of its relative simplicity compared to dynamic models, the bulk of economic evaluations of vaccination programmes continue to use static models, such as decision analysis Markov models and cohort models, and therefore do not take into account the indirect effects produced by herd-immunity. Furthermore authors using static models occasionally claim to be taking account of herd-immunity effects (Rothberg et al., 2002). This comes from a misunderstanding of what herd-immunity is, what its effects are, and how to incorporate it into decision analyses.

In this section we illustrate and describe the effect of herd-immunity on the dynamics of infection using routine varicella vaccination as an example. We compare results from a dynamic model with those of a static model to illustrate and quantify the impact of incorporating herd-immunity externalities. It should be noted that results from the dynamic model used here is a simplified version of the one used in section 3.2. These simplifications are made for ease of exposition.

3.3.1 METHODS

3.3.1.1 Mathematical Models

The dynamic model used here is the realistic age-structured deterministic model of varicella presented in section 3.2 (see Appendix 5 for a description of the model). The single difference between the static model and the dynamic model, used here, is that the force of infection (per-susceptible rate of infection, sometimes termed the attack rate) in the static model remains constant through time, whereas in the dynamic model the rate at which susceptibles become infected is assumed to be a function of the number of infectious individuals in the population at a given point in time, multiplied by the effective contact rate between susceptibles and infectious individuals. That is:

λ = fixed (static)

$\lambda(t) = \beta I(t)$ (dynamic)

where λ is a $(1*k)$ vector representing the force of infection in each of the k age groups, β is a $k*k$ matrix representing the effective contact rate between individuals by age group, and I(t) gives the number of infectious individuals in each age group at time t. Static models are usually applied to a single ageing cohort (Sonnenberg and Beck JR, 1993), whereas dynamic models are run for many years to allow the full effects of the intervention to become apparent. For comparability the static model presented here is applied to multiple cohorts. It should be noted that in a cohort model, since the force of infection is constant with respect to time, the cost-effectiveness results are identical for single or multiple cohort models provided that all cohorts are followed for the same length of time (usually until death) (Edmunds *et al.*, 1999).

3.3.1.2 Parameter Estimates

Simulations were performed for a population with characteristics similar to England and Wales. The population and average life expectancy was assumed to be 50m and 75 years respectively. The age-specific force of varicella infection (the per susceptible rate of infection) in England and Wales was taken from pre-vaccination data (Chapter 2).

The different health outcomes were taken from Chapter 2. The predicted number of cases of varicella was estimated directly from the models. The estimated varicella case-fatality was applied to the predicted number of cases. For simplicity we assume that vaccine is perfect: that is, all vaccine recipients will derive life-long immunity after a single dose.

3.3.1.3 Vaccination programmes

All simulations are with 80% coverage unless otherwise stated. The different vaccination strategies investigated were:

- Routine vaccination at 1 year of age *(Infant vaccination)* and,
- Routine vaccination at 11 years *(Adolescent vaccination)*.

3.3.2 THE DYNAMICS OF VACCINATION

The introduction of routine infant mass vaccination typically produces dynamical effect which are composed of three phases (Figure 3.12a):

- *Honeymoon period*: Shortly after the start of vaccination (at high levels of coverage), the number of susceptibles falls to such low levels that continued endemic transmission is no longer possible. This results in a period of very low incidence, which is commonly called the ''honeymoon period''.
- *Post-honeymoon epidemic*: Over time, the low incidence of infection allows susceptibles (here, individuals who have not been vaccinated) to accumulate via births. Once a threshold of susceptibles is surpassed an epidemic occurs which is called the ''post-honeymoon epidemic''.
- *Post-vaccination endemic equilibrium:* After the post-honeymoon epidemic infection settles into a new equilibrium with much lower incidence than before vaccination.

Such dynamics have been observed following measles and mumps vaccination (Atkinson *et al.*, 1992; Cochi *et al.*, 1988; Chen *et al.*, 1994). Static models cannot capture these dynamics; instead the incidence of infection steadily declines as the number of cohorts vaccinated increases in the population (Figure 3.12b). Figure 3.12c shows the predicted incidence of varicella following vaccination using both

the static and dynamic model. The impact of herd-immunity on the *incidence of infection* can be visualized as the difference between the dynamic (full line) and the static model (dotted line). Quantitatively, with the *infant strategy* (80% coverage), herd-immunity (difference between the two models) is estimated to prevent 10m cases of varicella over the first 80 years of vaccination in a country similar to England and Wales (50m).

The extent of protection conferred by herd-immunity depends on the amount of continuing infection in the community. If only a small proportion of the population is immunized (low coverage and/or targeted vaccination and/or poor vaccine efficacy) then vaccination confers little or no herd-immunity since the force of infection acting on those who remain susceptible remains relatively unchanged. Here, we illustrate this point using *adolescent vaccination* against varicella as an example. The predicted number of cases of varicella over time is similar using the dynamic and static approaches (Figure 3.12c). This is expected since the bulk of cases (85%) are in children under 11 years, thus vaccinating 11 year olds has little effect on the overall force of infection of varicella (i.e. the risk of children getting chickenpox).

3.3.3 SHIFT IN THE AGE AT INFECTION AND MORBIDITY OF DISEASE

Routine infant vaccination will cause the average age at infection to rise (Anderson and May, 1991). The shift in the age at infection is due to two factors:

- *Cohort effect*: For routine infant immunisation, as vaccinated cohorts age, infection becomes concentrated in the older unvaccinated cohorts. This *cohort effect* can be clearly seen with the static model (Figure 3.12b) since herd-immunity effects do not confound it. In Figure 3.12b, incidence first declines in children while it is constant in the older age groups. Hence, the *proportion*

of adult cases increases. Only when all cohorts are vaccinated does this effect disappear.

- *Herd-immunity effect*: Vaccination at high levels of coverage leads to reduced circulation of infection. As a result, susceptibles are less likely to come into contact with infectious individuals and therefore tend to be older when they eventually become infected. The shift in the age at infection can clearly be seen in Figure 3.12a. The number of cases of varicella in adults over 45 years of age is expected to increase by more than three fold after vaccination. Note that here the *number* of adult cases increases, not just the *proportion*. Also remember that there is no waning immunity: waning vaccine-induced immunity is not necessary to induce an increase in the number of adult cases.

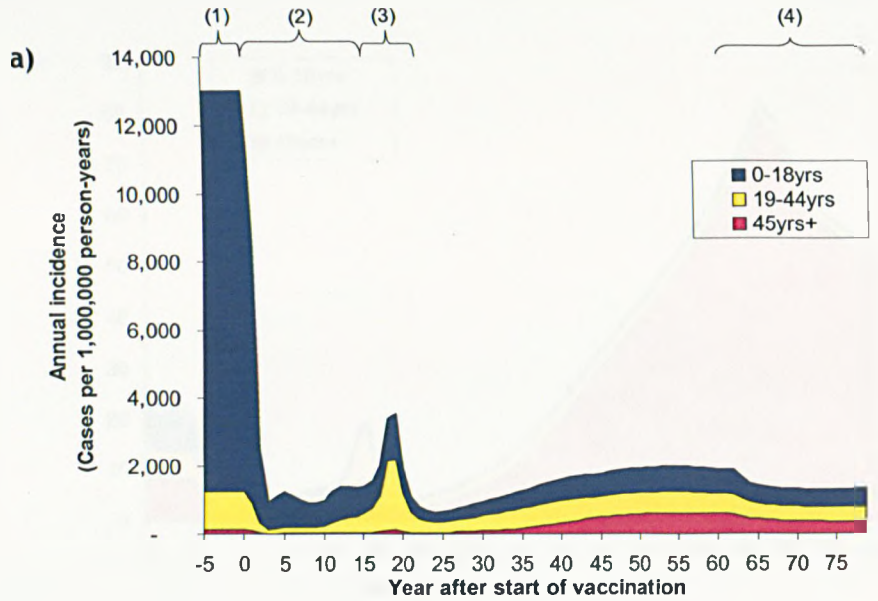
An increase in the *number* of adult cases can lead to a rise in mortality and morbidity if disease severity increases with age at infection. Many viral infections are more severe if contracted as adults; examples include polio, hepatitis A virus, and mumps, and such perverse outcomes arising from mass infant vaccination have been observed for rubella in Greece (Panagiotopoulos *et al.*, 1999) (rubella is a benign childhood infection, which can have devastating effects on the foetus if a mother contracts the virus during pregnancy). These shifts in the age at infection can also have beneficial effects if disease is most severe in young children - e.g. pertussis and measles in developing countries.

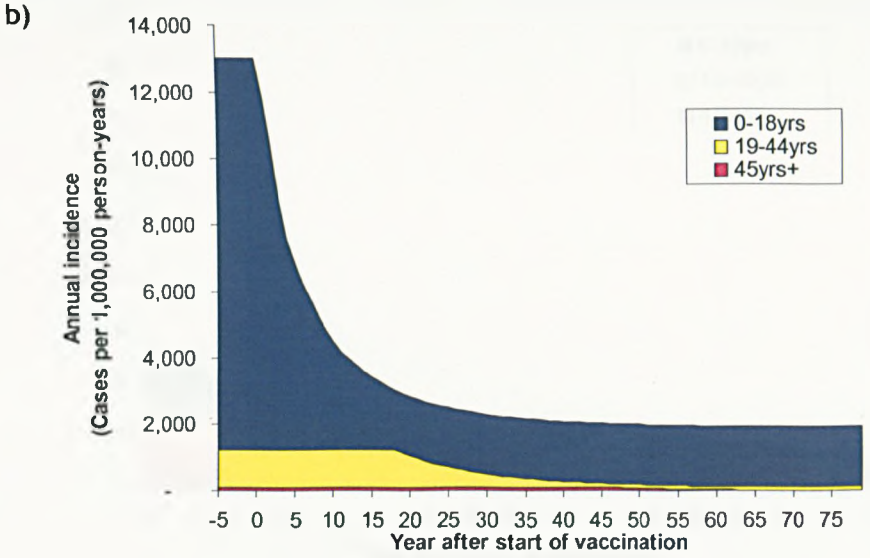
Since static models cannot predict an absolute increase in adult cases, the choice of model can have an important impact on the overall assessment of the benefit of vaccination. We illustrate this by comparing the predicted number of varicella deaths in England and Wales following vaccination using the dynamic and static models (Figure 3.13). Varicella deaths are used as an example since varicella-

associated case-fatality increases dramatically with age. The dynamic model initially produces a rapid decrease in deaths following vaccination (Figure 3.13a). However, after 50 years the number of deaths due to varicella rises and surpasses the pre-vaccination level due to the increase in the number of cases in adults. In contrast, using the static model the number of deaths falls as the number of cohorts that are vaccinated increases (Figure 3.13b). Over the first 80 years of vaccination, the dynamic model predicts that vaccination will produce 315 deaths over the pre-vaccination level while the static model predicts that 765 deaths will be prevented. Thus, herd-immunity (difference between the two models) is estimated to cause 1,080 deaths over the first 80 years of vaccination in England and Wales.

The extent to which the average age at infection will rise following routine infant vaccination depends on the amount of continuing infection in the community. As the proportion of immunized individuals increases in the population so does the average age at infection due to increased herd-immunity. To illustrate this, in Figure 3.14 we present the estimated number of varicella deaths in England and Wales at post- vaccination equilibrium by vaccine coverage. Here, coverage is equal to the proportion immunized since the vaccine is assumed to be perfect. For the dynamic model the proportion of deaths in adults increases between 0 and 60% coverage (Figure 3.14a). Furthermore, only when coverage exceeds 80% does vaccination seem to diminish varicella transmission sufficiently to reduce adult mortality to levels below the pre-vaccination state. In contrast, without herd-immunity (Figure 3.14b), the number of deaths decreases linearly with increased coverage and there is no shift in the age distribution of deaths - e.g. 50% coverage will reduce the number of deaths by 50% in all age groups. This leads to our final point, for the static model the number of cases or deaths prevented per

immunised individual is independent of the overall number of individuals vaccinated (coverage). This means that the cost-effectiveness ratio is independent of coverage (overall size of the vaccine programme), assuming there are no fixed or constant marginal costs associated with setting up the programme. However, Figure 3.14a clearly shows that if herd-immunity is taken into account, the size of the programme has a major impact on effectiveness and thus cost-effectiveness.





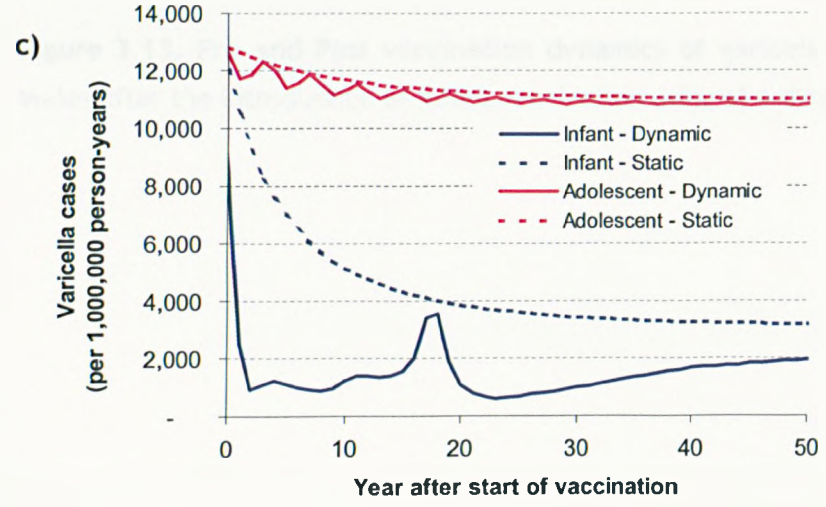


Figure 3.12. Pre and Post vaccination dynamics of varicella infection Estimated age-specific incidence of natural varicella after the introduction (at time zero) of infant vaccination using a) a dynamic and b) a static model. (80% coverage, perfect vaccine). The various epidemiological phases are: (1) pre-vaccination; (2) honeymoon period; (3) post-honeymoon epidemic; and (4) equilibrium. C) Estimated varicella incidence over time by vaccine strategy (80% coverage, perfect vaccine) using a dynamic (full line) and static model (dotted line).

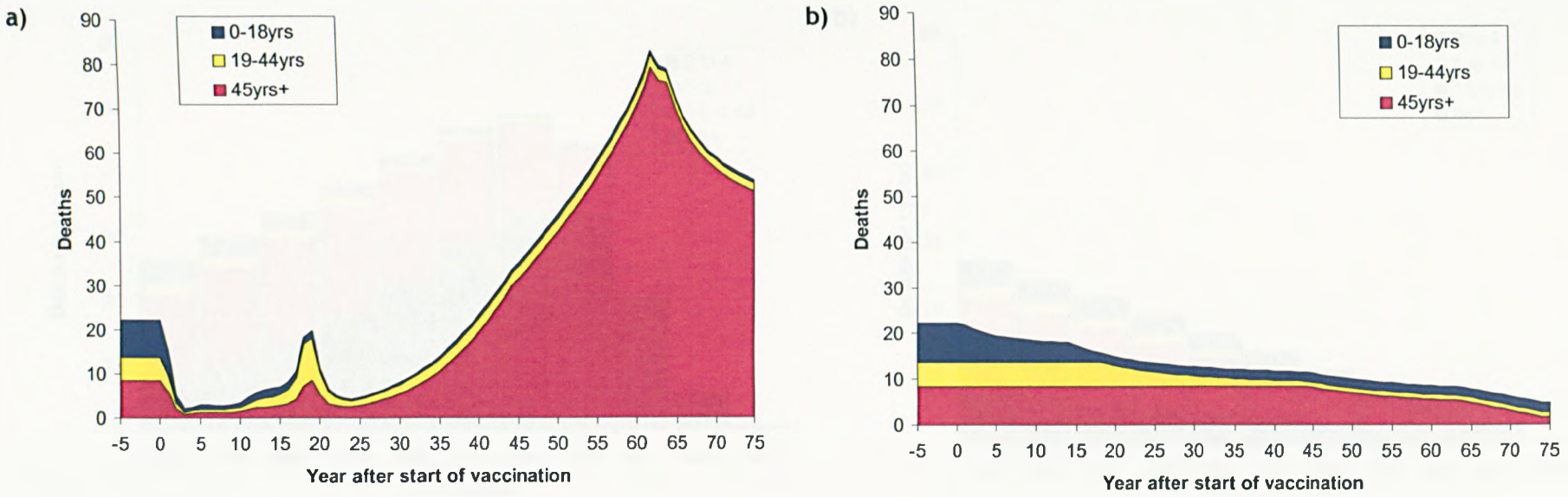


Figure 3.13. Pre and Post vaccination dynamics of varicella infection Estimated age-specific mortality due to varicella in England and Wales after the introduction of infant vaccination using a) a dynamic and b) a static model. (80% coverage, perfect vaccine).

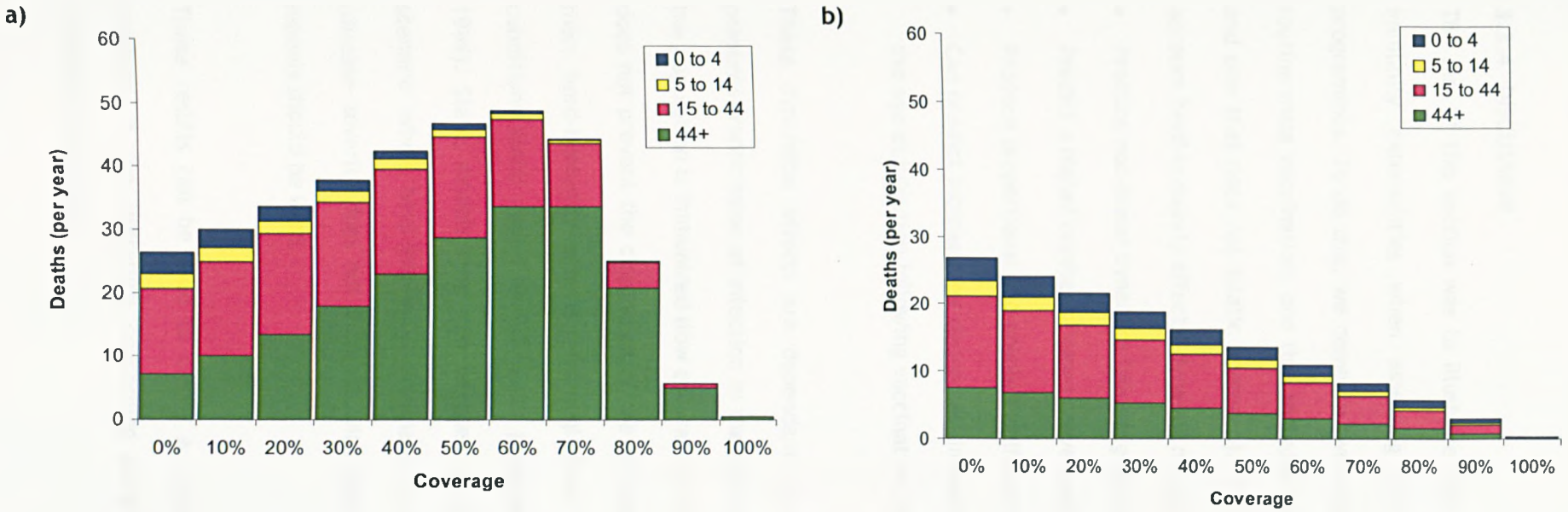


Figure 3.14. Post vaccination equilibrium. Predicted age distribution of varicella associated deaths in England and Wales at equilibrium by vaccine coverage using a) a dynamic and b) a static model (perfect vaccine).

3.3.4 DISCUSSION

The aim of this section was to illustrate the importance of incorporating herd-immunity externalities when assessing the health benefits of vaccination programmes. To do this, we compare two methods of estimating the benefits of routine mass vaccination, one that includes herd-immunity (dynamical approach) and one that does not (static approach). We show that because they take into account herd-immunity effects, dynamic models:

- Produce non-linear dynamics following vaccination (Figure 3.12a)
- Predict a higher number of cases prevented by vaccination (Figure 3.12c)
- Produce proportional and absolute shifts in the age at infection (Figure 3.13a)
- Can predict increases (or decreases) in morbidity and mortality due to shifts in the age at infection following vaccination (Figure 3.13-3.14).

These dynamical effects are dependant on the extent to which vaccination prevents transmission of infection in the population. If only a small proportion of the population is immunized (low coverage or targeted vaccination) or the vaccine does not prevent the circulation of the pathogen (as occurs with some vaccines) then herd-immunity effects are negligible (Figure 3.12, 3.14). Under such conditions static and dynamic model produce similar results (Edmunds *et al.*, 1999). Static models may also be used as a tool to estimate the worst-case scenario when herd-immunity externalities cannot produce negative effects (disease severity does not increase with age). In other circumstances dynamic models should be used.

These results can be used to clarify a number of misconceptions, which are common in the literature concerning herd-immunity and dynamical effects produced by models:

- *Herd-immunity is always a good thing*: We show that herd-immunity can cause the age at infection to increase, which can cause serious deleterious consequences (Figure 3.13-3.14). It is not always a conservative assumption to ignore herd immunity effects. Indeed, a static model may grossly overestimate the effectiveness of mass vaccination at preventing serious disease if the risk of developing complications increases with age at infection, as is shown here for chickenpox.
- *Waning vaccine-induced immunity is necessary to cause an increase in adult cases.* While waning vaccine-induced immunity can exacerbate increases in the average age at infection it is not necessary, as we have demonstrated here.
- *Static models can give rise to shifts in the age at infection*: If a static model is applied to successive cohorts then the models can produce a temporary shift in the age at infection. These shifts are due to a cohort effect (the vaccinated cohorts make up the younger age groups) and not herd-immunity. Once all the cohorts have been vaccinated the age distribution of infection will be identical to the pre-vaccination state. Furthermore, this will only produce a temporary proportional increase in adult infections (as opposed to absolute increases) as the rate of infection in the older (unvaccinated) cohorts remains the same as it was before vaccination. Hence, static models cannot investigate whether shifts in the age at infection following vaccination will produce increases (or indeed decreases) in morbidity.

There is a large literature on models of infectious disease transmission dating back to Bernouilli in the 18th century (for a comprehensive textbook on the subject see Anderson and May (1991) or Bailey (1975)). Analysts who ignore this literature (because of complexity) and assume that the disease in question is not infectious (as static models implicitly assume) do so at the risk of biasing results of economic analysis and can mislead public health decision makers.

3.4 SUMMARY

First, in this chapter we examined the potential impact of varicella vaccination on VZV disease. As described in Chapter 2, mass vaccination has two dangers; it could increase the number of varicella cases in adults, where severity is greater, and increase cases of zoster. A deterministic realistic age-structured model (RAS) was built to study these concerns. Model parameter estimates were derived from a literature review and surveillance data from England and Wales. Different vaccine efficacy scenarios, vaccine coverages and vaccination strategies were investigated. The model predicts that, although an upward shift in the age at infection occurs resulting from more cases in adults, the overall morbidity due to varicella is likely to decrease following mass infant vaccination. On the other hand, cases of zoster may significantly increase in the first 50 years following vaccination.

Secondly, we illustrated the importance of incorporating herd-immunity externalities when assessing the effectiveness of vaccination programmes. To do this, we compared two methods of estimating the benefits of routine mass vaccination, one that includes herd-immunity (dynamical approach) and one that did not (static approach). Finally, we used the results to clarify a number of misconceptions, which are common in the literature concerning herd-immunity and dynamical effects produced by models. These results show that, in certain circumstances, ignoring the herd-immunity externality can lead to gross miscalculations of the effectiveness and thus the cost-effectiveness of vaccination programmes.

The research in this chapter has been published in full (or in part) in the following peer reviewed articles:

- **Brisson M**, Edmunds WJ, Gay NJ. Varicella vaccination: Impact of vaccine efficacy on the epidemiology of VZV. J Med Virol 2003;70 Suppl 1:S31-7.
- **Brisson M**, Edmunds WJ. Economic evaluation of vaccination programmes: The impact of herd-immunity Med Decis Making 2003; 23:76-82.
- **Brisson M**, Gay NJ, Edmunds WJ, Andrews NJ. Exposure to Varicella Boosts Immunity to Herpes-zoster: Implications for mass vaccination against chickenpox. Vaccine 2002; 20: 2500-2507.
- Edmunds WJ, **Brisson M**. The effect of vaccination on the epidemiology of varicella zoster virus. Journal of Infection 2002; 44: 211-219.
- **Brisson M**, Edmunds WJ, Gay NJ, Law B, De Serres G. Modelling the impact of immunisation on the epidemiology of varicella zoster virus. Epidemiol Infect 2000; 125:651-669.
- **Brisson M**, Edmunds WJ, Gay NJ, Law B, De Serres G. Analysis of varicella vaccine breakthrough rates: Implications for the effectiveness of immunisation programs. Vaccine 2000; 18(25):2775-2778.

Chapter 4
Valuing the Benefit of Vaccination Programmes

4.0 INTRODUCTION

The specific objectives of chapter 4 are to:

1) Estimate the willingness to pay for varicella vaccination and the Quality Adjusted Life-Years (QALY) lost due to chickenpox and shingles using different elicitation techniques,
2) Examine and compare the different elicitation techniques and their outcomes,
3) Assess the importance of the different attributes of immunisation,
4) Examine how individual preferences can be aggregated to estimate the overall population's value of the benefit of vaccination taking into account externalities and non-health effects.

In the first section, we examine what are individual's preferences regarding chickenpox vaccination and how they can be measured and valued (individual perspective). We estimate the average willingness to pay for varicella vaccination and the QALY lost due to chickenpox (no such information exists within the international literature). We then attempt to identify what attributes of vaccination are important to vaccinees and what elicitation technique can capture these components.

In section 2, we examine how to measure the benefit of vaccination at the population level (population perspective). That is, we explore different methods of aggregating individual revealed preferences to the population level taking into account externalities (herd-immunity and zoster, see Chapter 3) as well as the non-health benefits of vaccination (estimated in the first section of this Chapter).

Results from this chapter should provide a better understanding of how the choice of valuation technique, outcome measure and method of aggregation can affect the results of economic evaluation of vaccination programmes and therefore influence resource allocation decision-making.

4.1 VALUE OF VARICELLA VACCINATION - INDIVIDUAL PERSPECTIVE

4.1.0 BACKGROUND

In order for economic evaluation of health programmes to be comparable, a common methodology must be used to estimate benefits. However, there is no consensus on the technique that should be used. This stems, in part, from a theoretical disagreement on how economic analysis should be performed. There are two competing views on economic evaluation in health care: Welfarism and extra-welfarism (Tsuchiya and Williams, 2001; Brouwer and Koopmanschap, 2000). The first is based on the theory of welfare economics, on which the theoretical foundation of economic evaluation was built. Welfarism is the perspective where the benefit of an intervention depends solely on individuals' self-assessed preferences (Brouwer and Koopmanschap, 2000; Johansson, 1991). Welfarists believe that Cost-Benefit analysis with monetary valuation of benefits should be used. The second view, extra-welfarism, is that other types of measure can be used, and may be more pertinent, than individual preferences in the context of

resource allocation in health care (Culyer, 1990; Wagstaff, 1991; Brouwer and Koopmanschap, 2000). Extra-welfarists believe that the benefits of health interventions should be based on quantifiable and comparable effectiveness measures such Life-years and QALYs gained (McGuire, 2001) and therefore that Cost-Effectiveness or Cost-Utility analysis should be performed. It has been argued that QALYs do not only measure health outcomes but can measure preferences (utilities) and that Cost-Utility analysis (Cost per QALY-gained) can be consistent with Cost-Benefit under certain assumptions (Bleichrodt and Quiggin, 1999). These theoretical issues have been extensively debated in the literature (Blomqvist, 2002; Dolan and Edlin, 2002; Bleichrodt and Quiggin, 1999; Garber and Phelps, 1997; Johannesson, 1995). The aim of this section is not to study under which theoretical assumptions Cost-Utility and Cost-Benefit would yield different or similar resource allocation or what theoretical perspective should be taken as the correct basis for judging the benefit of health interventions. Rather, the aims of this section are to compare various valuation techniques and examine empirically what attributes of health intervention they can capture. That is, we focus on empirical problems rather than theoretical issues. This, in the context of vaccination.

Most elicitation techniques have been developed for interventions that treat chronic diseases in adults. Vaccination has different characteristics, which may have an impact on which measures of benefit should be used when assessing the impact of immunisation campaigns. Vaccination is different from most health interventions found in the literature because: 1) it is a preventative intervention (in contrast to curative), 2) it protects against infectious disease, 3) the diseases it prevents are usually short-lived and self-limiting (and can be mild), 4) most vaccines are given to young children from whom it is very difficult to elicit

health/program preferences. Because of its unique characteristics, vaccination may possess its own specific benefits. At the time of this study, to our knowledge no study has attempted to measure the different attributes of the benefit of vaccination.

It has been argued that health is not the only source of well being derived from public health interventions (Mooney, 1994; Birch *et al.*, 1999; Olsen and Smith, 2001). For vaccinees, the overall benefit of vaccination can be separated into 4 possible dimensions: 1) the direct effect on health, 2) caring (altruism), 3) security (reduction of uncertainty), and 4) productivity effects.

Direct effect on health. The principal benefit that can be derived from vaccination is that it prevents the vaccinee from acquiring disease and thus losing health related quality of life. Health related quality of life being defined as a state of physical, mental and social well-being and not merely absence or presence of disease (World Health Organisation, 1947). Other direct effect on health could be the side-effects related to the vaccine itself.

Caring externality (Altruism). Preventing (or treating) infection in a proportion of individuals in the population offers a degree of protection to others in the population. Because of this, the vaccinee (or vaccinees parent) may derive benefit from the knowledge that by being vaccinated they will not infect other children (e.g. their siblings and friends). Such a benefit can be called caring (*paternalistic* or *altruistic* Altruism). In this section, *altruism* indicates *paternalistic* or *altruistic* altruism.

Security (Insurance type benefits). Immunisation offers protection against the uncertain future event of catching disease and its consequences. In these terms, being vaccinated can be viewed as taking insurance against disease. Because individuals are generally risk averse (afraid to take risks) in relation to health, they may find an added benefit in the knowledge that they are protected against disease.

Productivity effect (Work loss). Individuals may also find benefit in that vaccination can also prevent them missing time off work or other inconveniences and welfare enhancing activities.

In this section we examine three different valuation techniques to measure the benefit of varicella vaccination: 1) Contingent valuation (Monetary value), 2) Standard Gamble (QALY) and the Health Utilities Index mark 2 (HUI2) questionnaire (QALY).

Monetary value of health outcomes has gained renewed interest in recent years with the increased popularity of Contingent Valuation (CV) and the Willingness to pay (WTP) measure (Olsen and Smith, 2001; O'Brien and Gafni, 1996; Klose, 1999; Diener et al., 1998; Johannesson, 1993). The main arguments to CV's superiority, as a measure for health intervention, is that it is theoretically correct, because of its base on economic theory (welfare economics) and that it values benefits in the same unit as the costs and therefore allows direct comparison (Olsen and Smith., 2001, Birch *et al.*, 1999, Bala *et al.*, 1998; O'Brien and Viramontes, 1994; O'Brien and Gafni, 1996; Klose, 1999). Other aspects/qualities of CV and WTP are particularly appropriate for evaluating the benefit of vaccination (Birch *et al.*, 1999). First, it is a method of valuation that is sensitive to small changes in well-

being at the individual level. Many vaccines that are now available prevent self-limiting, short lasting and/or mild diseases (e.g. varicella and influenza). Second, it imposes no restrictions on which dimensions of a vaccine programme individuals are allowed to express a value for. That is, theoretically, WTP should be capable of capturing the different non-health benefits of vaccination described above (altruism, uncertainty, work loss). On the other hand, the principal disadvantage of the CV and other WTP techniques is that the hypothetical WTP is usually found to be higher than the actual WTP and may be oversensitive to small changes in health or programme benefits (Seip & Strand, 1992; Duffield and Patterson; 1991, Clarke, 2002) (see Chapter 1 for further detail on WTP and CV).

QALYs are the most used method for measuring outcomes (Elixhauser *et al.*, 1998), mainly because of the widespread reluctance of clinicians and policymakers in the healthcare sector to evaluate health changes in monetary terms (Drummond *et al.*, 1997; Johannesson, 1996; Brouwer and Koopmanschap, 2000). The concept of QALY was developed to capture simultaneously gains from reduced morbidity and reduced mortality, and to combine these into a single measure. It has been suggested that QALYs cannot capture non-health benefits (Olsen and Smith, 2001; Donaldson *et al.*, 1997). Here, we test this hypothesis using two very different methods of estimating QALYs. First, we use the standard gamble (SG) because it is a standard technique that has a basis in economic theory (i.e. based on von Neumann-Morgenstern utility theory (von Neumann and Morgenstern, 1944). Second, it is similar to the CV in that it uses the economic concept of opportunity costs under uncertainty. For the SG, individuals are asked to trade-off probability of survival or risk of returning to a worse health state (in contrast to money with WTP) in return for health improvement. The main disadvantage of using SG for vaccine preventable disease is that many are acute and/or mild and therefore the

risks individuals must trade-off are too small for them to comprehend. The use of SG and TTO to value morbidity for acute diseases has well documented measurement and evaluation problems (Bala, and Zardin, 2000; Bala *et al.*, 1999; Stalmeier *et al.*, 1996; Gafni, 1994; Dolan and Gudex, 1995; Stiggelbolt, 1995; Bleichrodt, Johannesson; 1997). Furthermore, SG has shown to be insensitive to small changes in health status (De Wit *et al.*, 2000). The main reasons for choosing SG over TTO was that it resembles more the CV technique (uses the concept of opportunity costs under uncertainty) and that it has the potential of measuring non-health benefits of vaccination. Within the TTO framework it would have been very difficult to include scenarios that are close to vaccination. Within the TTO framework trade-offs are made between durations of current health states without the concept of uncertainty. On the other hand, a vaccine scenario is easily included in the SG framework. That is, the respondent can be asked to choose the probability of immediate death (or some other outcome worse than the one being valued) they are prepared to accept from vaccination to avoid the chance of acquiring the future disease being valued. Furthermore, SG can capture risk aversion, which is the basis of the insurance type benefit and the disutility related to insecurity about potential vaccine adverse events. As stated below due to ethic committee concerns a vaccination scenario was not included in the final questionnaire. Nevertheless, the SG technique was chosen here as the electronic questionnaires were programmed and the insights gained by using the SG technique will be used for future work on measuring the (dis)utility related to risk aversion of vaccine adverse events and non-health benefits.

The second technique used to measure QALYs lost due to chickenpox is the health status index (Health Utilities Index mark 2 (HUI2)) (see Chapter 1 for description). Multi-attribute health status indices, such as HUI2, are a simple alternative to the

complex task of measuring preference through SG (or other similar techniques). Furthermore, it can capture small changes in heath status (De Wit *et al.*, 2000; de Vries *et al.*, 1998), which is of particular interest for vaccine preventable diseases.

The feature that distinguishes between techniques of economic evaluation is the way in which the benefits of health care programmes are valued. Surprisingly, only very few studies have directly compared WTP and QALYs (Bala *et al.*, 1998; O'Brien and Viramontes, 1994; Stavem K, 2002). The results raise questions as to whether QALYs and WTP would lead to similar decisions concerning the allocation of health resources. Furthermore, no study has compared QALYs and WTP for immunisation, small changes in well-being or have examined if QALYs are truly incapable of measuring individuals non-health benefits.

The objectives of this section are threefold: 1) to estimate willingness to pay for varicella vaccination and the Quality Adjusted Life Years (QALY) lost due to chickenpox, 2) to compare results, and 3) identify what attributes of vaccination (i.e. direct health effect, non-health effects, spill over effects) these elicitation techniques can capture.

4.1.1 METHODS

4.1.1.1 Ethical approval

Because it was the intention to interview mothers of healthy young children in health care settings in which they ordinarily would make the decision to vaccinate, it was felt necessary to seek approval from an ethics committee even though no medical intervention or invasive procedure was being proposed. Ethical approval was initially sought from the *Camden* and *Islington* Community Health

Services NHS trust in July 2001. The project was rejected by the Deputy Director of Primary Care in *Camden* and *Islington* in October 2001 and thus was not reviewed by the ethics committee. The questionnaires were slightly different at this stage. We intended to elicit the impact of vaccine adverse events into the CV questionnaire. The main reason for refusal was that, because of the anxiety about the Measles-Mumps-Rubella (MMR) vaccine, ''parents may confuse some of the 'risk' themes of the project with other immunisations that their children are receiving''.

The questionnaire was revised and questions relating to the risk of vaccination were removed. In October 2001, application for ethical approval was sent to the PHLS ethics committee and the *Barnet, Enfield* and *Haringey* Local Research Ethic Committee. In June 2002, ethical approval was granted from both committees. Ethical approval was difficult to obtain primarily because CV and SG questionnaire were new to the members of the various ethical committees.

4.1.1.2 Sampling and survey design

The study population consists of parents. Parents were used as proxies for their children since at the time of chickenpox vaccination (or disease) the child is too young to reveal his/her preferences (incapable of answering the valuation questionnaires (Friedman, 1990; Torrance, 1986; Vogels et al., 1998)). Furthermore, it is the parent who decides whether or not their child is vaccinated. We recruited all parents regardless of whether or not their children had prior history of varicella. For ethical reasons, the only inclusion/exclusion criteria was age greater than 18 years.

Parents and caregivers were recruited from primary Health Centres in Enfield, London at the time of routine infant and child check-ups. Parents were approached in the waiting room where they were given an information leaflet (see Appendix 6) and asked to participate in the study. Those consenting to participate were given a computer active interview. The interview took place at the moment of consent.

4.1.1.3 Questionnaire and experimental design

The computerised questionnaire was programmed in Visual Basic within Microsoft Access (the questionnaire was programmed by Richard Bois and Marc Brisson).

Before the start of the main study, a pilot study was conducted to finalize the questionnaire. The computer active pilot questionnaire was administered to 89 parents (20 SG and 69 CV). From the pilot we concluded that respondents had little difficulty answering the questionnaires and that the bidding scales used produced adequate distributions. This lead to some changes in wording. The final computer active questionnaire is structured into 3 parts (see Appendix 7, 8, 9 and 10 for questionnaires).

Part 1: Socio-demographic questionnaire. In *part 1*, respondents are asked standard socio-demographic questions such as their age, sex, level of education and annual income (see Appendix 7). Other questions are more specific to chickenpox vaccination. Respondents are asked whether their children are fully vaccinated for their age in order to have an idea of the parent's general attitude towards vaccination; if they need to take time off work when their child is sick, and whether any of their children have had chickenpox.

Part 2: Contingent Valuation or Standard Gamble questionnaire. In *part 2*, respondents are given one of two different types of questionnaire: 1) CV (Appendix 8) and 2) SG (Appendix 9). Each parent or caregiver responded to only one type of question. Interviews using the CV and SG questionnaires were given on different days.

Contingent Valuation: The respondents are given a description of the health profile of a child with chickenpox (the description of chickenpox was written in collaboration with Natasha Crowcroft, PHLS Consultant Epidemiologist - see Appendix 8 part 1). In a first instance we ask respondents to assume that their child has chickenpox and that a drug exists which can cure their child immediately. We then elicit the maximum the respondent is willing to pay for the drug. In the second section of the CV questionnaire, respondents are asked the maximum they are willing to pay to vaccinate their child against chickenpox (i.e. to prevent their child having chickenpox sometime in the future). With CV, there are two measures of utility change: compensating variation and equivalent variation. Under compensating variation individuals are maintained on the initial level of utility before the health intervention whereas equivalent variation keeps the individual at the new level of utility attained after the intervention (Johansson, 1991). Here, compensation variation was used since the questionnaire measures the maximum amount that must be taken from the gainer to maintain the level of utility he/she had before the health intervention. We used the ex-post user-based perspective (respondents are asked to assume they are at the point of intervention) for comparability with the standard gamble, which has a similar perspective. However, as mentioned earlier, immunisation offers protection against the uncertain future event of catching disease. In this respect, the second section (vaccination question) has also characteristics of insurance-based

questions (i.e. respondents are at the point of intervention (vaccination) but not in the disease state). Table 4.1 presents a summary description of the CV questionnaire, used here, following O'Brien and Gafni's (1996) conceptual framework.

Table 4.1. Description of CV questionnaire

Question	Consideration
What question do we want to answer?	Problem Definition: Project appraisal for resource allocation. Current Status of Program: Program does not currently exist (Dis)Utility of program to respondent: Gain in utility from program
What type of measure is used?	Monetary measure of utility change: Compensating Variation "Direction" of measurement: Willingness to pay
What is asked of whom?	Externality and option value: Diseased (Treatment) Non-diseased: At future risk (Vaccination) Framing of program consumption and payment: Ex-post user-based question
What characteristics of the program are important for determining how it is valued?	Program outcome description: Certain outcomes (Efficacy 100%) Uncertain outcomes (Efficacy 85%)
What question format was used?	Valuation scenario: Scenarios are holistic and decomposed. Value elicitation method: Bidding Games

Adapted from O'Brien and Gafni (1996)

Respondents were given randomly one of 4 different contingent valuation questionnaires (Appendix 8). The questionnaires differ in their description of the effectiveness and consequences of the intervention. Table 4.2 describes the

different components included in the 4 questionnaires. By comparing the willingness to pay between and within the different questionnaires it is possible to estimate the value parents place on vaccination and its different attributes.

Overall benefit of chickenpox vaccination in vaccines: Clinical trials and post vaccine surveillance have shown the varicella vaccine to be 85% effective (Vazquez *et al.*, 2001). Therefore, the overall benefit of chickenpox vaccination in vaccinees is estimated by assessing the average willingness to pay for chickenpox vaccination when efficacy is 85% (Appendix 8 part 2 and 3).

Attributes of vaccine programmes: The *direct health effect* of preventing a case of chickenpox will be measured by estimating the average willingness to pay for chickenpox treatment when efficacy is 100% (Appendix 8 part 4). It should be pointed out that, due to ethical reasons, parents were told that vaccination and treatment had no side effects. The value parents' put on preventing their child infecting others (*altruism*) is measured by comparing the WTP from questionnaires highlighting/stressing this effect (Appendix 8 part 2 and 4) to those in which the effect is not mentioned (Appendix 8 part 3 and 5). The benefit of security (*insurance type benefit*) will be measured by comparing the difference in parent's willingness to pay for treatment and vaccination. Finally, the value of *parental work loss* will be measured by estimating whether parents who must take time off work when their child is ill are willing to pay more to prevent chickenpox than those who do not, controlling for factors such as household income. It should be noted that many adults will not lose financially from being off work although their employers will. Therefore, WTP will only capture a portion of the welfare losses.

Table 4.2. Attributes varied in the CV questionnaires

	Efficacy		Altruism
	100%	85%	
Appendix 8 part 2		×	×
Appendix 8 part 3		×	
Appendix 8 part 4	×		×
Appendix 8 part 5	×		

× indicates that the attribute is included in the description of the intervention

Standard Gamble: A separate group of respondents were asked to imagine that their child is in an imaginary health state for 15 years (see Appendix 9 part 1 for description). The duration of 15 years was chosen so that parents would trade risks of death for intervention and it is the time-span of childhood. Apart from the duration of disease, the health profile is identical to the description of chickenpox, though the patients were not told that the disease in question was chickenpox. Interviews using the CV and SG questionnaires were given on different days so that parents could not compare questions and thus associate the disease description in the SG questionnaire to chickenpox.

The SG questionnaire asks the parent what risk of death they would theoretically be willing to take to cure their child. Respondents are given randomly one of 2 different SG questionnaires (see Table 4.3 and Appendix 9). The only attribute varied in the SG questionnaire was *altruism*. *Altruism* is included by specifying that treatment will prevent the child from giving the disease to other children. Probabilities were presented numerically and visually to make clear the risks that were being traded-off (see Appendix 9 Part 2 and 3). Visual aids were similar to those presented by Appel *et al.* (1990).

Table 4.3. Attributes varied in the SG questionnaires

	Altruism
Appendix 9 part 2	
Appendix 9 part 3	×

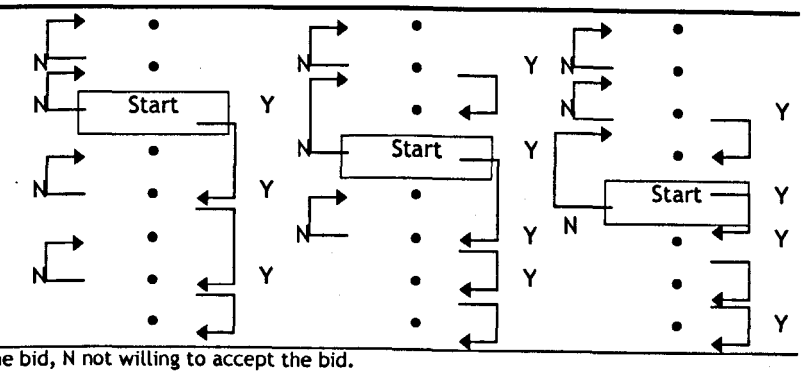
× indicates that the attribute is included in the description of the intervention

The experimental design used, here, is a combination of conjoint analysis and CV or SG. That is, we present individuals with various scenarios that include different attributes (conjoint analysis) and from which we obtain preferences using CV or SG. Such a technique has been used to estimate the value of product attributes for antihistamine drugs (Reardon and Pathak, 1990). We did not ask parents to value directly the different attributes to prevent warm glow effects (Olsen, 1997).

Respondent's maximum WTP or maximum acceptable risk to return to perfect health (SG) is assessed using bidding algorithms. Bidding algorithms is a standard approach in which the interview (computerized in this case) follows a pre-programmed search strategy of probing accept/reject/indifferent questions at different bids, each one conditional on the person's previous response (O'Brien and Gafni, 1996). Starting point bias has been identified in such algorithms (O'Brien and Viramontes, 1994; Stalhammar, 1996). To test and control for starting point bias, we used three randomised starting bids for the CV and SG questions. The starting point and bidding algorithms, for both the CV and SG questionnaires, are presented in Table 4.4.

Table 4.4. Bidding Scales and Bidding algorithms for WTP and SG questions

WTP Bid Scale	SG Bid Scale	Bid Algorithm 1	Bid Algorithm 2	Bid Algorithm 3
£0	0.1%			
£10	0.5%			
£25	1%			
£50	2%			
£75	5%			
£100	10%			
£150	15%			
£200	20%			



Y, willing to accept the bid, N not willing to accept the bid.

For SG, if a person is indifferent we stop the bidding.

Part 3: Health Utilities Index mark 2 (HUI2) questionnaire. In part 3 we ask the respondents to rate the health state that has been described to them (chickenpox (CV) or the imaginary disease (SG)) using an existing generic health status index (Health Utilities Index mark 2 (HUI2)). This enables us to estimate the QALY loss due to chickenpox as well as validate the WTP and SG responses. Preferences for the HUI2 scoring function were measured on a random sample of parents of schoolchildren in the City of Hamilton (Canada) and surrounding district using both the SG and a visual analogue score (Torrance *et al.*, 1996). Because it was developed for childhood diseases using parents as proxies and utilities were derived using SG, HUI2 is an ideal tool to compare responses from Part 2 (CV and SG questionnaires).

4.1.1.4 Data Analysis

CV and SG model. The respondents' answers to the questions do not directly reveal their maximum WTP (CV) or their maximum acceptable risk to return to perfect health (SG). The responses only provide bounds. For example, a respondent who responds *yes* to £100 but *no* to £150 is assumed to have a WTP value between £100 and £150. Furthermore, the data is both right and left

censored. That is, the lowest bid for WTP is £0 (0.1% for SG) and highest is £200 (20% for SG).

Interval regression was used here because it can estimate models for point, interval and censored data. Using this method we estimate the average WTP for chickenpox treatment and vaccination (CV) and average acceptable risk (SG). Furthermore, we test which intervention and respondent attributes affect the results as well as whether there is starting point bias. The variables and attributes included in the regression are listed and described in Table 4.5.

Interval regression can be described as follows. Let a_{li} and a_{ui} be the lower and upper bounds for each respondent and y_i represents the true WTP or risk (SG). We assume that y_i is represented by the following function:

$$y = x\beta + \varepsilon \qquad (1)$$

Where, x is the vector of variables, β is the vector of regression coefficients and ε is the error term. The model assumes that $\varepsilon \sim N(0,\sigma^2 I)$. The probability of y_i falling between the lower and upper bounds is:

$$Pr[a_{li} \leq y_i < a_{ui}] = Pr[(a_{li} - x_i\beta \leq \varepsilon_i < a_{ui} - x_i\beta)] \quad (2)$$

The log likelihood function, derived from this, is (StataCorp, 2002):

$$L = \left[\begin{array}{l} -1/2 \sum_{J \in C} \left\{ \left(\frac{y_i - x\beta}{\sigma} \right)^2 + \log 2\pi\sigma^2 \right\} + \sum_{J \in L} \log \Phi \left(\frac{y_{Li} - x\beta}{\sigma} \right) \\ + \sum_{J \in R} \log \left\{ 1 - \Phi \left(\frac{y_{Ri} - x\beta}{\sigma} \right) \right\} + \sum_{J \in I} \log \left\{ \Phi \left(\frac{a_{li} - x\beta}{\sigma} \right) - \Phi \left(\frac{a_{ui} - x\beta}{\sigma} \right) \right\} \end{array} \right] \quad (3)$$

where observations $j \in C$ are point data (y_i), $j \in L$ are left-censored ($y_i < y_{Li}$), $j \in R$ are right-censored ($y_i \leq y_{Ri}$) and $j \in I$ are interval data ($a_{li} \leq y_i < a_{ui}$).

Analyses were carried out in Stata v.7.0. (StataCorp, 2002). Regression was performed using the **intreg** function. The data generated from the study sample was re-weighted (using the **pweight** function) to be representative of the population of parents with children of vaccine age in England. Weights for the CV and SG analyses are presented in Tables 4.6 and 4.19 respectively.

The final multivariable models used to estimate the average WTP and SG and to identify significant variables were selected using the following method. Firstly, univariable analyses identified variables that were significant ($p<0.2$ level) for inclusion in the multivariable models. Secondly, the identified variables were added to the model and retained if they remained significant ($p<0.1$ level). Finally, the variables that were excluded at the univariable stage were included one by one to assess whether they became significant.

Residuals were tested for normality. Furthermore, we compared the log likelihoods for the interval regression and the ordered probit regression (**oprobit** command, stata v.7.0) since both model interval and censored data and their likelihoods are discrete.

Table 4.5. Variable specification

Variable	Description
Gender	0=female, 1=male
Age	age in years
Degree	0=degree, 1=no degree
Work	0=does not work, 1=works
Vaccinated	0=children are fully vaccinated for their age, 1=children are not fully vaccinated, 9=don't know or did not answer
Work loss	0=Need to take time off work when child is sick, 1=Does not need to take time off work
Children	1=1 child, 2=2 children, 3=3 children, 4=4 or more children, 9=did not answer
Chickenpox[A]	0=at least one child has had chickenpox, 1=no child has had chickenpox, 9=don't know or did not answer
People	1=1 person in the household, 2=2 people in the household, 3=3people in the household, 4=4 people in the household, 5=5 people in the household, 9=did not answer
Income	0=annual household income before tax is less than £15,000, 1=£15,000-24,999, 2=£25,000-39,999, 3=£40,000-59,999, 4=more than $60,000, 9= did not answer
Altruism[B]	0=altruism, 1=no altruism
Efficacy[A,B]	0=100% efficacy, 1=85% efficacy
HUI2[B]	QALY weight of chickenpox as measured by the HUI2 system
Start Bid	0= start bid is £25 (CV) or 1% (SG), 1= start bid is £50 (CV) or 2% (SG), 2= start bid is £75 (CV) or 5% (SG)

A. Not included in the SG analysis (see Appendix 7). B. Not included in the HUI2 analysis.

Analysis of refusals. In the CV questionnaire respondents have the option to refuse chickenpox treatment and vaccination for their children (that is, would not accept the intervention even if cost was zero). We used logistic regression (Stata v.7.0, **logistic** function) to examine which variables determined whether or not parents refused intervention. In the analysis, the dependant variable is 0 if the respondent refused intervention and 1 otherwise with independent variable presented in Table 4.5.

QALY-weight estimation from SG. As described above, the average maximum risk of instant painless death (P) parents are willing to accept for their children is estimated using interval regression. From this a QALY-weight can be estimated. The standard gamble questionnaire elicits the probability P that makes the respondent indifferent between the current condition:

$$Q * T + 1 * (L - T) \qquad (3)$$

and the expected benefit of treatment:

$$(1-P) * L * 1 + P * 0 \qquad (4)$$

where, Q is the QALY-weight, T is duration of disease (15 years in the SG questionnaire), ω is the current life expectancy of the child (we assume 75 years) and P is the probability of instant painless death following the intervention. From equations 3 and 4 we have:

$$Q = \{(L *(1-P))- (L - T)\} /T \qquad (5)$$

We do not use discounting, here, because it is inconsistent with the QALY utility model (Mehrez and Gafni, 1989; Johannesson et al., 1994). Furthermore, these equations assume constant-proportional trade-off (Pliskin et al., 1980).

QALY-weight estimation from HUI2. QALY-weights can directly be measured from the HUI2 system using the scoring formula published by Torrance *et al.* (1996). The overall average QALY-weight and significant variables will be assessed using linear regression (Stata v.7.0, **reg** function). The variables included in the regression are listed and described in Table 4.5. Both responders to the CV and the SG filled in the HUI2. The description of disease was identical in the two questionnaires apart from duration, that is in the CV questionnaire the disease is

assumed to be for a week and in the SG it is assumed to last for 15 years (see Appendices 8 and 9 for descriptions). In this section, we term HUI2-CV and HUI2-SG the health state described to CV and SG respondents respectively. By comparing HUI2-CV and HUI2-SG we test whether duration of disease has an impact on HUI2, which it should not if the SG QALY model works.

4.1.2 WILLINGNESS TO PAY - CV QUESTIONNAIRE

4.1.2.1 Characteristics of respondents

Table 4.6 shows the characteristics of respondents to the CV questionnaire. Two hundred parents answered the questionnaire, 91% of whom were women. Because the setting was in baby clinics, the parents interviewed had very young children (53% were younger than 1 year, 36% between 1 and 4 years). This was intended, as we sought to recruit parents of children that were close to the age of vaccination and who were susceptible to chickenpox. Compared to ONS statistics , the parents of the sample were older, more educated and had a higher household income than average (see Table 4.6 for details). This is controlled for in the WTP analysis.

Table 4.6. Characteristics of respondents - CV questionnaire

	Study		ONS	Under-representation
	N	%	%	
Gender				
Male	18	9%		
Female	183	91%		
Age (years)				
< 20	5	2%	8%[A]	0.31
20-29	65	32%	47%	0.68
30-39	124	61%	43%	1.43
40+	8	4%	2%	1.98
Degree				
Yes	96	48%	28%[B]	1.70
No	106	52%	72%	0.73
Work				
No	84	42%	46%[C]	0.90
Yes	118	58%	54%	1.07
Number of ***children***				
1	123	61%		
2	63	31%		
3	14	7%		
4+	2	1%		
Age of children (years)				
0	149	53%		
1-4	100	36%		
5+	32	11%		
Children fully ***vaccinated***				
yes	186	92%	86-94%[D]	
no	9	4%		
don't know or n.a.	7	3%		
Work loss when child is sick				
yes	83	41%		
no	119	59%		
Child with ***chickenpox***				
yes	42	21%	23%[E]	0.90
no	157	78%		
don't know or n.a.	3	1%		
Number of ***people*** in household				
1	1	0%		
2	14	7%		
3	102	50%		
4	65	32%		
5+	19	9%		
na	1	0%		
Household ***income*** before tax				
<£15,000	19	9%	12%[F]	0.78
£15,000-24,999	27	13%	17%	0.79
£25,000-39,999	51	25%	31%	0.81
£40,000-59,999	47	23%	17%	1.37
£60,000+	36	18%	12%	1.49
na	22	11%	11%	1.00

A. Birth Statistics, 1999: age of mother: Live births; B. Labour Force Survey, 2000 - women aged 25-44; C. Labour Force Survey, 2000 - Economic activity status of women: by marital status and children aged less than 5 years; - Proportion of fully vaccinated children by 24 months in UK; E. Predicted % of seropositive children using the sero-profile estimated in Chapter 2; F. Family Expenditure Survey 1999-2000 - Characteristics of households: by children aged less than 5 years.

4.1.2.2 Distribution of WTP responses

All respondents to the CV questionnaire (202 parents) were asked their WTP for both chickenpox vaccination and treatment. The distribution of WTP responses is presented in Figure 4.1. Twenty-nine and 31 parents said they would not have their child treated and vaccinated, respectively, even if it was free. Of the parents who were willing to have their children both treated and vaccinated, 49 were WTP more for vaccination, 5 were WTP more for treatment and 111 provided identical WTP (Figure 4.2). Using McNemar's test for paired data, the WTP for vaccination was found to be significantly higher than for treatment (χ^2=34, p-value<0.0001). This suggests that parents find an added benefit in prevention - i.e. that *insurance type benefits* exit.

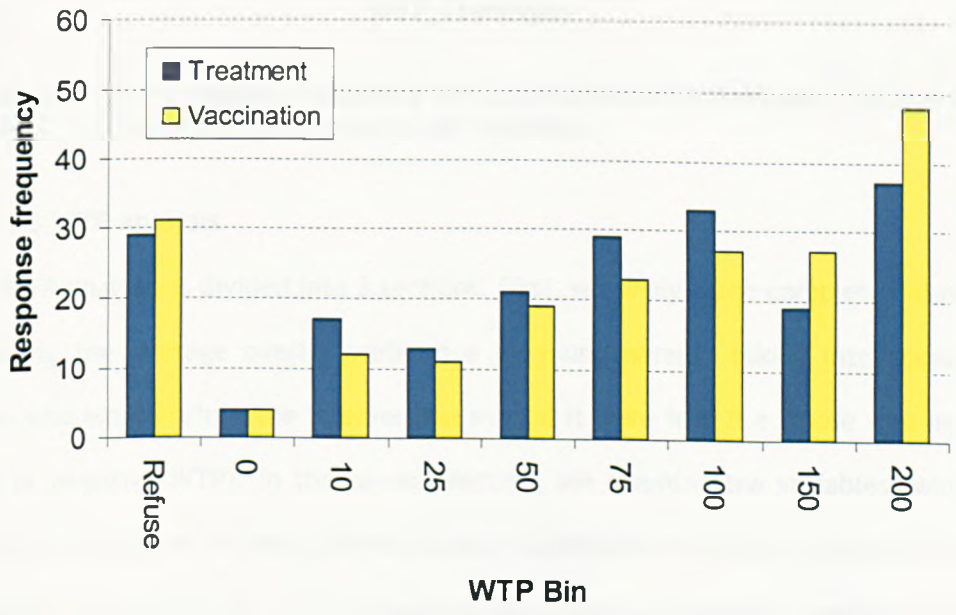


Figure 4.1. Response frequency to the CV questionnaire.

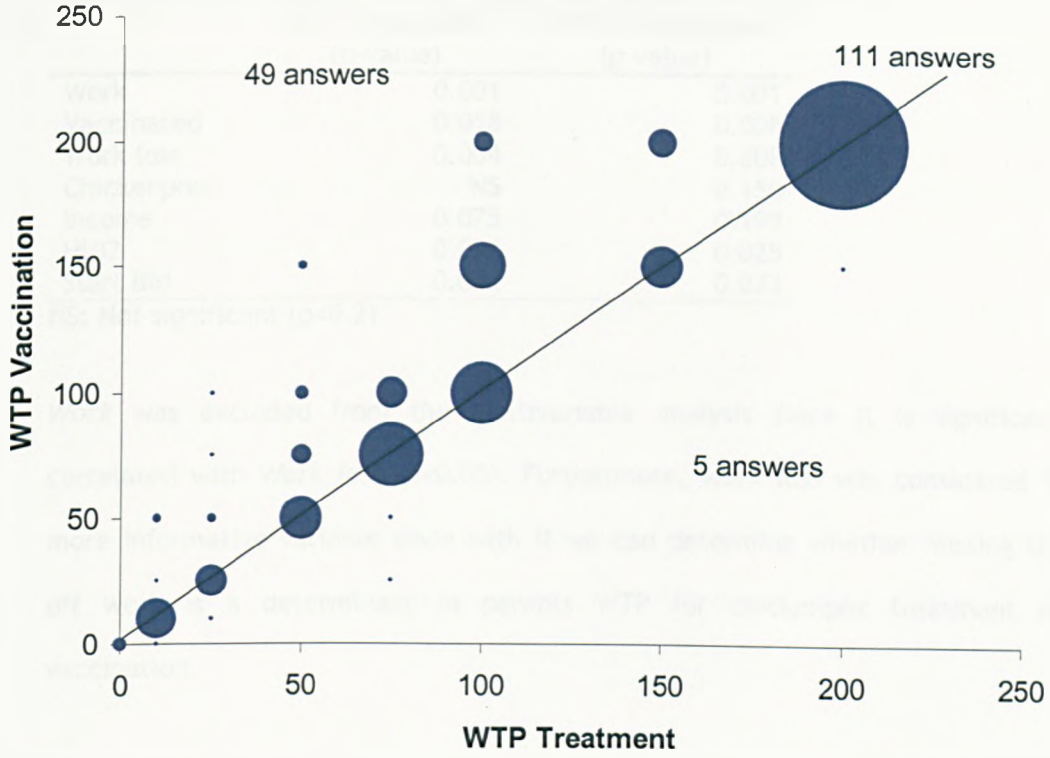


Figure 4.2. WTP response frequency for vaccination and treatment. The size of the dots is a function of the frequency of responses.

4.1.2.3 WTP analysis

The WTP analysis is divided into 3 sections. First, we analyse the complete dataset assessing the average overall preference of young parents taking into account those who would refuse the intervention even if it were free (i.e. those who have zero or negative WTP). In the second section, we examine the variables, which determine whether or not parents refuse chickenpox treatment or vaccination. Thirdly, we analyse the WTP of parents who desire chickenpox treatment and vaccination for their children.

A. WTP analysis with refusals.

Empirical results. The significant parameters identified by the univariable analysis are presented in Table 4.7.

Table 4.7. Univariable analysis - significant parameters ($p<0.2$)

	WTP Treatment (p-value)	WTP Vaccination (p-value)
Work	0.001	0.001
Vaccinated	0.018	0.008
Work loss	0.004	0.008
Chickenpox	NS	0.150
Income	0.075	0.199
HUI2	0.004	0.025
Start Bid	0.092	0.033

NS: Not significant ($p<0.2$)

Work was excluded from the multivariable analysis since it is significantly correlated with *Work loss* ($p<0.05$). Furthermore, *work loss* was considered the more informative variable since with it we can determine whether missing time off work is a determinant in parents WTP for chickenpox treatment and vaccination.

Results from the interval regression model are presented in Tables 4.8 and 4.9. Significant variables ($p < 0.05$) for both the WTP for treatment and vaccination were *Vaccinated, Work Loss, Income, HUI2* and *Start Bid.* Parents of children who are fully vaccinated for their age (*Vaccinated*=0) are willing to pay £107 and £134 more for chickenpox treatment and vaccination, respectively. Furthermore, controlling for other variables, parents who must take time of work when their children are sick (*Work loss*=0) are WTP £32 (£38) more for treatment (vaccination). Results also suggest there is starting point bias. WTP for treatment and vaccination is significantly higher for respondents who were given the £75 starting bid (*start bid*: $p<0.05$ Tables 4.8 and 4.9). Finally, as expected by theory, WTP increases with the household income (*income*: $p<0.05$) and with perceived severity of chickenpox (*HUI2*: $p<0.05$). It should be noted that *altruism* and *efficacy* were not found to be significant factors in parents WTP for chickenpox treatment and vaccination.

Residuals from the interval regression were normally distributed (see Appendix 11). Ordered probit regression (**oprobit** command, stata v.7.0) was performed to validate model results since, as interval regression, it can model interval and censored data and their likelihoods are discrete. The ordered probit models produced the same significant variables and similar log likelihoods to the interval regression models (-391 and -392 for treatment and vaccination respectively). We chose interval regression although it produced slightly lower log likelihoods because coefficients are in natural units and, contrary to **oprobit**, it is possible to measure mean WTP.

Table 4.8. WTP for treatment - Interval regression model with refusals

	Coef	[95% CI]	P>|z|
Constant	169.44	(89.48 to 249.39)	0.000**
Vaccinated			0.009**
0	0	Baseline	
1	-107.36	(-173.68 to -41.04)	
9	-53.61	(-139.89 to 32.66)	
Work loss			0.023**
0	0	Baseline	
1	-31.55	(-58.78 to -4.32)	
Income			0.062*
0	0	Baseline	
1	13.44	(-41.48 to 68.36)	
2	35.29	(-14.02 to 84.60)	
3	66.81	(16.95 to 116.67)	
4	58.51	(5.23 to 111.79)	
9	44.38	(-14.14 to 102.91)	
Start Bid			0.037**
0	0	Baseline	
1	-2.55	(-34.69 to -29.58)	
2	35.10	(2.64 to 67.56)	
HUI2	-131.11	(-213.35 to -48.86)	0.002**
σ	89.18	(77.52 to 100.83)	
Log likelihood	-408.63		
Null Log-likelihood	-430.06		
LR $\chi^2(12)$	42.83		0.000**
Sample size	202		

* Significant at p<0.1; ** Significant at p<0.05

Table 4.9. WTP for vaccination - Interval regression model with refusals

	Coef	[95% CI]	P>|z|
Constant	187.39	(87.02 to 287.77)	0.000**
Vaccinated			0.012**
0	0	Baseline	
1	-134.24	(-220.12 to -48.36)	
9	-55.45	(-161.18 to 50.28)	
Work loss			0.028**
0	0	Baseline	
1	-38.12	(-72.11 to -4.12)	
Income			0.098*
0	0	Baseline	
1	18.15	(-50.13 to 86.43)	
2	41.50	(-19.64 to 102.63)	
3	74.16	(11.92 to 136.40)	
4	64.64	(-2.01 to 131.30)	
9	34.04	(-39.11 to 107.18)	
Start Bid			0.014**
0	0	Baseline	
1	-28.50	(-68.81 to 11.83)	
2	30.87	(-9.55 to 71.28)	
HUI2	-130.44	(-233.61 to -27.27)	0.013**
σ	109.75	(94.00 to 125.50)	
Log likelihood	-395.26		
Null Log-likelihood	-414.02		
LR $\chi^2(12)$	37.52		0.000**
Sample size	202		

* Significant at p<0.1; * *Significant at p<0.05

Table 4.10. Average WTP for treatment and vaccination - Interval regression model with refusals

	Average WTP	[95% CI]
Treatment		
Sample	98.38	(83.95 to 112.81)
England[A]	90.08	(75.21 to 104.95)
Vaccination		
Sample	105.42	(87.58 to 123.26)
England[A]	96.16	(78.92 to 113.41)

A. Data generated from the study sample re-weighted to represent the population of parents with children of vaccine age in England. Weights used are presented in Table 4.6.

WTP estimates. Table 4.10 presents the estimated average WTP for chickenpox treatment and vaccination for the study sample and the population of England. The sample has a higher WTP because it has a higher income, higher level of education and older population. The difference between vaccination and treatment is approximately £8. Even though, in Table 4.10, the 95% confidence

intervals of WTP for treatment and vaccination overlap, results from the paired test presented in section 4.1.2.2 show that the difference is significant ($p<0.0001$).

B. Analysis of refusals.

Tables 4.11 and 4.12 report the results from the logistic regression of acceptance/rejection of chickenpox treatment and vaccination. Significant variables are *Vaccinated*, *Work* and *HUI2*. Parents of children who are fully vaccinated for their age (*Vaccinated*=0) are estimated to be 6 (1/0.16) fold more likely to accept treatment or vaccination. Furthermore, parents who work (*Work*=1) were 3 times more likely to accept intervention against chickenpox. Finally, those who accepted treatment or vaccination thought chickenpox to be more severe then those who did not.

Table 4.11. Wanted treatment - Logistic regression model

	Odds Ratio	[95% CI]	P>|z|
Vaccinated			0.034**
0	1	Baseline	
1	0.16	(0.03 to 0.83)	
9	0.25	(0.03 to 1.99)	
Work			0.010**
0	1	Baseline	
1	3.29	(1.41 to 7.68)	
HUI2	0.001	(0.00 to 0.08)	0.002**
Log likelihood	-74.08		
Null Log likelihood	-89.93		
Model $\chi^2(4)$	30.99		0.000**
Sample size	200		

* *Significant at p<0.05

Table 4.12. Wanted vaccination - Logistic regression model

	Odds Ratio	[95% CI]	P>|z|
Vaccinated			0.003**
0	1	Baseline	
1	0.16	(0.04 to 0.72)	
9	0.11	(0.01 to 0.79)	
Work			0.004**
0	1	Baseline	
1	2.93	(1.39 to 6.20)	
HUI2	0.07	(0.00 to 1.04)	0.041**
Log likelihood	-90.86		
Null Log likelihood	-103.26		
Model $\chi^2(4)$	23.87		0.000**
Sample size	200		

* *Significant at p<0.05

C. WTP analysis without refusals

This section analyses the WTP of parents who desired chickenpox treatment or vaccination for their children.

Empirical results. The significant parameters identified by the univariable analysis are presented in Table 4.13. Work was excluded from the multivariable analysis since it is significantly correlated with work loss.

Table 4.13. Univariable analysis no refusals-significant parameters (p<0.2)

	WTP Treatment (p-value)	WTP Vaccination (p-value)
Degree	0.059	0.171
Age	0.087	0.173
Work	0.037	0.117
Work loss	0.007	0.011
Income	0.003	0.001
HUI2	NS	0.184

NS: Not significant (p<0.2)

Tables 4.14 and 4.15 report the results from the interval regression model of WTP values for treatment and vaccination. Significant variables for both the WTP for treatment and vaccination were *Work Loss* and *Income*. Controlling for other variables, parents who must take time of work when their children are sick (*Work*

loss=0) are willing to pay £26 (£24) more for treatment (vaccination). Interestingly, the perceived severity of chickenpox was not significant in the amount parents were WTP. Thus, perceived severity seems to be a significant factor in whether or not parents would want their child to be treated (or vaccinated - Tables 4.11 and 4.12) against chickenpox but not the amount they are WTP (Tables 4.14 and 4.15). Once parents have decided they were willing to treat (or vaccinate) their children, the most important factor in their maximum WTP for intervention is their income (i.e. their capacity to pay). *Altruism* and *efficacy* were not found to be significant factors in parents WTP.

Table 4.14. WTP for treatment - Interval regression model no refusals

	Coef	[95% CI]	P>|z|
Constant	88.28	(48.05 to 128.512)	0.000**
Work loss			0.050**
0	0	Baseline	
1	-26.15	(-49.95 to -2.36)	
Income			0.010**
0	0	Baseline	
1	22.89	(-24.51 to 70.29)	
2	44.07	(2.36 to 85.77)	
3	61.49	(19.77 to 103.21)	
4	60.09	(14.94 to 105.24)	
9	84.90	(34.02 to 135.79)	
σ	73.73	(64.06 to 82.68)	
Log likelihood	-354.54		
Null Log-likelihood	-365.71		
LR $\chi^2(6)$	22.34		0.001**
Sample size	173		

* *Significant at p<0.05

Table 4.15. WTP for vaccination - Interval regression model no refusals

	Coef	[95% CI]	P>|z|
Constant	97.24	(52.28 to 142.21)	0.000**
Work loss			
0	0	Baseline	0.074*
1	-24.41	(-51.17 to 2.34)	
Income			
0	0	Baseline	0.005**
1	34.16	(-18.8 to 87.15)	
2	42.20	(-3.81 to 88.21)	
3	79.58	(32.38 to 126.77)	
4	82.13	(30.40 to 133.86)	
9	84.19	(27.06 to 141.33)	
σ	79.43	(68.50 to 90.37)	
Log likelihood	-320.63		
Null Log-likelihood	-332.27		
LR $\chi^2(6)$	23.28		0.001**
Sample size	171		

* *Significant at p<0.1; * *Significant at p<0.05

Table 4.16. Average WTP for treatment and vaccination - Interval regression model no refusals

	Mean WTP	S.E.	[95% CI]
Treatment			
Sample	121.61	6.23	(109.39 to 133.81)
England[A]	104.63	7.85	(89.25 to 120.01)
Vaccination			
Sample	140.45	7.16	(126.42 to 154.50)
England[A]	120.21	8.69	(103.18 to 137.24)

A. Data generated from the study sample re-weighted to represent the population of parents with children of vaccine age in England. Weights used are presented in Table 4.6.

WTP estimates. Table 4.16 reports the descriptive statistics about the WTP for varicella treatment and vaccination. The average WTP values reveal the same pattern as results that included those who refused intervention. The WTP for chickenpox vaccination is significantly greater than for treatment (£18 for the sample and £16 for England) suggesting that insurance type benefits exist. Furthermore, the average WTP for the sample is higher than for England.

Table 4.17. Mean average value of vaccination attributes (£).

	England	Sample
Direct Health Benefit	93.81	110.89
Altruism	0.00	0.00
Insurance Type Benefit	15.68	18.84
Parental Work loss	10.72	10.72

From Table 4.14, 4.15 and 4.16 it is possible to estimate the monetary value of the various attributes of varicella vaccination. *Altruism* was not significant in the WTP models. In our sample, the *insurance type benefit* is estimated to be £18.84 (£140.45 - £121.61, Table 4.16). Furthermore, the average value of parental *work loss* in the sample was £10.72 (£26.41*Proportion of parents who do not take time of work (41%), Table 4.6 and 4.14).

4.1.3 QUALITY-ADJUSTED LIFE-YEARS - SG QUESTIONNAIRE

4.1.3.1 Characteristics of respondents

Because, there were fewer attributes tested in the SG questionnaire, the sample size (63) was lower than the CV questionnaire. Table 4.18 presents the characteristics of the 63 respondents to the SG questionnaire and how they compare to women with children under 5 years in the general population of England. The characteristics of parents who responded to the SG questionnaire (Table 4.18) were similar to those who responded to the CV questions (Table 4.6). Compared to ONS statistics , the parents of the SG sample were older, more educated, worked more and had a higher household income (see Table 4.18 for details). This is controlled for in the SG analysis.

Table 4.18. Characteristics of respondents - SG questionnaire

	Study N	Study %	ONS %	Under-representation
Gender				
Male	7	11%		
Female	56	89%		
Age (years)				
< 20	2	3%	8%[A]	0.40
20-29	25	40%	47%	0.84
30-39	31	49%	43%	1.14
40+	5	8%	2%	3.97
Degree				
Yes	31	49%	28%[B]	1.76
No	32	51%	72%	0.71
Work				
No	22	35%	46%[C]	0.76
Yes	41	65%	54%	1.21
Number of Children				
1	43	68%		
2	15	24%		
3	4	6%		
4+	1	2%		
Age of Children (years)				
0	43	48%		
1-4	33	37%		
5+	13	15%		
Children fully vaccinated				
yes	56	89%	86-94%[D]	
no	5	8%		
don't know or n.a.	2	3%		
Work loss when child is sick				
yes	30	48%		
no	28	44%		
don't know	5	8%		
Number of people in household				
1	1	2%		
2	3	5%		
3	35	56%		
4	17	27%		
5+	6	10%		
na	1	2%		
Household income before tax				
<£15,000	2	3%	12%[E]	0.27
£15,000-24,999	10	16%	16%	0.97
£25,000-39,999	22	35%	30%	1.17
£40,000-59,999	12	19%	16%	1.16
£60,000+	8	13%	12%	1.10
na	9	14%	14%	1.00

A. Birth Statistics, 1999: age of mother: Live births; B. Labour Force Survey, 2000 - women aged 25-44; C. Labour Force Survey, 2000 - Economic activity status of women: by marital status and children aged less than 5 years; D. Proportion of fully vaccinated children by 24 months in UK; E. Predicted % of seropositive children using the sero-profile estimated in Chapter 2; F. Family Expenditure Survey 1999-2000 - Characteristics of households: by children aged less than 5 years.

4.1.3.2 Distribution of SG responses

The distribution of risk of instant death elicited from the SG questionnaire is presented in Figure 4.3. The most prevalent response was a 10% risk of death.

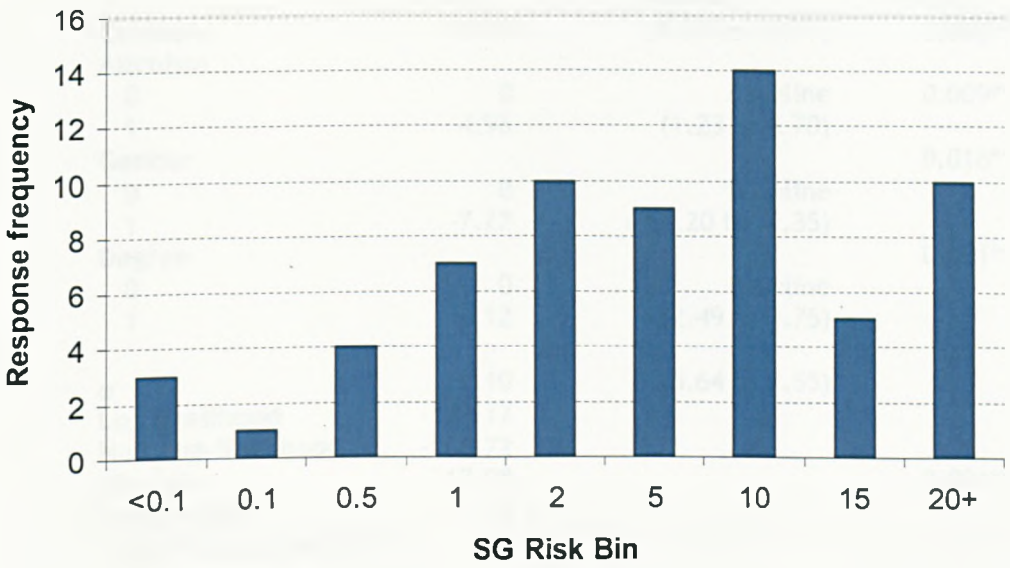


Figure 4.3. Response frequency to the SG questionnaire.

4.1.3.3 SG analysis

The SG analysis is divided into 2 sections. First, we present the average risk parents are willing to accept to return their children to normal health and investigate whether SG can capture non-health benefits. In the second section, we present the average QALY-weight estimated from the SG questionnaire.

Empirical results. Table 4.19 reports results from the interval regression model of parents' maximum acceptable risk. The significant variables of this model are *Gender*, *Degree* and *Altruism*. Fathers were willing to take, on average, a 5% greater risk of death for their child to return to normal health than mothers. Furthermore, respondents without a degree were, on average, willing to take a 6% higher risk than those with a degree. Parents who were told their child could

transmit the imaginary disease to other children were willing to accept a 5% greater risk of death than those who did not.

Table 4.19. SG - Interval regression model

	Coef	[95% CI]	P>|z|
Constant	10.05	(4.34 to 15.77)	0.000**
Altruism			
0	0	Baseline	0.009**
1	4.96	(1.23 to 8.70)	
Gender			0.016**
0	0	Baseline	
1	-7.27	(-13.20 to -1.35)	
Degree			0.001**
0	0	Baseline	
1	6.12	(2.49 to 9.75)	
σ	7.10	(5.64 to 8.55)	
Log likelihood	-158.17		
Null Log-likelihood	-166.72		
LR $\chi^2(3)$	17.08		0.001**
Sample size	63		

* *Significant at p<0.05

QALY-weight estimates. The average risk accepted by respondents was 9% (95%CI 7%-11% - Table 4.20). This corresponds to a QALY-weight of 56% (95% CI: 45%-66%). The average risk of death that would be acceptable to parents is predicted to be higher for England (14%), and therefore produce a lower QALY-weight (31%). This is because the study sample has a high proportion of parents with a degree.

Table 4.20. Average risk of death - Interval regression model

	Mean Risk	[95% CI]
Sample	8.88	(6.80 to 10.95)
England[A]	13.74	(8.43 to 19.05)

A. Data generated from the study sample re-weighted to represent the population of parents with children of vaccine age in England. Weights used are presented in Table 4.18.

4.1.4 QUALITY-ADJUSTED LIFE-YEARS - HUI2 QUESTIONNAIRE

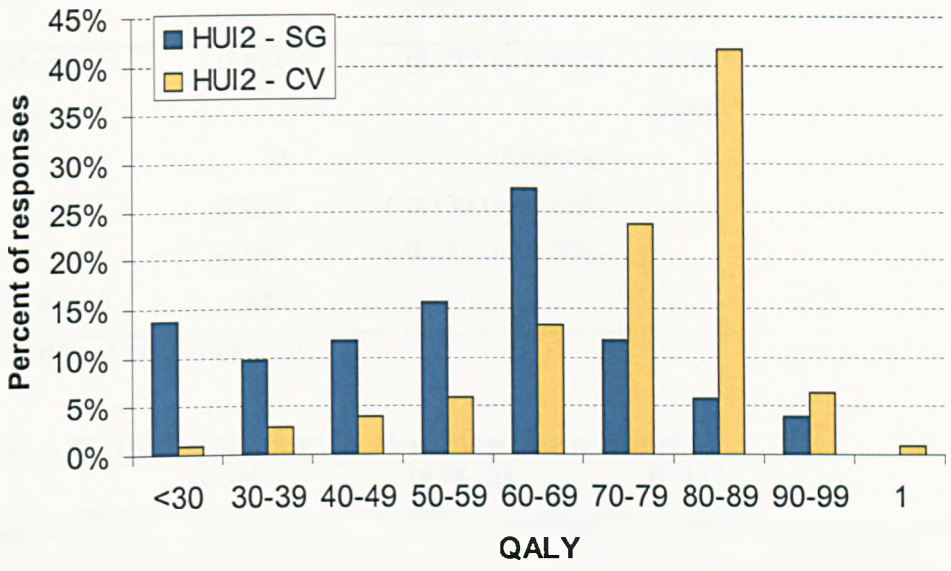
4.1.4.1 Distribution of HUI2 responses

The distribution of QALY-weights estimated from the HUI2 responses are very different between respondents who were given the CV and SG questionnaires (Figure 4.4a). This, despite the fact that the description of disease was identical except for duration, and in the CV questionnaire we specify to parents that they are valuing chickenpox (see Appendices 8 and 9). Furthermore, of those who responded to the CV questionnaire, the distribution of QALY-weights elicited differed between parents whose children have had chickenpox and those who have not.

4.1.4.2 HUI2 analysis

Tables 4.21 and 4.22 report results from the regression model of QALY-weights elicited from respondents of the CV and SG questionnaires, respectively, using the HUI2 system. For respondents of the CV questionnaire, the single significant variable was *Chickenpox*. Respondents whose children never had chickenpox (*Chickenpox=1*) believed chickenpox to be more severe (lower QALY-weights). For respondents of the SG questionnaire, *Altruism* was the lone significant variable. Parents who were given the *altruistic* questionnaire had a significantly lower QALY-weight.

a)



b)

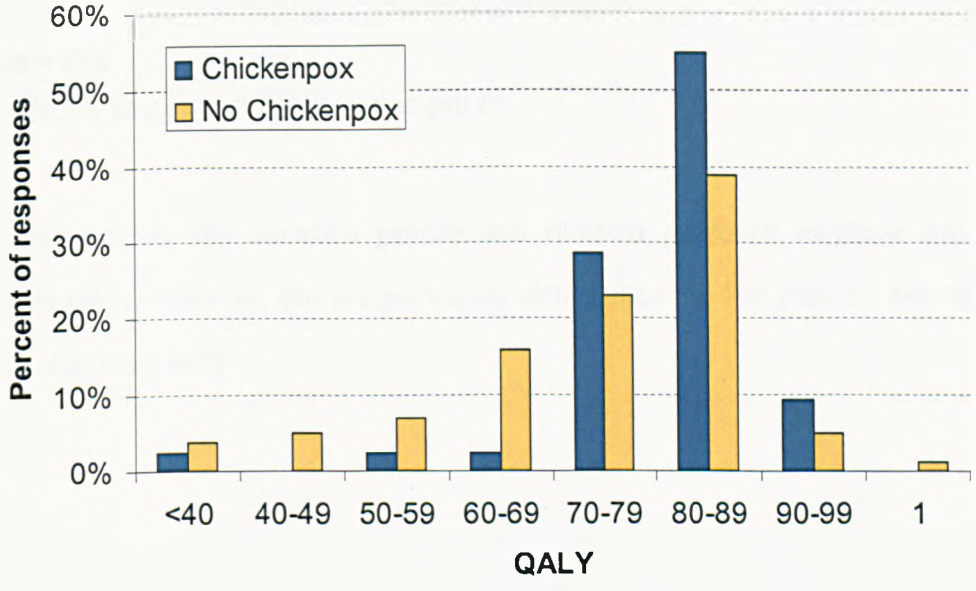


Figure 4.4. QALY-weight distribution elicited from HUI2. a) Distribution of QALY-weights elicited from CV and SG respondents. b) Distribution of QALY-weights elicited from CV respondents stratified into whether or not the parent has a child with a previous history of chickenpox.

Table 4.21. HUI2 - CV questionnaire - Regression model

	Coef	[95% CI]	P>|z|
Constant	0.824	(0.777 to 0.872)	0.000**
Chickenpox			0.008**
0	0	Baseline	
1	-0.077	(-0.130 to -0.023)	
9	-0.188	(-0.371 to -0.004)	
Sample size	202		

* *Significant at p<0.05

Table 4.22. HUI2 - SG questionnaire - Regression model

	Coef	[95% CI]	P>|z|
Constant	0.608	(0.546 to 0.670)	0.000**
Altruism			0.034*
0	0	Baseline	
1	-0.101	(-0.194 to -0.008)	
Sample size	63		

*Significant at p<0.1; **Significant at p<0.05

For the sample, the standard gamble and HUI2-SG produced identical QALY-weights (56%). However, this is significantly different to the 76% (95% CI: 74%-78%) calculated from HUI2-CV.

Table 4.23. Average QALY-weight for chickenpox from HUI2

	Mean QALY	[95% CI]
HUI2-CV[A]		
All children		
Sample	0.76	(0.74 to 0.78)
England[B]	0.75	(0.72 to 0.78)
Children with history of chickenpox		
Sample	0.82	(0.77 to 0.87)
England[B]	0.81	(0.75 to 0.87)
HUI2-SG[C]		
Sample	0.56	(0.52 to 0.61)
England[B]	0.57	(0.48 to 0.66)
SG questionnaire		
Sample	0.56	(0.45 to 0.66)
England[B]	0.31	(0.05 to 0.58)

A. Data generated from the study sample re-weighted to represent the population of parents with children of vaccine age in England. Weights used are presented in Table 4.6; B. See Appendix 8 part 1 for description of chickenpox; C. See Appendix 9 part 1 for descrition of imaginary disease.

4.1.5 DISCUSSION

In this section we used various elicitation techniques (CV, SG and HUI2) to estimate parent's WTP for varicella vaccination and the QALY lost due to chickenpox and to identify the different attributes of vaccination.

Conjoint valuation. The average WTP for parents who desired varicella vaccination, corrected to represent the population of England, was £120.21. Three attributes of vaccination were measured: 1) *direct health benefit*, 2) *insurance type benefit*, and 3) parental *work loss* (Table 4.17). The *direct health benefit*, *insurance type benefit* and *work loss* represented 79%, 13% and 8% of the average WTP for vaccination respectively. To our knowledge, this is the first study to show, empirically, that individuals prefer vaccination (prevention) to treatment and that quantifies parent's WTP to prevent *work loss*.

WTP for vaccination was significantly greater than for treatment indicating that individuals find an added benefit in the security that their child will not develop chickenpox (*insurance type benefit*). In theory, this is expected since individuals are risk averse and therefore there exists a potential for improving welfare by reducing or eliminating uncertainty. Previous studies have shown that the expected WTP assuming risk neutrality (WTP to treat, ex post, multiplied by the risk of the event) is lower than the elicited WTP using the ex ante insurance-based question (O'Brien *et al.*, 1998; Neumann and Johannesson, 1994). Here, there is a difference in that both the treatment and vaccination questions are ex post user-based. Furthermore, the risk of acquiring chickenpox is 100%. Hence, contrary to previous studies (O'Brien *et al.*, 1998; Neumann and Johannesson, 1994), the *insurance type benefit* that is quantified cannot be biased because of differences in the valuation perspective (ex ante vs ex post) or individuals misunderstanding of the prior risks of disease they have been presented. It should be pointed out that, in our calculation of the *insurance type benefit,* we do not take into account discounting, which would render the added benefit of vaccination greater. Since chickenpox occurs on average at 6 years of age, the present value of treatment (assuming discounting) will be lower than the elicited WTP, which supposes the child is currently diseased.

Work loss was a significant factor in parents WTP for vaccination after controlling for other factors such as income. Prevention of parental *work loss* thus seems to be a benefit of preventing children having disease. This raises questions of whether prevention of *work loss* should be included in the denominator of CB ratio (is a benefit), should be included in the numerator (is a societal productivity gain) or both. Care must be taken when conducting Cost-benefit analysis not to double count these cost/benefits.

Although other studies have found evidence of *altruism* (Johannesson *et al.*, 1993; Onwujekwe *et al.*, 2002; Arana and Leon, 2002), it was not identified as a significant variable in this study. Previous studies measured *altruism* by comparing private versus public WTP for an intervention (Johannesson *et al.*, 1996b). That is, they measured respondent's preference for subsidizing fellow citizens' health care (caring externality - Olsen, 1997). Here, we attempted to measure a different type of *altruism,* which is specific to vaccination (or prevention) of infectious disease. We estimated whether individuals derive benefit from not infecting others (i.e. family and friends) because they are immunized. Here, this type of altruism may not have been detected because of the lack of power of the study to measure very small differences in WTP, chickenpox is too mild to produce such altruistic benefits or because this particular type of *altruism* does not exist. The interval regression coefficient for *altruism* was £1 (95% CI, -£33 to £35) for the WTP for vaccination and £1 (95% CI -£27 to £28) for the WTP for treatment, which suggests that the value of *altruism* is very small or does not exist for chickenpox. Although inconclusive, this study is the first to attempt to measure *altruism* related to vaccination. Further research is needed to examine if such *altruism* exists or is measurable for diseases with greater severity.

As expected by economic theory, WTP increased with perceived severity of disease (*HUI2*) and *income*. That richer people are WTP more than poorer people for a programme which provides the same level of well-being could lead to inequalities in the distribution of heath care if CBA is used by policy makers. That is, CBA based on CV can potentially bias towards programmes that treat/prevent diseases that typically affect richer individuals in society (men vs. women, older vs. younger adults).

Finally, from the CV questionnaire it is possible to estimate the uptake of varicella vaccination if it was covered by the NHS (free at point of consumption). Of the 202 parents who answered the CV questionnaire, 85% said they would vaccinate their child against varicella if it were free. Thus, the expected uptake of varicella vaccination would be 85%. This is similar to a recent study in Australia, which estimated the average coverage of varicella to be 88% using stated preference discrete modelling (Hall *et al.*, 2002). Such levels of coverage would produce very similar dynamics to those presented in Chapter 3, where 90% coverage was used as a base case scenario. Parents who desired vaccination had a positive attitude towards vaccination in general (their children were fully vaccinated for their age), thought chickenpox to be more severe (higher QALY-lost weight as measured by the HUI2 system) and worked (Table 4.11-4.12). These results are coherent with the literature (Bennett and Smith, 1992; Bond *et al.* 1998). However, contrary to other studies, effectiveness of the vaccine was not found to be a significant factor in parent's decision to vaccinate (Streefland, 2001; Bond *et al.* 1998). This is most likely because parents were told that although the vaccine had 85% vaccine efficacy, cases among vaccinated children were very mild. However, the interval regression coefficient for *efficacy* was -£11 (95% CI, -£37 to £14) for the WTP for vaccination, which suggests that the sample size may have been too small to assess a significant difference.

Validations of CV studies are very difficult due to the hypothetical nature of the questions (Drummond, 1997; O'Brien and Viramontes, 1994). Ideally, results should be compared to actual market observations (*criterion validity*). This is very difficult in the UK and other countries where the population do not pay directly for health care (i.e. where the market does not actually exist). Because of this problem, other validation tests have been suggested. First, *construct validation*

consists of examining whether the CV results are consistent with economic theory (Drummond, 1997; O'Brien and Viramontes, 1994). This usually consists of testing whether WTP increases with income but eventually at a decreasing rate (positive income elasticity). The NOAA recognized validity problems with CV studies and recommended the use of test of scope in their guidelines (National Oceanic and Atmospheric Administration, 1993). The test of scope consists of assessing whether increase in benefit relates to an increase in WTP. In this study, responses to the CV questionnaire were consistent with expected theory. WTP for vaccination (and treatment) increases with income until a point at which it starts to decline (*construct validity* - Tables 4.8, 4.9, 4.14 and 4.14). Secondly, the perceived severity of disease as measured by the HUI2 system significantly affected parents overall WTP for chickenpox vaccination and treatment, which demonstrates *convergent validity* and that WTP increases with perceived benefits (Tables 4.8 and 4.9). Tests of reliability were not performed. However, test-retest reliability of CV has been shown to be comparable to other preference measures (O'Brien and Viramontes, 1994).

Standard Gamble. The average QALY-weight estimated from the SG analysis is 56% for the sample and 31% for England.

Work loss was not found to be a significant factor of the SG. This result is consistent with the general belief that QALYs cannot capture non-health benefits (Olsen and Smith, 2001; Donaldson *et al.*, 1997).

The effect of *Altruism, Gender* and *Degree* were significant (Table 4.19). The QALY-weight elicited from parents who were told that intervention would prevent their child giving the disease to other children was 0.25 lower than those who did

not have this attribute. This may be an *altruistic* or a *paternalistic* externality or a *direct health* valuation. That is, parents may be willing to take a greater risk to protect their other children (*paternalistic* externality), protect other individuals (*altruistic* externality) or believe, with this added attribute, that the disease is more severe (e.g. child is more isolated). We show in section 4.1.5.2 that parents who were given the *altruistic* scenario believe that the disease was more severe (the QALY-weight derived from the HUI2-SG questionnaire was significantly higher (Table 4.22)). Hence, it is more likely that the SG did not capture externalities but actual valuations of health.

Fathers were willing to take greater risks to return their children to normal health (QALY-weights were 0.35 lower than for mothers). This is consistent with other studies, which show that for an identical health state QALY-weights elicited from women are higher (Jacobs et al., 2002; Dolan *et al.*, 1996). Finally, having a *degree* was found to be significant, which suggests that understanding of risk may be an important factor in standard gamble elicitation despite the fact that visual aids, similar to those presented in Appel *et al.* (1990), were used (see Appendix 9). This corroborates a previous study, which suggested that risk misunderstanding was associated with respondents' educational attainment (O'Brien *et al.*, 1998). That gender and level of education influence SG responses is a concern for resource allocation (raises equity concerns). If these results are generalisable then disease interventions, which affect men and individuals with lower education will have lower Cost-Utility ratios (if QALYs are based on SG questionnaires) - i.e. diseases in men and people with less education will be valued as more severe.

Health Utility Index mark 2. The QALY-weight distributions estimated from the HUI2 system are very different between HUI2-CV and HUI2-SG questionnaires. The

HUI2-SG produced a much lower average QALY-weight (0.56 vs. 0.76 - Table 4.22). The only difference between the CV and SG disease descriptions were that duration of disease was extended to 15 years in the SG questionnaire (in order for parents to trade-off probabilities that they could understand). Furthermore, parents who were given the CV questionnaire were told they were valuing chickenpox. The average QALY-weight from HUI2-SG and SG questionnaires were similar. This suggests that, as expected, SG and HUI2 elicit similar QALY-weights for a same disease state.

Difference between the QALY-weight elicited from HUI2-CV, HUI2-SG and the SG questionnaires illustrate the measurement problems of estimating QALY-weights for acute diseases using SG and similar elicitation methods. The main problem is that, for acute and mild diseases, such as chickenpox, the rational risk that individuals should be willing to trade-off is too small for most to comprehend. To get around this we can increase the duration of the disease state, assuming constant proportional trade-off (U(H)T = U(H,T) (Pliskin et al., 1980), while keeping the same health state description, that is increasing T but keeping H constant. Here, this technique does not seem to work. This can be due to two reasons. Firstly, the proportional trade-off assumption may not hold. Many studies in the literature show that, the QALY-weight is dependant on the time individuals are in the disease state (i.e. duration of disease has an impact on individual's perception of severity (Stalmeier, 1996; Dolan and Gudex, 1995; Bala and Zarkin, 2000; Gafni, 1994; Bala et al., 1999)). The second problem is that by increasing duration of disease and refraining from mentioning chickenpox, individuals are actually rating an imaginary disease that they have difficulty understanding. That is, parents are rating a different disease. This seems to be the case as HUI2-CV and HUI2-SG give different QALY-weights. It should be pointed out that chained

methods have previously been used to address the problem of assessing QALYs for temporary health states within the SG framework (Jansen et al., 1998). However, to our knowledge none have been used for health states that are as short and as mild as chickenpox. Because the duration of varicella is very short, chaining will be difficult (e.g. use of many anchor levels) and the opportunity of including bias will be large. Nevertheless, in future work chained procedures should be considered as an alternative to the method chosen here.

As mentioned earlier, the HUI2 system and other multi-attribute health status classification systems have two major advantages over SG when estimating the morbidity of infectious disease: 1) they are simple to understand and answer and, 2) they can capture small changes in heath status (De Wit et al., 2000; de Vries et al., 1998). In this study individuals who responded to the HUI2-CV had little difficulty responding to the questionnaire. This was aided by the fact that chickenpox was known to most parents. Despite this, QALY-weights were significantly higher for parents of children with positive history of the disease (Table 4.23), which raises the question about who should be answering elicitation questionnaires. Should it be those who are at risk or affected by the disease or the general public. De Wit *et al.* (2000) consider this question in detail.

Limitations of the analysis. The analysis presented here has four main a priori limitations: 1) it uses parents as proxies, 2) a bidding algorithm was used, 3) the impact of vaccine side effects and risk of disease on WTP and SG were not directly elicited, 4) a vaccination scenario was not included in the SG questionnaire.

Parents are used as proxies. Vaccination is mainly carried out on very young children, from whom it is impossible to elicit preferences. We used parents as

proxies as they are the ones who are responsible for the health of their children and decide whether they receive vaccination. A number of problems have been observed when using parents as proxies (Petrou, 2003). Firstly, for multi-attribute health systems, although results are correlated between parents and children, parents report a greater effect of illness on the quality of life of their child (Eiser and Morse, 2001; Ennett *et al.*, 1991; Graham *et al.*, 1997; Theunissen, 1998). This has also been observed to be true when comparing elicitation techniques between patients and other proxies (De Wit *et al.*, 2000). On the other hand, parents may be more risk averse for their children than for themselves. Hence, SG using parents as proxies is likely to underestimate the QALYs lost. Secondly, if parents are used as proxies, QALY and WTP measures may integrate to some degree the indirect effects on the parents (e.g. psychological, monetary). A good example of this is that parents who must take time off work are willing to pay more for vaccination. See Petrou (2003) and Eiser and Morse (2001) for more information on the methodological issues raised by preference based approaches to measure the health status of children.

Impact of vaccine side effects and risk of disease on coverage and WTP. Decision to immunise or not is influenced by individuals' fear of side effects and the severity of disease (Hall *et al.*, 2002). However, as mentioned above, we could not measure the extent to which these factors have an effect on vaccine coverage and WTP for vaccination because of ethical considerations. Although varicella vaccine side-effects are rare and mostly mild (Krause and Klinman, 1995; Krause and Straus, 1999; Wise *et al.*, 2000), results from the CV may overestimate parents WTP for vaccination.

It has also been suggested that perceived risk or prevalence of disease can have an important impact on demand of prevention programmes of infectious disease (Geoffard & Phlipson, 1996; Geoffard & Phlipson, 1997; Philipson, 2000). The central assumption is that high levels of coverage are difficult to maintain because demand for vaccine is correlated with prevalence of disease (e.g. if disease prevalence decreases demand for vaccine decreases). However, analysis of vaccine coverage data from the UK clearly shows that while incidence of pertussis and diphtheria have virtually been eliminated, the coverage of these diseases has remained relatively constant (see Figure 4.5). In Figure 4.5, the drop in pertussis coverage during late 1970s was due to a scare about the safety of the vaccine, which suggests that perceived risk of vaccination is as mentioned above, important in vaccine uptake.

To test the relationship between the demand for vaccine and perceived risk of disease, we imbedded into our study, a small pilot study eliciting parents' maximum WTP for vaccination for different base-line risks of varicella infection. This was done using a similar computer active CV questionnaire to the one presented in the methods section (see Appendix 12 for questionnaire). Although not statistically significant, parents' average WTP for vaccination was £109 (n=16, Standard Deviation=61), £97 (n=16, Standard Deviation=79) and £102 (n=16, Standard Deviation=79) assuming their children's lifetime risk of chickenpox without intervention was 100%, 50% and 25% respectively. Hence, results suggest that WTP for varicella vaccination is not a function of the risk of disease. Clearly, more work is needed in this field.

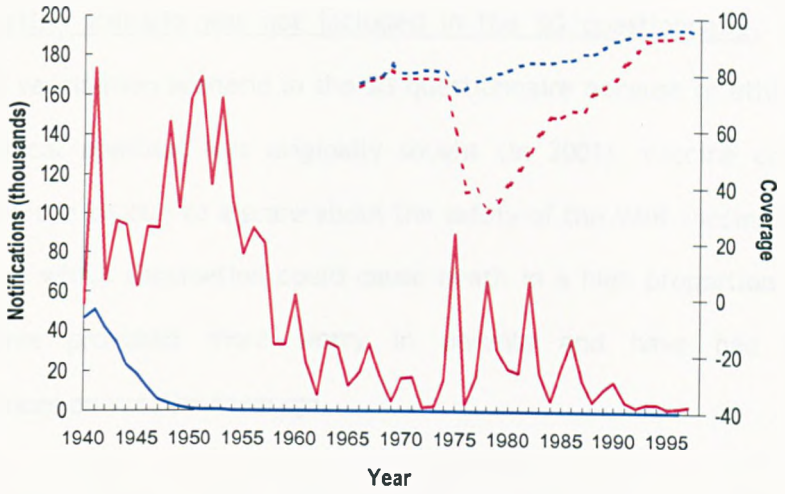


Figure 4.5. Pertussis and diptheria notifications and vaccine coverage, England and Wales 1940-1999. The blue and red lines represent diptheria and pertussis respectively. Full-lines represent notification rates (Figure courtesy of the Public Health Laboratory Service).

Bidding game. To increase precision and the power of our study to detect attributes, we used a bidding game (iterative-close ended questioning approach) to elicit maximum WTP. This method has been shown to induce starting-point bias in environmental economics (Rowe *et al.*, 1980; Brookshire *et al.*, 1980; Boyle, 1985), and in health economics (Stalhammar, 1996; Dalmau-Matarrodona, 2001; Eastaugh 2000). Starting point-bias was identified in the WTP for vaccination and treatment (when including responses of those who refused intervention) against chickenpox for their children. Those who were given a starting point of £75 gave, on average, responses that were approximately £30 hirer than those who were given starting bids of £25 and £50 (Tables 4.8 and 4.9). It should be noted that starting-point bias was controlled for when estimating the values of the different attributes of vaccination. Furthermore, starting-point bias was not a significant factor when assessing the maximum WTP for vaccination or treatment when excluding responses of those who refused intervention.

A vaccination scenario was not included in the SG questionnaire. We did not include a vaccination scenario in the SG questionnaire because of ethical reasons. When ethical approval was originally sought (in 2001), vaccine coverage had dropped in the UK due to a scare about the safety of the MMR vaccine. Including a scenario in which vaccination could cause death in a high proportion of children could have provoked more worry in parents and have had deleterious consequences on vaccine coverage.

Sample size. Although the sample size was 63 for the SG questionnaire, it can be seen by Figure 4.3 that responses had a clear distribution. Furthermore, significant variables were as expected by the literature.

Strengths of the analysis. The analysis presented here expands the health economic literature of infectious disease prevention in two major areas. We present for the first time empirical evidence that individuals prefer vaccination to treatment (*insurance type benefit* exist) and that in their decision to treat or vaccinate their children parents value the benefit of preventing time off work (*work loss* benefit). This study is also the first to assess, using empirical results, the advantages/disadvantages of different elicitation techniques in the context of valuing the benefit of vaccination.

For the CV questionnaire we follow Carson et al.'s (1991) conditions for a valid CV scenarios and NOAA recommendations (National Oceanic and Atmospheric Administration, 199). The CV scenario is theoretically accurate, policy relevant, understandable by the respondent as intended, plausible to the respondent and meaningful to the respondent. As recommended by the NOAA panel we use face-to-face interviews, remind respondents that the money is from their own

disposable income (out-of-pocket), use a binary CV format and demonstrate sensitivity of scope.

In the next section, WTP and QALY values estimated here will be aggregated to assess the overall population value of vaccination.

4.2 ESTIMATION OF WTP AND QALY VALUES FOR ZOSTER AND PHN

4.2.1 WTP FOR ZOSTER TREATMENT

4.2.1.1 Method

We used a convenient sample of individuals who work at the Public Health Laboratory Service in London. Individuals were asked to participate in the study. Those consenting to participate were given a computer active interview.

We adapted the computerised CV questionnaire of varicella treatment and vaccination presented in Chapter 4. The questionnaire is structured into 3 parts. In part 1 (see Appendix 13 Part 1), respondents are asked a combination of standard socio-demographic questions (e.g. age, gender) and zoster specific questions (e.g. have you had shingles). In part 2, respondents are randomly given a description of mild or severe zoster (the health profile descriptions are identical to those presented in Bala et al. (1998) - see Appendix 13 Part 2A,B). We then elicit the maximum the respondents would be willing to pay to for a drug that would cure them of zoster (Appendix 13 Part 2D). In part 3, we elicit the willingness to pay for a drug that would cure PHN (see Appendix 13 Part 3). Respondent's maximum WTP is assessed using bidding algorithms. As in Chapter 4, interval regression was used here to estimate the average WTP for mild and severe zoster and PHN.

4.2.1.2 Results

The number of respondents was 38. Results from the interval regression model are presented in Tables 4.24 and 4.25. Men were WTP significantly more for zoster and PHN treatment (£190 and £862 more respectively). Furthermore, as expected by theory, WTP increased significantly with zoster severity. Using this model, the average WTP for mild and severe zoster and PHN is £201, £352 and £1369 respectively. The average willingness to pay for a case of zoster, £236, was calculated by using the proportion of zoster cases that experience mild (77%) and severe pain (23%).

Table 4.24. WTP for zoster treatment - Interval regression model

	Coef	[95% CI]	P>|z|
Constant	335.44	(215.60 to 455.28)	
Gender			0.003**
0	0	Baseline	
1	-191.46	(-316.52 to -66.41)	
Severity			0.029**
0	0	Baseline	
1	113.88	(19.34 to 282.94)	
σ	177.68	(128.87 to 226.50)	
LR $\chi^2(12)$	13.27		0.001**
Sample size	38		

* Significant at p<0.1; ** Significant at p<0.05

Table 4.25. WTP for PHN treatment - Interval regression model

	Coef	[95% CI]	P>|z|
Constant	1892.48	(1409.50 to 2375.47)	
Gender			0.005**
0	0	Baseline	
1	-862.49	(-1468.25 to -256.52)	
σ	887.92	(652.55 to 1123.28)	
LR $\chi^2(1)$	7.28		0.007**
Sample size	38		

* *Significant at p<0.05

4.2.1 QALY WEIGHTS FOR ZOSTER AND PHN

QALY estimates for zoster were estimated from the literature. Bala et al. (1998) estimated the utility, or QALY-weight, of pain due to zoster. They interviewed 114

65-70 year olds, and elicited their QALY-weights using standard gamble techniques. The two disease states the respondents were asked to consider were: mild zoster pain, described as "A tingling, burning, pin-prick sensation in the affected area. Any contact with the affected area is uncomfortable"; and severe zoster pain, described as "A constant, excruciating pain, like an electric shock. Patients often cannot sleep, concentrate, or perform common household tasks". The resulting mean QALY weights they obtained were 0.73 (95% Confidence Interval 0.68-0.78) for mild pain and 0.47 (95% CI 0.41-0.53) for severe pain. Bala et al.'s results cannot be used directly to estimate the average QALY loss from zoster, as they did not measure what proportion of zoster patients would have severe and mild pain as they define it. However, Mauskopf et al. (1994) report the proportion of zoster patients who fall into four definitions of pain that can be dichotomised into two categories which are very similar to those used by Bala et al. Namely, "Pain can be ignored" (43% of individuals with pain) and "Pain cannot be ignored but has no effect on activities" (34 %) can be regarded as mild pain (as defined by Bala et al., see above); and "Pain interferes with sleep and concentration" (19%) and "Pain interferes with all activities" (4%) taken together are very similar to Bala et al.'s definition of severe pain (see above). Thus, for the base-case, we assumed that 77% (43%+34%) of those with pain would have "mild pain" and 23% (19%+ 4%) would have "severe pain". We assume that the same proportion of zoster patients as PHN patients experience "mild" and "severe" pain with equal QALY weights to PHN patients. Finally, to estimate the number of QALYs lost per acute zoster and PHN case we multiply the QALY-weights by the average length of time that patients spend in these health states (see Chapter 2 for duration of zoster and PHN). The parameter values are given in Table 4.26.

Table 4.26. QALY estimates

Parameter	Value	Data Source
Mean length of zoster	2 weeks	Paparatti *et al.*, 1999
Mean length of PHN	1.4 years	Chapter 2
Average QALY lost zoster	0.01	
Average QALY lost PHN	0.46	

4.3 VALUE OF VARICELLA VACCINATION - POPULATION PERSPECTIVE

4.3.0 BACKGROUND

Economic evaluation involves comparing the total costs of a programme with total benefits (WTP, QALYs gained, Life-years gained). To estimate total benefit of a programme, individuals' welfare/utilities/health gains must be aggregated to the population level. There are many techniques available/used to aggregate benefits, each with their own theoretical and empirical problems.

The social welfare function (SWF), introduced by Bergson (1938) and Samuelson (1947), provides the conceptual framework of aggregating individual's benefits. The aim of economic analysis is to maximise the utility functions of all individuals in society (SWF) subject to a budget constraint. However, Arrow (1950, 1951) showed that the only possible way to use the SWF was to assume that individuals' utilities are cardinal and comparable (Arrow Impossibility Theorem). The Arrow impossibility theorem has been extensively examined and it has been suggested that weaker forms of comparability can permit making consistent social welfare judgements, satisfying all of Arrow's requirements (Sen, 1977; Sen, 1999).

Aggregation of WTP (Welfarism). The change in SW can be assessed by adding individual's maximum WTP (CV), adjusted for individuals' marginal utility of income and multiplied by equity weights placed on these individuals' marginal

utilities (Johansson, 1995). Although WTP is measurable, the welfare weight that society attributes to each household in the economy and marginal utility of income are generally unobservable. To overcome this, it is assumed that if the government can redistribute incomes over individuals so that the social marginal utility of income becomes equal for all individuals (assuming conversion of potential Pareto improvement (Hicks, 1939; Kaldor, 1939) is possible) the unweighted sum of WTP can lead to SW maximisation. In this section we aggregate the unweighted WTP estimated of vaccination from section 4.1.

Aggregation QALY and Life-years gained (Extra-welfarism or efficiency health maximisation). There are two distinct views of QALYs: 1) as a utility, and 2) as a measure of health (Wagstaff, 1991). Utilitarians believe that QALYs are a measure of utility and seek to maximize the sum of utilities whereas others believe QALYs to be a measure of health and seek to maximize the population's health (Culyer, 1990).

To be considered as a measure of utility, QALYs must first satisfy the assumptions of expected utility theory (i.e. Neumann-Morgenstern axioms (von Neumann and Morgenstern, 1947)): 1) independence, 2) desire for high probability of success, and 3) compound probabilities. Pliskin *et al.* (1980) identified further assumptions necessary for QALYs to be a valid utility function: 1) health states worse than death do not exist, 2) mutual utility independence (i.e. utility in one time period is independent of previous utility), 3) constant proportional trade-off, 4) risk neutrality and constant relative risk-aversion (Liljas and Lindgren, 2001). The literature shows that these assumptions are violated too often for QALYs to be considered a valid utility and to be included into a utilitarian SWF framework (Blomqvist, 2002; Dolan and Edlin, 2002; Bleichrodt and Quiggin, 1999; Garber and

Phelps, 1997; Johannesson, 1995; Dolan and Stalmeier, 2003).

It has been argued that components such as health (QALYs or Life-years gained) can be separated from utility measures and be considered in isolation when aggregating benefits of intervention (Culyer, 1990, Wagstaff 1991). Wagstaff (1991) shows that maximisation of QALYs gives rise to a SWF that resembles the utilitarian SWF, which meets the requirement of comparability and cardinality. Similarly to aggregation of unweighted WTP this can lead to distributional concerns. Here, we use this conceptual framework of health maximisation when aggregating the benefits of vaccination in terms of QALYs and Life-years gained.

The aim of this section is not to examine the above-mentioned theoretical assumptions related to aggregation. Rather, we aim to examine the empirical problems related to the aggregation of WTP, QALYs and Life-years gained in the context of immunisation, using varicella vaccination as an example. Firstly, for each outcome measure we intend to examine how externalities and non-health benefits can be aggregated using the dynamic model presented in Chapter 3. Secondly, we compare results, from different outcome measures, to better understand the implications of omitting external effects and non-health benefits from economic analysis. This, to gain a better understanding of how the choice of valuation technique, outcome measure and method of aggregation can affect the results of economic evaluation of vaccination programmes and therefore influences resource allocation decision-making.

Externalities can be classified into two broad categories: selfish and altruistic (Labelle & Hurley, 1992; Johannesson, 1996). Selfish externalities exist when individual A cares about individual B's consumption of health services because B's

consumption of health services affects A's (expected) health status (the classic example is herd-immunity). Altruism occurs when individual A cares about individual B's consumption of health care and/or health status enters A's utility function (individuals may find benefit in vaccination because it prevents them infecting others). We focus our analysis on two spill-over effects of varicella vaccination. The first is herd-immunity, which is the classic example of a selfish externality (Weisbrod, 1961). As shown in Chapter 3, herd-immunity can produce both positive and negative effects (e.g. protects non-vaccinated susceptibles against infection but can increase overall morbidity and mortality by shifting the age at infection). The second externality examined, here, is the impact of varicella vaccination of children on the incidence of zoster in adults who have not been vaccinated. As described in the first section of this chapter, it is possible that vaccination can produce altruistic externalities if vaccinees derive benefit from the knowledge that they will not infect others because they are immunized. In the case of WTP for varicella vaccination, although *altruism* was not found to be significant in section 4.1, we examine how it can be incorporated into the aggregation functions. We also formalise how *direct health* effects, *insurance type benefits* and *work loss* benefits can be aggregated at the population level.

4.3.1 METHODS

4.3.1.1 Aggregation of WTP

We use the utilitarian-type social welfare function where social welfare (W_{it}) in state of the world i and time t is given by:

$$W_{it} = \sum_{j=1}^{N} \alpha_j V_{ijt}(p,y,h,k) \Big/ (1+d)^t \quad \text{for j=1,....., N individuals at time t.} \qquad (4)$$

where α_j is the welfare weight that society attributes to individual j; $V_{itj}(p,y,h,k)$ is the level of utility experienced by individual j in state i at time t; V is a function of prices (p), post-tax income (y), health (h), and non-health outcomes (k); d is the discount rate.

Given that the willingness to pay for an intervention, which moves individuals from state 0 to state 1, using compensating variation can be defined as (Johannesson, 1996):

$$V_{1jt}(p,y-WTP,h_1,k_1)=V_{0jt}(p,y,h_0,k_0) \quad (5)$$

The present value of the overall benefit of intervention (B) over l years can be described as follows:

$$B=\sum_{t=0}^{l}\Delta W_t=\sum_{t=0}^{l}(W_{1t}-W_{0t})=\sum_{t=0}^{l}\sum_{j=1}^{N}r^t\alpha_j V_{1jt}(p,y,z_1,k_1)-\sum_{t=0}^{l}\sum_{j=1}^{N}r^t\alpha_j V_{0jt}(p,y,z_0,k_0) \quad (6)$$

where $r^t=1/(1+d)^t$. Substituting (5) into (6) yields:

$$B=\sum_{t=0}^{l}\sum_{j=1}^{N}r^t\alpha_j V_{1jt}(p,y,z_1,k_1)-\sum_{t=0}^{l}\sum_{j=1}^{N}r^t\alpha_j V_{1jt}(p,y-WTP,z_1,k_1)=\sum_{t=0}^{l}\sum_{j=1}^{N}r^t\alpha_j v_j WTP_{jt} \quad (7)$$

where v_j is the marginal utility of income of individual j.

Assuming that society weights all individuals equally (α_j=1) and marginal utility of income is the same for all individuals (v_j =1), the present value of the benefit of an intervention can be described as follows:

$$B=\sum_{t=0}^{l}\sum_{j=1}^{N}r^t\alpha_j v_j WTP_j=\sum_{t=0}^{l}r^t N_t WTP \quad \text{for j=1,....., } N_t \text{ individuals at time t.} \quad (8)$$

where *WTP* is the average willingness to pay for the intervention.

As shown in Chapter 3, varicella vaccination not only protects vaccinated individuals but also those who are not vaccinated. Furthermore, varicella vaccination increases the incidence of zoster in non-vaccinees. The total benefit of vaccination (*B*) should thus be the sum of the direct health and non-health benefits of preventing chickenpox in vaccinees (B^{vac}) and non-vaccinees (B^{nvac}) as well as its negative effect on zoster (B^{z}).

$$B = B^{vac} + B^{nvac} + B^{z} \tag{9}$$

From equation (8) we can formalise the present value of the overall benefit of varicella vaccination over l years in vaccinees:

$$B^{vac} = WTP^{vac} \sum_{t=0}^{l} r^{t} N_{t}^{vac} \tag{10}$$

where, N^{vac}_{t} is the number of individuals vaccinated at time t. WTP^{vac} is the average willingness to pay for varicella vaccination among those who would accept the vaccine. Here, we assume that WTP^{vac} is the sum of the *direct health* benefit on chickenpox (WTP^{health}), the *insurance type* benefit (WTP^{ins}), prevention of *work loss* (WTP^{work}) and *altruism* (WTP^{alt}), which were estimated in section 4.1 (see Table 4.27 for values and sources, it should be noted that we reduce the WTP values elicited in section 4.1 and Appendix 13 by 50% as recommended by the NOAA panel (NOAA,1993)). The NOAA recommendation mainly stems from a study conducted by Dickie *et al.* (1987) and re-analysed by Diamond *et al.* (1992), which found that, for ordinary market goods, the CV approach tended systematically to overestimate actual quantities demanded at each price, sometimes by as much as 50% (http://www.darp.noaa.gov/pdf/cvblue.pdf). Hence, to be conservative in

our results we reduced WTP estimates by 50% (in the economic analysis (Chapter 5) extensive sensitivity analysis is performed on this assumption).

Estimating the benefit of vaccination in non-vaccinated individuals (B^{nvac}) is more complex, which is why these benefits are rarely included in cost-benefit analysis of vaccination programmes. The overall benefit of herd-immunity (health benefits in individuals who are not vaccinated) can be expressed as follows:

$$B^{nvac} = \sum_{t=0}^{l}(W_{1t}^{nvac} - W_{0t}^{nvac}) = \sum_{t=0}^{l}\sum_{j=1}^{N^{nvac}} r^t \alpha_j \left(V_{1jt}(p,y,z_1,k_1) - V_{0jt}(p,y,z_0,k_0)\right) \quad (11)$$

By comparing V_{1jt} and V_{0jt} (state of the world with and without vaccination) to a state of the world where there is no chickenpox (i=2), we can estimate the benefit of herd-immunity:

$$\begin{aligned} B^{nvac} &= \sum_{t=0}^{l}\sum_{j=1}^{N^{nvac}} r^t \left[\begin{array}{l}\left(V_{2jt}(p,y,z_2,k_2) - V_{1jt}(p,y,z_1,k_1)\right) \\ -\left(V_{2jt}(p,y,z_2,k_{2+}) - V_{0jt}(p,y,z_0,k_0)\right)\end{array}\right] \\ B^{nvac} &= \sum_{t=0}^{l}\sum_{j=1}^{N^{nvac}} r^t \left[\begin{array}{l}\left(V_{2jt}(p,y,z_2,k_2) - V_{2jt}(p,y-WTP_{1j},z_2,k_2)\right) \\ -\left(V_{2jt}(p,y,z_2,k_2) - V_{2jt}(p,y-WTP_{0j},z_2,k_2)\right)\end{array}\right] \end{aligned} \quad (12)$$

By substituting (5) into (12).

$$\begin{aligned} B^{nvac} &= \sum_{t=0}^{l}\sum_{a} r^t c_{0at}^{nvac} WTP_a^{health} - \sum_{t=0}^{l}\sum_{a} r^t c_{1at}^{nvac} WTP_a^{health} \\ B^{nvac} &= \sum_{t=0}^{l}\sum_{a} r^t WTP_a^{health}(c_{0at}^{nvac} - c_{1at}^{nvac}) \end{aligned} \quad (13)$$

where, C_{iat}^{nvac} is the number of predicted chickenpox cases among non-vaccinees of age a, at time t, in state of the world i. We assume that only infected people are willing to pay for chickenpox treatment. Hence, the summation of benefits can be over varicella cases in non-vaccinees rather than all individuals who are not

vaccinated. WTP^{health} is used here as a proxy for the value of not getting chickenpox (see Table 4.27 for values and sources).

Similarly to (13), the impact of varicella vaccination on zoster can be estimated as follows:

$$B^z = \sum_{t=0}^{l} \sum_{a} r^t WTP_a^z (c_{0at}^z - c_{1at}^z) \qquad (14)$$

where, C_{iat}^z is the number of predicted zoster cases in individuals of age a, at time t and in state of the world i. WTP^z is the value of preventing zoster (see Table 4.27 for values and sources).

Table 4.27. Average WTP[A] used for aggregation of overall benefits

	(£)	(Source)
Varicella		
WTP^{Vac}	60.10	(Section 4.1, Table 4.10)
WTP^{health}	46.59	(Section 4.1, Table 4.17)
WTP^{ins}	7.84	(Section 4.1, Table 4.17)
WTP^{work}	5.36	(Section 4.1, Table 4.17)
WTP^{Alt}	0.00	(Section 4.1, Table 4.17)
WTP^{treat}		
Children[B]	46.59	(Section 4.1, Table 4.10)
Adults[C]	100.64	Assumption[D]
Zoster		
WTP^{z}	117.79	(Section 4.2, Table 4.24)
PHN		
WTP^{PHN}	684.72	(Section 4.2, Table 4.25)

A. We reduce the WTP values elicited in section 4.1-2 by 50% as recommended by the NOAA panel (NOAA,1993)
B. Children are aged between 0 and 15 years.
C. Here, adults are considered to be 15 years and older.
D. We assume that the WTP for the treatment of varicella in adults is equal to the WTP of treatment of mild zoster in adults as both have similar duration and severity.

Aggregation of QALYs and Life-years gained

To aggregate QALYs and Life-years (LY) gained we use the health maximisation approach (Wagstaff, 1991). That is, we assume that health can be separated from

the social welfare utility function and be considered in isolation when aggregating benefits of intervention. Here, we assume that benefits are additive.

The present value of Quality-Adjusted Life-Years (QALY) lost due to disease (X) at time t in state of the world i can be expressed as follows:

$$QALY_{it}^{x} = \sum_{a} C_{iat}^{x}\left(Q_{a}^{x} + p_{a}^{x} LYL_{a}\right) \tag{15}$$

where, C^{x}_{iat} is the number of cases of disease x in individuals of age a during time t, Q^{x}_{a} is the QALY-weight associated with disease x in individuals of age a, p^{x}_{a} is the case-fatality ratio of disease X in age a. Finally, LYL_{a} is the present value of the expected life years lost of an individual who dies at age a. Assuming ϖ is the average life expectancy at birth, LYL_{a} is:

$$LYL_{a} = \sum_{i=1}^{\varpi - a} r^{i} \tag{16}$$

The total QALYs gained from an intervention can thus be estimated as follows:

$$QALY_{gained}^{x} = QALY_{0}^{x} - QALY_{1}^{x} \tag{17}$$

where, $QALY^{x}_{1}$ and $QALY^{x}_{0}$ are the predicted number of QALYs lost due to disease x in a population with and without the intervention respectively.

In Chapter 3 we show that varicella vaccination can have an impact on the incidence of varicella and zoster. This should be taken into account when assessing the total impact of varicella vaccination on health. In the analysis, the total impact of vaccination on health can be expressed as:

$$QALY_{gained} = QALY_{gained}^{vac} + QALY_{gained}^{nvac} + QALY_{gained}^{z} \tag{18}$$

From equations (15) and (16), the QALYs gained attributed to varicella in vaccinees ($QALY^{vac}_{gained}$) and non-vaccinees ($QALY^{nvac}_{gained}$), and zoster ($QALY^{z}_{gained}$) can be expressed as follows:

$$QALY^{vac}_{gained} = \sum_{t=0}^{l}\sum_{a} r^t C^{vac}_{0at}\left(Q^{var}_a + p^{var}_a LYL_a\right) - \sum_{t=0}^{l}\sum_{a} r^t C^{vac}_{1at}\left(Q^{var}_a + p^{var}_a LYL_a\right) \quad (19)$$

$$QALY^{nvac}_{gained} = \sum_{t=0}^{l}\sum_{a} r^t C^{nvac}_{0at}\left(Q^{var}_a + p^{var}_a LYL_a\right) - \sum_{t=0}^{l}\sum_{a} r^t C^{nvac}_{1at}\left(Q^{var}_a + p^{var}_a LYL_a\right) \quad (20)$$

$$QALY^{z}_{gained} = \sum_{t=0}^{l}\sum_{a} r^t C^{z}_{0at}\left(Q^{z}_a + p^{z}_a LYL_a\right) - \sum_{t=0}^{l}\sum_{a} r^t C^{z}_{1at}\left(Q^{z}_a + p^{z}_a LYL_a\right) \quad (21)$$

where, Q^{var}_a are the age specific QALY lost associated with a case of varicella; Q^{z}_a, is the age specific QALY lost due to a case zoster; p^{var}_a is the age specific varicella case-fatality ratios, and; p^{z}_a is the age specific zoster case-fatality ratio. As explained in Chapter 3, cases of varicella in seroconverted vaccinated individuals, which we term breakthrough varicella, are less severe and therefore assume they produce a QALY loss equal to 0. Further, we assume that breakthrough cases do not result in death and that vaccinated individuals do not develop zoster. The overall QALY gained from varicella vaccination can be expressed as follows:

$$QALY_{gained} = \sum_{t=0}^{l}\sum_{a} r^t \begin{pmatrix} \left((C^{vac}_{0at} - C^{vac}_{1at}) + (C^{nvac}_{0at} - C^{nvac}_{1at})\right)\left(Q^{var}_a + p^{var}_a LYL_a\right) \\ + \left(C^{z}_{0at} - C^{z}_{1at}\right)\left(Q^{z}_a + p^{z}_a LYL_a\right) \end{pmatrix} \quad (22)$$

The case-fatality ratios (p^x) for variella and zoster are presented in Chapter 2. For life-years lost (*LYL*) calculations we assume that life expectancy at birth is 75 years. The base case average QALY (Q^{var}) lost due to chickenpox in children was

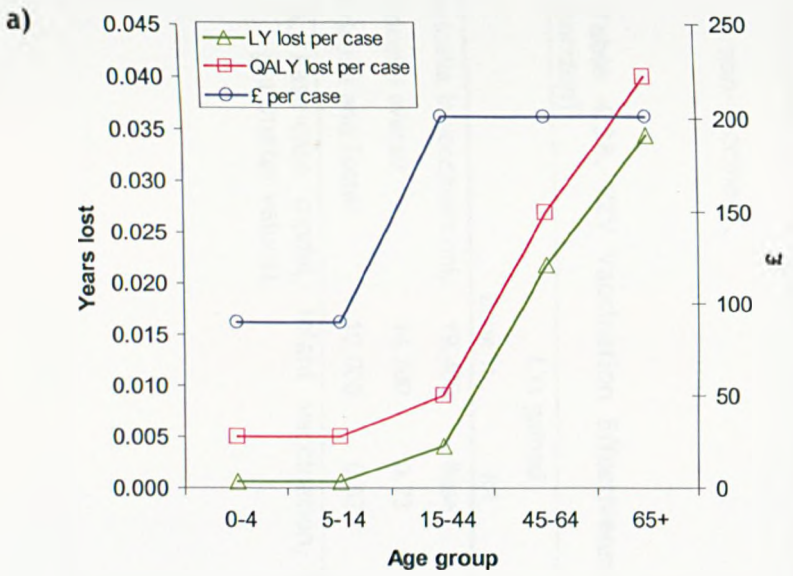
taken from the 42 parents of children with prior history of chickenpox who answered the HUI2 questionnaire in Chapter 4 (Table 4.10). We used QALY-weights elicited using HUI2 results because they were more realistic than those produced by the SG question (see section 4.1.7 for discussion). Furthermore, we chose the valuation of parents with children who had previously had chickenpox since they should have a greater understanding of quality of life lost due to the disease. The quality of life weighting of adults with chickenpox was assumed to be similar to that of mild zoster. The estimation of QALY-weights associated with zoster and PHN is described in Section 4.2 (see Table 4.26 for values). The average QALY lost per case (without LY lost) is the sum of the QALY-weight times the duration of disease. We assumed that duration of varicella, zoster and PHN were 1 week (Beneson, 1995), 2 weeks (Beneson, 1995) and 1.4 years respectively (Chapter 2).

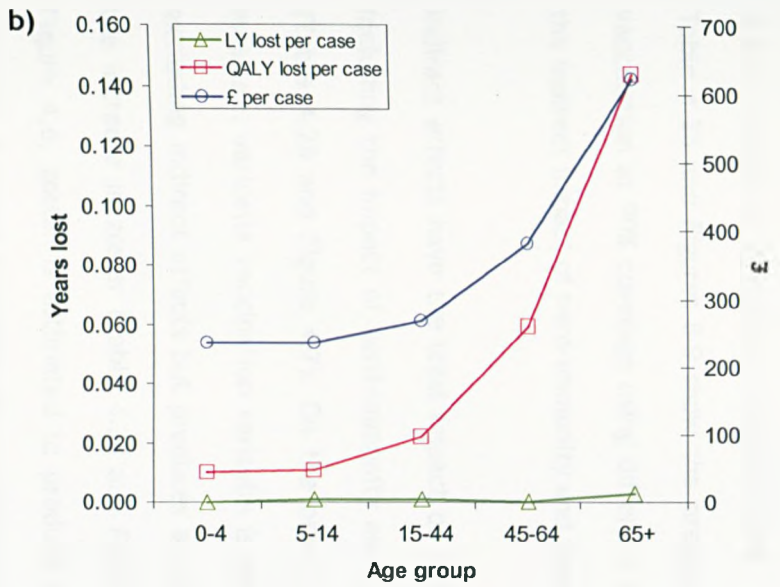
We use the base-case dynamic model presented in Chapter 3 to estimate the age-specific number of cases of varicella and zoster over time with and without vaccination. The strategy investigated here is infant vaccination at 90% coverage. Unless stated otherwise, benefits are discounted at 3% per year and aggregated over 80 years.

4.3.2 VALUE OF A CASE OF VARICELLA AND ZOSTER

Figure 4.6a,b shows the average age specific £ (WTP_a), Life-years lost (p_aLYL_a) and Quality-Adjusted Life-years lost (Q_a) due to varicella and zoster. LYs and QALYs lost due to varicella and zoster increase dramatically with age. LY lost due to zoster are lower than those for varicella as case-fatality for zoster is low and life-years remaining are small since zoster occurs mostly in the elderly. QALYs lost due to zoster are very high mainly because of the impact of PHN (see Appendix 13).

WTP is the outcome measure, which is the least sensitive to age at the time of disease and, proportionally, has the least difference between valuation of varicella and zoster. That is, WTP is least sensitive to severity of disease. This is illustrated in Figure 4.6c, which shows that WTP increases as QALYs increase but at a decreasing rate. For example, individuals are willing to pay up to 3 times more to prevent PHN than zoster even though QALYs lost due to PHN are estimated to be more than 30 times greater (Figure 4.6c).





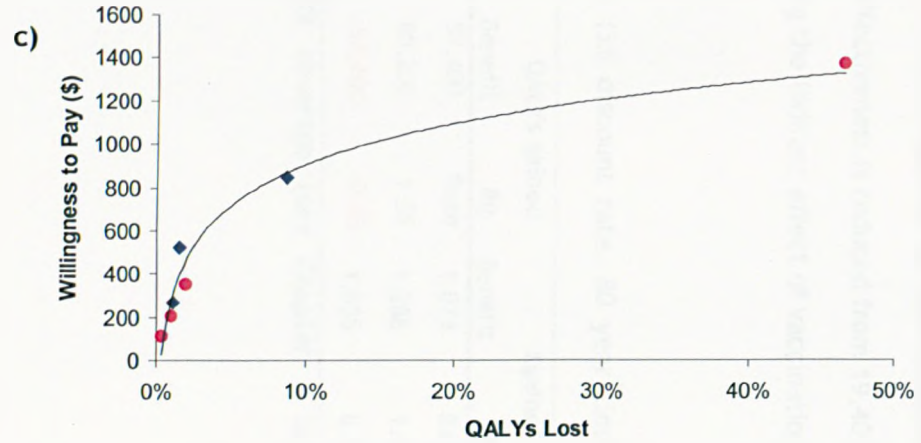


Figure 4.6. Average £, Life-year and Quality-Adjusted Life-year lost per case of a) varicella and b) zoster. c) Willingness to pay per Quality-adjusted life-year lost. The blue dots represent the average WTP per QALY loss for different levels of zoster severity (Bala *et al.*, 1998). Red circles represent the average WTP and QALY loss due to varicella in children and adults, zoster in adults and PHN (see section 4.1 and Appendix 13).

4.3.3 VALUE OF VARICELLA VACCINATION

Table 4.28 and Figures 8-9 show the predicted effectiveness of infant varicella vaccination at 90% coverage using different outcome measures with and without the indirect impact of herd-immunity and zoster.

Indirect effects have the least impact on overall effectiveness when using WTP. Including the impact of herd-immunity and zoster effects changes results by 2% (Table 4.28 and Figure 4.7). On the other hand, using QALYs as the outcome measure, varicella vaccination varicella is estimated to be highly effective when excluding indirect effects but produces an increase in morbidity when including the increase in zoster (Table 4.28 and Figure 4.8). This is because, as seen in Figure 4.6, zoster is estimated to produce much greater losses in QALYs than varicella. It should be noted that the shift in the age at infection has a significant effect on overall effectiveness when using Life-years gained as the outcome measure (Table 4.25 and Figure 4.8). Overall effectiveness is reduced from 19,400 to 14,200 life-years gained (27%) when including the indirect effect of vaccination on non-vaccinees.

Table 4.28. VZV Vaccination Effectiveness[A] (3% discount rate, 80 year time horizon)

	LYs gained		QALYs gained		£gained	
	Benefit	RR	Benefit	RR	Benefit	RR
Varicella in vaccinees only	19,400	Base	59,400	Base	1,073	Base
Varicella overall	14,200	0.73	80,200	1.35	1,286	1.20
Varicella and Zoster	10,000	0.52	-54,400	-0.92	1,035	0.98

A. Base-case model, infant vaccination, 90% coverage (see Chapter 3 for parameter values).

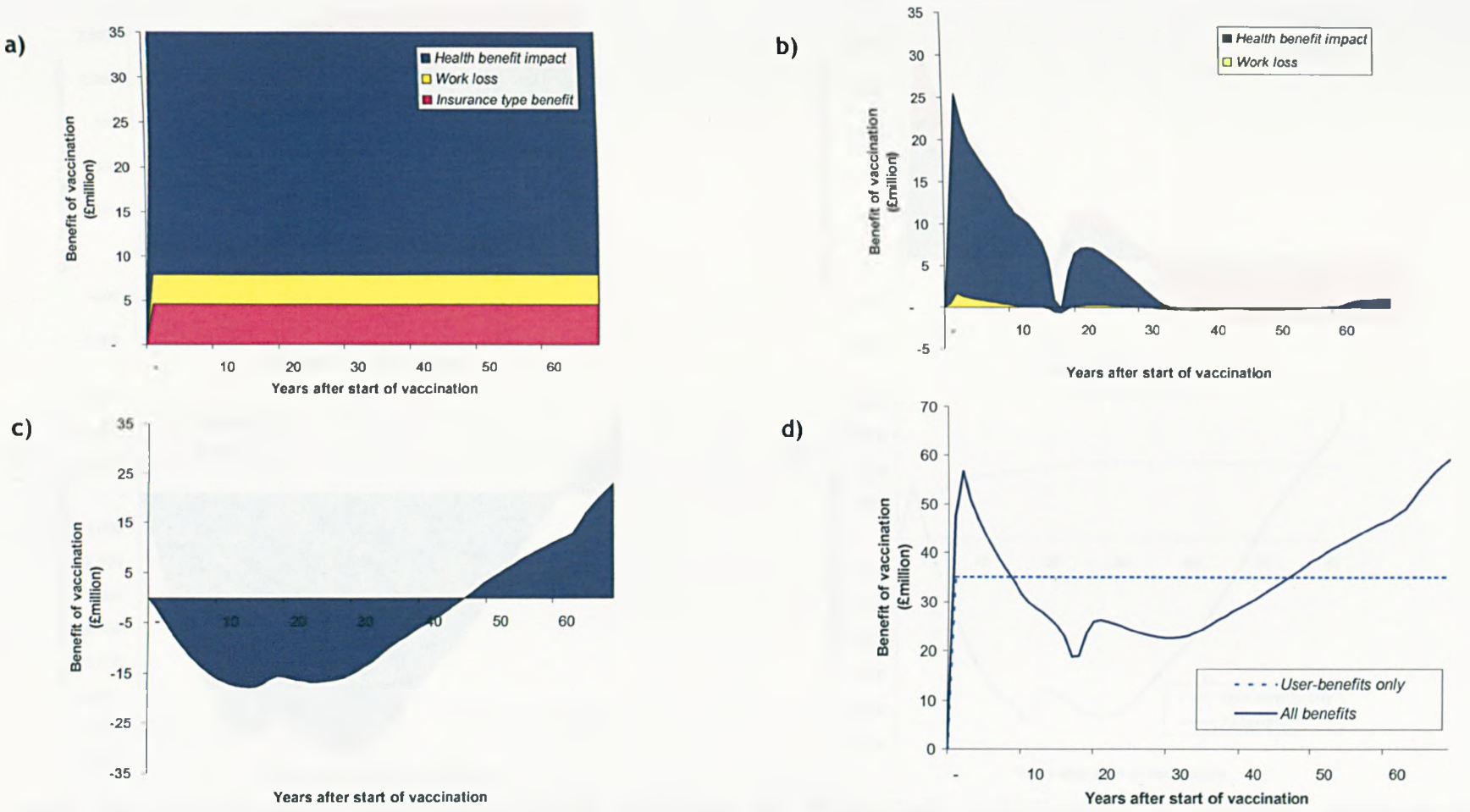


Figure 4.7. Benefit of varicella vaccination (no discounting). a) Benefit (£million) vaccination among vaccines (B^{vac}), b) Benefit of reducing varicella in non-vaccinees (B^{nvac}), c) impact of vaccination on zoster (B^{z}) and , d) overall benefit of vaccination with and without externalities over time.

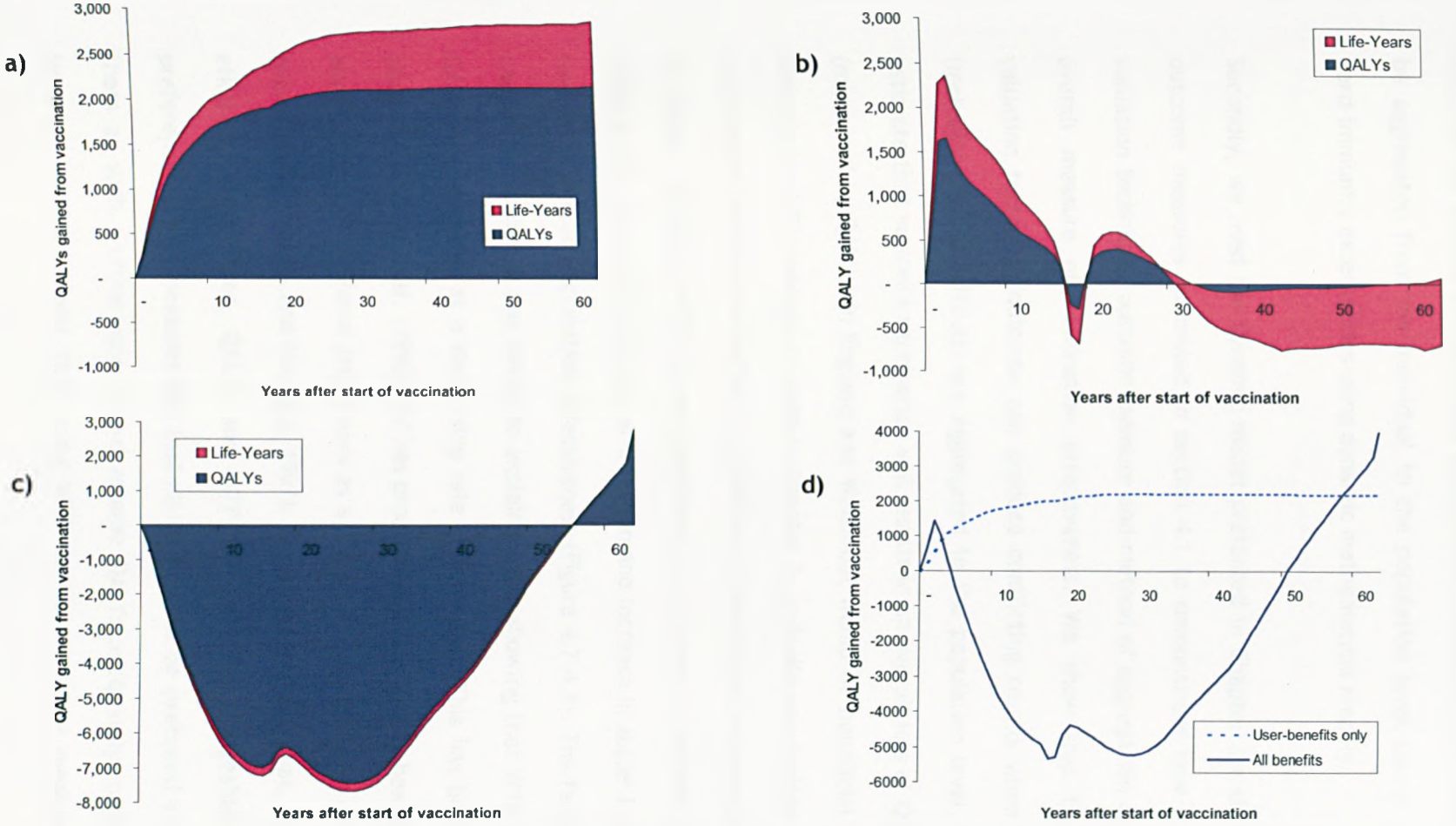


Figure 4.8. Lys and QALYs gained from varicella vaccination (no discounting). a) QALYs-gained by vaccination among vaccines ($QALY^{vac}_{gained}$), b) QALYs-gained by reducing varicella in non-vaccinees ($QALY^{nvac}_{gained}$), c) impact of vaccination on zoster ($QALY^{z}_{gained}$) and, d) overall QALYs-gained by varicella vaccination with and without externalities over time.

4.3.4 DISCUSSION

First, in this section we illustrated formally how different outcome measures can be aggregated from the individual to the population level taking into account herd-immunity externalities using dynamic mathematical models.

Secondly, we used the dynamic model presented in Chapter 3 and the different outcome measures estimated in section 4.1 to demonstrate how the choice of valuation technique, outcome measure and method of aggregation can affect the overall measure of vaccination effectiveness. We show that the choice of valuation technique/outcome can produce conflicting results when all benefits (including indirect effects) are aggregated to the population level. That is, we estimate that varicella vaccination will results in an overall loss of Quality of Life (measured by QALYs) in England and Wales but would be beneficial in monetary units (using WTP values). As seen in Chapter 3, varicella vaccination is predicted to increase the age at infection from children to adults and increase the incidence of zoster. Because, WTP is less sensitive to increases in severity than QALYs (Figure 4.6), the shift in the age at infection and increase in zoster have less of an impact on overall vaccination effectiveness (Figure 4.7-4.8). The fact that WTP is capped by ability to pay seems to explain results showing that WTP increases as QALYs increase but at a decreasing rate Figure 4.6c). This has been previously observed by Bala et al. (1998) and has produced concern among health economists about using the welfarist framework as a basis for the allocation of health care resources (Weinstein and Manning, 1997). Our results suggest that, under current elicitation techniques, QALYs and WTP are not interchangeable/comparable preferenced-based measures and that caution should be exercised in interpreting them as such. Furthermore, if we assume QALYs adequately measure disease severity, results suggest that using WTP as the outcome measure may bias

resource allocation towards less severe diseases, which may, as illustrated in this chapter, lead to reduction in overall quality of life thus justifying extra-welfarists' concerns.

In the next chapter we illustrate how, concretely, the choice of outcome measure can affect cost-effectiveness results and thus resource allocation decisions.

4.4 SUMMARY

First, in this chapter we estimated, using electronic questionnaires, parents willingness to pay for varicella vaccination and the QALY lost due to chickenpox. Different attributes of vaccination were identified. Using the (CV) method we demonstrate, for the first time, that vaccination possesses different non-health attributes such as *insurance type benefits* (i.e. individuals prefer vaccination to treatment). Furthermore, we show that prevention of *work loss* is an important intervention attribute for parents. Finally, results elicited using the CV questionnaire were found to possess construct validity. On the other hand, consistent with economic theory, QALYs did not capture non-health benefits. However, for a given health state description, QALYs elicited from Standard Gamble and HUI2 produced similar results.

Secondly, we illustrated formally, for the first time, how individual preferences or health outcomes can be aggregated to estimate the overall population's value of the benefit of vaccination taking into account externalities and non-health benefits. Results suggest that WTP and QALY are not interchangeable and that this can produce conflicting results when all benefits are aggregated to the population level taking into account externalities.

Chapter 5
Economic Analysis of Vaccination Programmes

5.0 INTRODUCTION

The specific aims of chapter 5 are to:

1) Estimate the cost-effectiveness, cost-utility and cost-benefit of varicella vaccination,
2) Examine and compare the results from the different economic evaluation techniques, and
3) Illustrate the importance of model and methodological assumptions on the economic desirability of vaccination (in particular, the choice of outcome measure and the impact of including externalities).

First, in this chapter, we estimate the cost-effectiveness (cost per life-years gained), cost-utility (cost per QALY gained) and cost-benefit (cost per benefit (as a measured by WTP)) of varicella vaccination. To our knowledge this is the first work that estimates the economic desirability of an intervention using the three major evaluation techniques. Secondly, we compare the different types of economic evaluation to illustrate how the different technique might affect resource allocation. Finally, we use univariate and multivariate sensitivity analysis to assess the impact of model and methodological assumptions on the results of

economic evaluation. Here, we focus on the impact of using dynamic models (including herd-immunity) and, the choice of discount rate and time frame of analysis. This should allow decision makers and health economists to better understand how the results of economic evaluation of vaccination programs are influenced by the methods used.

5.1 ECONOMIC ANALYSIS OF VARICELLA VACCINATION

5.1.0 BACKGROUND

As mentioned in Chapters 2 and 3, three main public health concerns have limited the widespread introduction of the vaccine. First, vaccination could lead to an upward shift in the average age at infection, which could result in increasing the overall morbidity due to varicella (Health Canada Proceedings of the National Varicella Consensus Conference, 1999). Secondly, a high proportion of breakthrough cases of varicella (modified varicella in immunized individuals) have been reported in vaccine efficacy trials (Krause and Klinman, 1995; Brisson *et al.*, 2000). Most importantly, mass vaccination will increase the incidence of zoster if exposure to varicella reduces the rate of reactivation by boosting immunity to VZV (Garnett and Grenfell, 1992a; Garnett and Grenfell 1992b). These concerns were investigated in Chapter 3. The dynamic model of VZV indicates that, although a shift in the average age at infection is likely to occur, the overall incidence and morbidity of varicella is expected to decline after mass vaccination of 12-month-old children. On the other hand, varicella vaccination is estimated to increase the incidence of zoster in the short to medium term. Due to the higher severity of zoster, a small increase in zoster incidence could counterbalance the reduction in varicella morbidity compromising the effectiveness and cost-effectiveness of varicella vaccination. As seen in Chapter 4, the choice of outcome (£ (WTP),

QALY-gained, LY-gained) has a major impact on the overall benefit of varicella vaccination.

Many economic evaluations of routine childhood varicella vaccination have been published (see Table 5.1 for description of studies). Previous economic evaluations have shown varicella vaccination to be either marginally cost-effective (Lieu *et al.*, 1994; Beutels *et al.*, 1996) or cost-ineffective (Getsios *et al.*, 2002; Brisson *et al.*, 2002) from the health care payers perspective, though cost saving from the societal perspective (Lieu *et al.*, 1994; Beutels *et al.*, 1996; Getsios *et al.*, 2002; Scuffham *et al.*, 1999; Scuffham *et al.*, 2000; Diez Domingo *et al.*, 1999; Preblud, 1985; Huse *et al.*, 1994; Banz *et al.*, 2003). However, only Brisson *et al.* (2002) has addressed all three principal dangers of varicella vaccination as mentioned above. Lieu *et al.* (1994), Coudeville *et al.* (1999), Brisson *et al.*, (2002) and Banz *et al.* (2003) incorporated herd-immunity into their analyses. However, with the exception of Brisson *et al.* (2002), these studies used the optimistic vaccine efficacy parameters estimated by Halloran et al. (1994 - see Chapter 2) and, more importantly, did not model the possible impact of varicella vaccination on the incidence of zoster. All other previous economic analyses did not incorporate herd immunity effects (such as a shift in the average age at infection) and are therefore of limited value as aides to decision-making (as shown in Chapters 3 and 4).

Furthermore, all previous economic evaluations of varicella vaccination have used either direct cost, cost-consequence and/or cost-effectiveness analysis (Table 5.1). That is, no cost-benefit or cost-utility analysis has been performed for varicella vaccination. Since varicella is a mild disease, which causes little mortality and the vaccine is effective against complications, the main goal of

varicella vaccination is reducing morbidity. Therefore, it could be argued that a more appropriate (pertinent) outcome for the economic evaluation of VZV vaccination should be cost per quality-adjusted life years (QALY) gained or cost-benefit (using WTP).

In this section, we use the dynamic mathematical model of VZV transmission developed and presented in Chapter 3 to explore the possible economic desirability of different routine varicella immunization programs in English and Welsh children. To do so, we use the three major economic evaluation techniques (cost-effectiveness, cost-utility and cost-benefit). Furthermore, we use sensitivity analysis to illustrate the importance of model and methodological assumptions on the economic desirability of vaccination.

Table 5.1. Summary of methods and results included in published economic evaluations of infant routine varicella vaccination - Costs are in 1997 $US (modified from Thiry et al. (2003))

Reference	Study design								Vaccination[B]		Results[D]	
	Country	Perspective	Discount rate (%)	Time Horizon	Outcome Measures	Study Type[C]	Model type	Zoster	Cost	Coverage (%)	HCP	Societal
Preblud et al. (1985)	USA	HCP Societal	Cost: 5 Ben: NA	30	None	Cost	Static	No	23	90	BCR: 0.3	BCR: 6.9
Huse et al. (1994)	USA	Societal	Cost: 5 Ben: NA	25	None	Cost	Static	No	56	Not Stated	NA	BCR: 2.4
Lieu et al. (1994)	USA	HCP Societal	Cost: 5 Ben: 0,5	30	Life-years saved Consequences	CEA CC Cost	Dynamic	No	48	97	CER: $19,288/LYS CCR: $5/CA BCR: 0.9	BCR: 5.4
Beutels et al. (1996)	Germany	HCP Societal	Cost: 5 Ben: 0,5	70	Life-years saved Consequences	CEA CC Cost	Static	No	41	70	CER: $11,897/LYS CCR: $11/CA BCR: 0.8	BCR: 4.6
Diez Domingo et al. (1996)	Spain	Not Stated	Cost: 5 Ben: NA	20	None	Cost	Static	No	30	95	BCR: 0.5	BCR: 1.6
Coudeville et al. (1999)	France	Patient Societal	Cost: 5 Ben: NA	30	None	Cost	Dynamic	No	15	80	NA	NA
Scuffham et al. (1999)	New Zealand	HCP Societal	Cost: 5 Ben: 0,5	30	Consequences	CC Cost	Static	No	43	80	CCR: $58/CA BCR: 0.7	BCR: 2.8
Scuffham et al. (2000)	Australia	HCP	Cost: 5 Ben: NA	30	Consequences	CC Cost	Static	No	40	80	CCR: $49/CA BCR: 0.2	NA
Brisson et al. (2002)[A]	Canada	HCP Societal	Cost: 5 Ben: NA	30	Life-years saved Consequences	CEA CC Cost	Dynamic	Yes	50	90	CER: $99,318/LYS[E] CCR: $15/CA BCR: 0.6	BCR: 5.2
Getsios et al. (2002)	Canada	HCP Societal	Cost: 5 Ben: NA	70	Life-years saved Consequences	CEA CC Cost	Static	No	55	90	CER: $71,021/LYS CCR: $35/CA BCR: 0.6	BCR: 1.7
Banz et al. (2003)	Germany	HCP Societal	Cost: 5 Ben: NA	30	Consequences	Cost	Dynamic	No	50	85	BCR: 1.7	BCR: 4.1

A.HCP: Healthcare Provider, B. Vaccine efficacy was similar in all studies, between 90 and 95% (Thiry et al., 2003). C. Cost: Benefit to Cost ratio (Dollars saved per dollars invested in vaccination program); CC: Cost-Consequence analysis (Cost per health outcome avoided); CEA: Cost-Effectiveness analysis (Cost per life-year saved). D. Results are discounted. E. CER with the impact of zoster; BCR and CCR without the impact of zoster.

5.1.1 METHODS

5.1.1.1 Model and methodological assumptions.

We compare three different vaccination strategies to no vaccination. The strategies are:

1) *infant strategy*, routine mass infant vaccination at 90% coverage,
2) *catch-up strategy*, *infant strategy* with catch-up (at 80% coverage) targeted at susceptible 2-11 year olds in the first year and;
3) *adolescent strategy*, routine vaccination of 11 year old susceptibles (at 80% coverage).

To assess the impact of vaccination on varicella and zoster, we used the model described in Section 3.2. Unless stated otherwise simulations are performed using the base-case estimates presented in Table 5.2 of Chapter 3.

We performed the economic analysis from the perspective of the health provider (NHS) and of society. The primary viewpoint is that of the health provider because data from this perspective is more complete for the UK. This perspective includes all direct medical costs including physician contacts, hospitalisations and prescription medications. The societal perspective includes all medical and work loss costs as well as household expenditures. Future costs and outcomes are discounted at 3% per year (Gold *et al.*, 1996). In the sensitivity analysis, results are presented with alternate discount rates, including those recommended in the UK (6% per annum for costs and 1.5% for health benefits (Department of Health, 1995)). Costs and benefits are presented over a 80-year time horizon.

Cost, cost-effectiveness, cost-utility and cost-benefit analysis are chosen as analytic techniques. The Departments of Health of England and Wales do not

recommend a specific cut-off value for cost-effectiveness and cost-utility analysis. On the other hand, the National Institute for Clinical Evidence (NICE) have stated that their 'range of acceptable cost effectiveness' is between £20,000 - £30,000 per QALY gained (NICE 2002,

. However, Devlin and Parkin

have analyzed decisions made by NICE and suggest that their cost-effectiveness threshold is slightly higher (between £35,000 and £40,000 per QALY gained). In this analysis we take the conservative value of £20,000 per QALY or life-year gained as being the limit below which vaccination is regarded, here, as being cost-effective. As a range of cost-effectiveness results are presented others can choose alternative threshold values. The outcomes measured are cases, consultations, hospitalizations, deaths, life-years gained, QALYs gained and monetary outcomes (i.e. £). The summary measures are the cost per life-year gained, cost per QALY gained and cost benefit (£).

5.1.1.2 Vaccine efficacy and epidemiological estimates

The vaccine efficacy parameters are presented in section 3.1. The different health outcome values and data sources are presented in Table 5.2.

We estimated the predicted number of cases of natural and breakthrough varicella, and zoster directly from the model. The estimated age-specific proportion of physician consultations, length of stay and deaths per case of varicella and zoster were applied to the predicted number of cases by age and time.

Natural varicella and zoster. The age-specific number of episodes of varicella and zoster which result in a consultation with a general practitioner (GP) and the

average (age specific) number of consultations per episode were taken from the Royal College of General Practitioners (RCGP) Weekly Returns Service data for 1991-2000 (see Chapter 2). Age-specific hospitalisation rates and length of stay data were taken from the Hospital Episodes Statistics for 1995-96, which covers all NHS inpatient episodes in England (numbers were multiplied up by the additional population size to include Wales) (see Chapter 2). The average number of deaths in England and Wales attributed to chickenpox and herpes zoster over the period 1993-2000 were used to calculate age-specific case-fatality ratios (Table 2.2 - see Chapter 2 for details).

Breakthrough infections and vaccine associated adverse events. Breakthrough cases were assumed to visit a physician at the same rate as natural varicella cases (Izurieta *et al.*, 1997), to have a 5-fold lower risk of hospitalisation (Beneson *et al.*, 1995) and not to result in death. We excluded adverse events from our analysis since they are rare (Wise *et al.*, 2000) and thus would not contribute significantly to the overall burden of the vaccine.

The age-specific population size was taken from the Office for National Statistics (ONS) estimates for mid 1998 (Office for National Statistics, 2000). We used the population distribution of mid-1998 and assumed that the birth and death rates will remain constant in the future.

5.1.1.3 Outcome measures

Table 5.2 presents the health outcome estimates included in the analysis. The outcome measures and their method of aggregation are described in detail in Chapter 4 (see section 4.2). It should be stressed that in the Cost-Benefit analysis, the WTP values elicited in Chapter 4 were reduced by 50% as recommended by the

NOAA (National Oceanic and Atmospheric Administration, 1993) to take into account the worry that WTP from CV overestimates actual WTP.

Table 5.2. Health Outcome estimates

Parameters	All	0-4	5-14	15-44	45-64	65+	Source
% cases consult GP							
Natural Varicella		45%	45%	72%	82%	100%	Chapter 2
Breakthrough Varicella		45%	45%	72%	82%	100%	[1]
Zoster		100%	100%	100%	100%	100%	Chapter 2
Number of visits per consultation							
Natural Varicella		1.18	1.24	1.29	1.40	1.43	[2,3]
Breakthrough Varicella		1.00	1.00	1.00	1.00	1.00	Assumption
Zoster		1.07	1.18	1.36	1.43	1.68	[2,3]
Hospitalisations per case							
Natural Varicella		0.37%	0.14%	0.62%	1.38%	3.14%	Chapter 2
Breakthrough Varicella		0.07%	0.03%	0.12%	0.28%	0.63%	Chapter 2
Zoster		1.12%	0.66%	0.50%	0.60%	2.28%	Chapter 2
Length of Stay							
Natural Varicella		2.22	2.96	3.97	5.77	10.57	Chapter 2
Breakthrough Varicella		2.22	2.96	3.97	5.77	10.57	Chapter 2
Zoster		3.53	3.35	4.58	5.23	13.54	Chapter 2
Case-Fatality							
Natural Varicella		0.001%	0.001%	0.009%	0.073%	0.689%	Chapter 2
Zoster		0.000%	0.001%	0.002%	0.002%	0.061%	Chapter 2
VZIG per Case		0.2%	0.2%	3.3%	0.2%	0.2%	Chapter 2
PHN per Zoster case		0%	1%	4%	11%	31%	[4]
Duration of PHN (Days)	511						[4]
QALY Lost per case							
Natural Varicella		0.004	0.004	0.005	0.005	0.005	Chapter 4, [5]
Breakthrough Varicella		0.001	0.001	0.001	0.001	0.001	Assumption
Zoster	0.010						[4]
PHN	0.462						[4]
Value (£) of a case or vaccination							
Vaccination[A]	60.10						Chapter 4
Varicella[B]		46.59	46.59	100.64	100.64	100.64	Chapter 4
Zoster	117.79						Chapter 4
PHN	684.72						Chapter 4

[1] Izurieta et al. 1997; [2] RCGP, 1999; [3] RCGP, 2000; [4] Edmunds *et al.*, 2001; [5] Bala *et al.*; A. WTP for varicella vaccination; B.Value of a case of varicella.

5.1.1.4 Cost data and assumptions

All costs are in £'s sterling and given in 2001 real prices as shown in Table 5.3. Costs estimated in previous years are inflated to 2001 values by the use of the

Hospital and Community Health Services (HCHS) Pay and Prices Index (NHS Executive, 2001).

Direct costs. The average cost per inpatient day and the average cost per GP consultation were taken from Unit Costs of Health and Social Care (Netten and Curtis, 2001). Varicella zoster immunoglobulin (VZIg) in England and Wales is administered by the Public Health Laboratory Service. Data from 2000 were used to estimate the average number of VZIg doses administered annually: 5426. Pregnant women given VZIg (4166 vials) were assumed to be 15 to 44 years. Each vial of VZIg costs £240 (Dr. Elizabeth Miller, Head of the Immunisation division, PHLS, personal communication).

Wreghitt et *al.* (1996) estimated the cost of infection control measures for a sample of 70 hospitalised patients with either varicella or zoster. Measures included serological diagnosis, staff exclusion, the use of VZIg and antiviral drugs and patient isolation. We assume that these measures result in an average fixed cost associated with each hospitalised patient (i.e. independent of their length of stay). Excluding the cost of administration of VZIg (to avoid double counting) this amounts to £722 per patient (in 2001£), two thirds of which is due to staff exclusion. In all analyses it is assumed that contact with a breakthrough case by an at-risk susceptible would be as likely to result in the use of VZIg as contact with natural varicella.

The 1998 Prescription Cost Analysis for England (Department of Health Statistics Division, 1999) was used to estimate the cost of community prescribed drugs for treatment of varicella and zoster (the cost of hospital prescriptions being included in the study by Wreghitt *et al.* (1999)) using assumptions described by Edmunds *et*

al. (2001). The average prescription cost per consultation for varicella and zoster is estimated to be £2 and £35 respectively.

In our base case analysis, we assumed the vaccine costs £30 per course. This is varied in the sensitivity analysis since in the UK the cost of the vaccine is unknown. For the *infant* strategy, we assume that varicella vaccination would be administered concurrently with MMR at 12-15 months and therefore will not incur additional costs such as practice nurse consultations. For the *catch-up* and the susceptible *adolescent* programmes, it is assumed that each susceptible that is targeted is vaccinated at an additional cost of £10 over that of an infant course to cover the cost of a practice nurse consultation (Netten and Dennet, 1999) and extra administration costs. For the *catch-up* and *adolescent strategies* only children with negative or uncertain history of varicella are vaccinated. In our base case scenario, the positive and negative predictive value of determining a person's varicella history at 11 years was estimated to be 97% and 70% respectively (Beutels *et al.*, 1996). This is varied in the sensitivity analysis.

Indirect costs. There are no published estimates of absenteeism caused by chickenpox in the UK, although estimates exist from other industrialised countries (Lieu *et al.*, 1994; Saddier *et al.*, 1998; Fornaro *et al.*, 1999; Sulivan-Bolyai *et al.*, 1987; Law *et al.*, 1999; Coudeville *et al.*, 1999; Domingo *et al.*, 1999; Beutels *et al.*, 1996; Beutels *et al.*, 2000). The average number of workdays lost per case of varicella that does not require hospitalisation was taken to be 0.6 for children, the value found in most studies conducted in European countries (Fornaro *et al.*, 1999; Coudeville *et al.*, 1999; Domingo *et al.*, 1999; Beutels *et al.*, 1996; Beutels *et al.*, 2000). For adults with varicella an estimate of 5.7 days off work was used (Coudeville *et al.*, 1999; Beutels *et al.*, 2000; Lieu *et al.*, 1994). In the base case,

we assume that breakthrough cases will also result in parents taking 0.6 days off work. In a study of varicella in a day-care centre the median period of absenteeism was 1 day for breakthrough cases (Izurieta *et al.*, 1997). Since there are no published estimates of absenteeism caused by zoster, the number of days off work was assumed to be the average age-specific duration of disease multiplied by the proportion of workdays in a week.

Work loss from hospitalised cases due to varicella and zoster were assumed to be twice the average age-specific length of stay multiplied by the proportion of workdays in a week to take into account pre and post-hospitalisation work loss.

To calculate the average cost of work loss, the average period of adult absence due to chickenpox or shingles in children was multiplied by the average daily female wage in 25-34 year olds (weighted by the proportion in full and part-time employment) (ONS New Earnings Survey, 1998). For adult cases, the average period of absence was multiplied by the age-specific average daily wage. It was assumed that there were no work loss costs caused by illness in those over 65 years of age. Household expenditures (e.g. non-prescription medications and babysitting) were based on literature from North America (Lieu et al., 1998; Law et., 1999a; De Wals et al., 2001) since no published data exists for the UK.

5.1.1.5 Sensitivity Analysis

The sensitivity of the results to variation in input parameters was explored by performing a probabilistic multivariate sensitivity analysis (uncertainty analysis). Input parameters were assigned probability distributions and combinations of these parameter values were drawn using Latin Hypercube Sampling assuming that they are independent of each other. For each vaccination scenario, the model was

run 1000 times to generate distributions of outcome variables using @risk Version 4 (Palisade Corporation, New York) running within Microsoft Excel. The parameter values and the assumed input distributions are given in Table 5.4. All input distributions were assumed to be triangular. Results are presented with 90% Credibility intervals (CrI), which show the 5th and 95th percentile of the outcome distributions. Univariate sensitivity analyses, in which parameters were varied one at a time, holding other parameter values at the base-case level, were also performed.

Table 5.3. Cost Estimates

Parameters	All	Natural Varicella	Breakthrough Varicella	Zoster	Source
Vaccination Costs					
Cost of vaccine course	30				Assumption
Extra cost per course for adolescent and catch-up	10				Assumption
Self-reported history of chickenpox					
Sensitivity	97%				[1-3]
Specificity	70%				[1-4]
Direct Costs					
Cost GP consult		22	22	22	[5]
Treat Cost GP consult		2	-	35	[6]
Cost Inpatient day		219	219	219	[5]
Av Treat Cost Hospitalisation		722	722	875	[7]
Cost Vzig		240			[8]
Indirect Costs					
Not Hospitalised					
Work days lost per case					
0-15		0.6	0.6	10	[1,8,9]
16+		5.7	5.7	10	[1,8,9]
Hospitalised					[1,8]
Work days lost					
0-4		3.17	3.17	5.04	Assumption
5-14		4.22	4.22	4.79	Assumption
15-44		5.67	5.67	6.54	Assumption
45-64		8.24	8.24	7.47	Assumption
Cost of a Work Day Lost					
0-15	30				[11]
16-17	15				[11]
18-20	23				[11]
21-24	32				[11]
25-29	51				[11]
30-39	61				[11]
40-49	63				[11]
50-59	52				[11]
60-64	24				[11]
Household expenditures					
0-15		15	-	-	[3,12,13]
16+		35	-	-	[3,12,13]

[1] Beutels et al., 1994, [2] Beutels et al. 2002, [3] Lieu et al., 1998; [4] Kelley et al., 1991; [5] Netten and Dennnet, 1999; [6] Department of Health Statistics Division, 1999; [7] Wreghitt et al., 1996; [8] Dr. Elizabeth Miller, Personal communication; [9] Coudeville et al., 1999; [10] Fornaro et al. 1999; [11] Office for National Statistics, 2000; [12] Law *et al.*, 1999a; [13] De Wals et al., 2001.

Table 5.4. Input values for the multivariate analysis

Parameter		Minimum (source)		Maximum (source)	
% cases consult GP[A]					
Varicella :	0-4	36%	RCGP	48%	RCGP
	5-14	26%	RCGP	45%	RCGP
	15-44	30%	RCGP	72%	RCGP
	45-64	48%	RCGP	100%	RCGP
	65+	57%	RCGP	100%	RCGP
Hospitalisation per case					
Varicella[B]:	0-4	0.4%	HES	0.5%	HES
	5-14	0.1%	HES	0.2%	HES
	15-44	0.6%	HES	0.8%	HES
	45-64	1.4%	HES	1.9%	HES
	65+	3.1%	HES	5.8%	HES
Zoster[B]:	0-4	1.1%	HES	1.4%	HES
	5-14	0.7%	HES	1.0%	HES
	15-44	0.5%	HES	0.8%	HES
	45-64	0.6%	HES	1.2%	HES
	65+	2.3%	HES	5.0%	HES
Length of Stay					
Varicella[B]:	0-4	2.2	HES	2.7	HES
	5-14	3.0	HES	3.6	HES
	15-44	4.0	HES	4.8	HES
	45-64	5.8	HES	7.9	HES
	65+	10.6	HES	15.8	HES
Zoster[B]:	0-4	3.5	HES	5.3	HES
	5-14	3.4	HES	3.4	HES
	15-44	4.6	HES	6.1	HES
	45-64	5.2	HES	8.7	HES
	65+	13.5	HES	17.4	HES
Case-Fatality					
Varicella[C]:	0-4	0.0006%	ONS	0.0017%	ONS
	5-14	0.0004%	ONS	0.0006%	ONS
	15-44	0.0063%	ONS	0.0167%	ONS
	45-64	0.0733%	ONS	0.1011%	ONS
	65+	0.3880%	ONS	0.8536%	ONS
Zoster[C]:	0-4	0.0000%	ONS	0.0000%	ONS
	5-14	0.0000%	ONS	0.0068%	ONS
	15-44	0.0000%	ONS	0.0086%	ONS
	45-64	0.0012%	ONS	0.0035%	ONS
	65+	0.0403%	ONS	0.0831%	ONS
PHN per Zoster case					
	0-4	0.0%	Edmunds et al, 2001	0.0%	Edmunds et al, 2001
	5-14	0.0%	Edmunds et al, 2001	1.7%	Edmunds et al, 2001
	15-44	2.6%	Edmunds et al, 2001	4.9%	Edmunds et al, 2001
	45-64	10.0%	Edmunds et al, 2001	11.9%	Edmunds et al, 2001
	65+	28.7%	Edmunds et al, 2001	33.4%	Edmunds et al, 2001
Duration of PHN		339	Edmunds et al, 2001	781	Edmunds et al, 2001
Value (£) of a case or vaccination					
Vaccination[A]		52	Chapter 4[D]	69	Chapter 4[D]
Varicella:	0-14	45	Chapter 4[E]	60	Chapter 4[E]
	15+	52	Chapter 4[F]	176	Appendix 13[F]
Zoster		76	Appendix 13[G]	176	Appendix 13[G]
PHN		523	Appendix 13[H]	847	Appendix 13[H]
QALY Lost per case					
Varicella:	0-14	0.01%	Chapter 4[I]	0.64%	Chapter 4[I]
	15+	0.32%	Chapter 4[J]	1.02%	Chapter 4[L]
Zoster		0.85%	Chapter 4[K]	1.67%	Chapter 4[L]
Cost Estimates		-25%Base		+25% Base	
Reported History of Chickenpox					
Sensitivity		90%	Scuffham et al., 2000	99%	Beutels et al., 1996
Specificity		50%	Ronan and Wallace, 2001	80%	Scuffham et al., 2000

A) Minimum is minimum number of varicella consultations observed in the RCGP data in a year between 1991-2000. Maximum is maximum number of varicella consultations in a year between 1991-2000. B) Minimum is varicella or zoster in the first diagnostic field (Hospital Episode Statistics (HES)). Maximum is varicella or zoster in any of the diagnostic fields. C) Minimum is minimum case-fatality in a year between 1991-2000 (Observed in ONS mortality statistics). Maximum is maximum case-fatality in a year between 1991-2000. D) 95%CI of WTP for vaccination, Chapter 4, Table 4.10. E) 95%CI of WTP for treatment, Chapter 4, Table 4.10. F) Average WTP for chickenpox and severe zoster. G) Average WTP for mild and severe zoster. H) 95%CI of WTP to prevent PHN. I) Distribution of QALY values obtained from 42 parents of children with prior history of chickenpox. J) Average of QALY value obtained from 10 specialist registrars working at CDSC using the HUI2 generic health status index. K) QALY value for Mild zoster. L) QALY value for severe zoster.

5.1.2 BURDEN OF VARICELLA AND ZOSTER

The overall burden of VZV related disease is substantial (Table 5.5). The predicted 651,000 cases of varicella per year in England and Wales result in an estimated 384,000 physician visits, 2,200 hospitalisations and 20 deaths. Comparatively, there are annually an estimated 189,000 cases of zoster and, 277,000 physician visits, 2,100 hospitalisations and 37 deaths. The estimated overall QALYs lost due to varicella and zoster is 18,000 (90% CrI 14,000-29,000), 80% of which are due to zoster.

The overall societal cost of VZV related disease in England and Wales is estimated to be £223m annually (90%CrI, £181m-£288m - Table 5.5), 76% (£169m) of which are attributable to zoster. Most of societal costs (£175m, 78%) are due to work loss, £12m are due to household expenditures and £35m are due to direct medical costs. Of the annual £35m VZV is estimated to cost the NHS, £13m is due to varicella (£20 per case) and £22m is due to zoster (£116 per case).

Due to the simplified age-specific mortality of the model, predictions of the overall burden (morbidity and costs) of zoster are slightly underestimated compared to those of Edmunds *et al.* (2001). Nonetheless, results indicate that although there are more cases of varicella, the overall burden of disease is significantly higher for zoster.

Table 5.5. Modelled Current Burden

	Varicella		Zoster	
	Base	(90%C$_r$I)	Base	(90%C$_r$I)
Health Outcomes				
Cases	651,000		189,000	
PHN cases			26,000	(25,000 : 27,000)
GP Visits	384,000	(308,000 : *)	277,000	
Hospitalisations	2,200	(* : 2,700)	2,100	(* : 3,500)
Deaths	20	(19 : 26)	37	(30 : 48)
Life Years Lost	900	(800 : 1,200)	400	(400 : 600)
QALY's Lost	3,500	(1,900 : 4,700)	14,000	(12,100 : 24,000)
Welfare Lost (£m)	35	(33 : 44)	38	(34 : 49)
Costs (£m)				
GP visits and VZig	10	(7 : 10)	16	(14 : 18)
Hospitalisation	3	(3 : 4)	6	(7 : 13)
Work Loss and Household Expenditures	41	(31 : 60)	146	(119 : 183)
Total	54	(41 : 74)	169	(140 : 214)

* Base Case is the minimum or maximum value of the parameter's distribution.

5.1.3 EFFECTIVENESS OF VARICELLA VACCINATION

The predicted dynamics of varicella and zoster cases following mass vaccination in England and Wales under base assumptions are shown in Chapter 3 and 4. The projected discounted (3%) health benefits over 80 years derived from vaccination are shown in Table 5.6.

Infant vaccination (*infant strategy*) with 90% coverage is predicted to reduce the number of varicella cases, physician consultations, hospitalisations and deaths by 15m (83%), 8m (79%), 47,000 (73%) and 22 (3%) respectively. If the *catch-up strategy* is introduced an additional 1.1m (6%), 0.7m (8%), 5,000 (9%) and 177 (23%) of these outcomes respectively are expected to be prevented. In comparison, routine vaccination of 11 year olds (*adolescent strategy*) with 80% coverage reduces cases, hospitalisations and deaths by 2m (12%), 11,000 (16%) and 128 (24%). Hence, although adolescent vaccination prevents a smaller proportion

of varicella cases it saves more deaths than the infant strategy because it prevents most mortality in adults and does not lead to an upward shift in the average age at infection.

Table 5.6. 80-year discounted (3%) varicella and zoster outcomes and costs

	Infant		Catch-up		Adolescent	
	Base	(90%C_rI)	Base	(90%C_rI)	Base	(90%C_rI)
Health Outcomes Avoided						
Varicella						
Cases (millions)	14.6		15.7		1.9	
GP consultations (millions)	8.0	(6.6 : *)	8.7	(7.1 : *)	1.5	(1.0 : *)
Hospitalisations (thousands)	46.9	(* : 58.6)	51.9	(* : 65.3)	10.5	(* : 12.6)
Deaths	22	(-23 : 126)	199	(109 : 296)	128	(111 : 210)
Life-years saved (thousands)	14.2		17.4		7.4	
QALYs saved (thousands)	80.2		88.5		18.6	
£m gained	1286		1421		NA[A]	NA[A]
Zoster						
Cases (millions)	-0.6		-0.7		-0.1	
GP consultations (millions)	-1.1		-1.3		-0.1	
Hospitalisations (thousands)	-15.5	(-31.1 : *)	-18.4	(-37.5 : *)	-1.5	(-2.9 : *)
Deaths	-444	(-550 : -336)	-526	(-650 : -393)	-41	(-51 : -31)
Life-years saved (thousands)	-4.1		-4.9		-0.4	
QALYs saved (thousands)	-134.6		-145.7		-11.0	
£m gained	-251		-295		NA[A]	NA[A]
Overall VZV disease						
Life-years saved (thousands)	10.0	(7.7 : 16.0)	12.5	(11.2 : 21.5)	7.0	(6.0 : 11.3)
QALYs saved (thousands)	-54.4	(-155.6 : -44.1)	-67.2	(-186.9 : -40.6)	7.6	(-1.0 : 13.2)
£m gained	1035	(907 : 1168)	1126	(934: 1202)	NA[A]	NA
Costs (£million)						
Vaccine Costs	524	(405 : 644)	698	(557 : 863)	183	(138 : 240)
Direct medical costs prevented						
GP consultations	134	(88 : 146)	141	(90 : 152)	30	(17 : 31)
Hospitalisations	-5	(-72 : -1)	-10	(-84 : -4)	10	(5 : 13)
Vzig	18		23		11	
Total NHS costs prevented	147		154		52	
Work Loss and Household Expenditures prevented	111	(-83 : 673)	271	(11 : 849)	293	(201 : 355)
Total societal costs prevented	258		425		344	
Total Net Costs (NHS)	377		544		-110	
Total Net Costs (Society)	266		273		-161	

* Base Case is the minimum or maximum value of the parameter's distribution. The willingness to pay for varicella vaccination was not measured for the adolescent programme.

Cases of zoster are likely to significantly increase in the 80 years following vaccination (see Chapter 3 and 4). Under base case assumptions, the model predicts that, with *infant* vaccination at 90% coverage the discounted number of cases, hospitalisations and deaths due to zoster will increase by 0.6m (10%), 16,000 (13%) and 444 (37%) respectively over 80 years (Table 5.6). Hence, if the increase in zoster is taken into account, *infant* vaccination would result in an extra 422 VZV related deaths (varicella and zoster) over 80 years. The increase in zoster morbidity is greater for the *catch-up strategy* (Table 5.6). On the other hand, the adolescent strategy has little impact on the burden of zoster. For the *adolescent strategy*, the model predicts that, with 80% coverage of susceptibles, the discounted number of cases, hospitalisations and deaths due to zoster increases by 0.1m (1%), 1,500 (3%) and 41 (5%) respectively over 80 years (Table 5.6).

Life-years gained. The model predicts that 10,000, 13,000 and 7,000 discounted life-years will be gained by *infant, catch-up and adolescent vaccination* over 80 years (Table 5.6). Although *infant* and *catch-up strategies* result in more discounted varicella and zoster deaths over 80 years they produce an increase in life years (Table 5.6). This is because the increase in zoster deaths following varicella vaccination are in the elderly while varicella deaths are mainly prevented in children.

QALYs gained. Under base case assumptions, *infant* and *catch-up vaccination* are expected to result in losses of QALYs over 80 years (-54,000 and -67,000 discounted (3%) QALYs gained respectively). Only adolescent vaccination results in overall health (QALY) gains when taking into account zoster (7,000 discounted QALYs gained over 80 years).

Monetary value of benefit (£). The predicted benefit of *infant* and *catch-up* vaccination in monetary terms over 80 discounted (3%) years is $1035m and $1126m respectively. Hence, as discussed in Chapter 4, our analysis predicts that, although routine childhood vaccination may produce losses in QALYs it may be deemed beneficial using Willingness to pay as a method of preference elicitation. This is because, WTP can capture non-health effects and it is less sensitive to increases in severity than QALYs (i.e. with WTP the increase in zoster has less of an impact on overall vaccination effectiveness).

It should be mentioned that we did not measure the willingness to pay for adolescent vaccination and hence could not assess the overall aggregated benefit of this strategy in monetary values.

5.1.4 COST ANALYSIS

The projected discounted costs of the *infant* and *catch-up* programs are £524m (90%CrI, £405m-£644m) and £698m (90%CrI, £557m-£863m) respectively, which is estimated to avoid £147m and £154m in direct medical costs (Table 5.6). Thus, under base case assumptions, infant vaccination (with or without catch-up) is estimated to result in a net cost from the NHS perspective. On the other hand, routine vaccination of 11 year olds (*adolescent* strategy) with 80% coverage is estimated to result in savings of £52m in direct medical costs over 80 years, but at a cost of £183m (90%CrI, £138m-£240m) (Table 5.6).

Of the strategies investigated only the adolescent strategy is cost saving from the societal perspective (present value of 161m over 80 years - Table 5.6). The *infant* and *catch-up* strategies are estimated to cost £266m and £273m over 80

discounted years respectively (Table 5.6). The 90% CrI of these values are wide (Table 5.6) since little is known of the indirect costs of zoster.

5.1.5 COST-EFFECTIVENESS, COST-UTILITY AND COST-BENEFIT OF VARICELLA VACCINATION

Cost-Effectiveness. Under base case assumptions, the model predicts that from the health care payer's perspective, the *infant, catch-up* and *adolescent strategies* cost £38,000, £44,000 and £19,000 per life-year gained respectively (Table 5.7). Although the *catch-up strategy* is the most effective vaccination strategy in terms of varicella reduction, it is estimated to be the least cost-effective strategy (Table 5.7).

Cost-Utility. Using QALYs as a measure of morbidity, the model predicts that *infant* and *catch-up vaccination* will produce more harm than good when taking into account the impact on zoster (i.e. negative QALYs gained - Table 5.6). Therefore, the cost-utility ratio is negative for these vaccination strategies (Table 5.8). The cost-utility ratio for the *adolescent vaccination* is positive (£18,000 per QALY gained).

Thus, only *adolescent vaccination* would be deemed cost-effective using £20,000 per QALY gained as the upper limit for an intervention to be considered as cost-effective.

Table 5.7. Cost-Effectiveness, sensitivity analysis - NHS perspective

	Infant	Catch-up	Adolescent
Base Case	£38,381	£44,251	£19,109
Vaccine and epidemiological parameters			
Vaccine Efficacy			
Best case	£35,892	£35,471	£19,599
Worst case	£21,012	£24,417	£17,913
Vaccine Coverage			
50% infants, 50% children	£243,114	£281,112	£22,694
95% infants, 90% children	£30,356	£34,244	£18,374
Physician visits per case of varicella			
Lower bound 90%C_rI^B	£44,361	£49,705	£21,709
Upper bound 90%C_rI^B	£37,819	£43,789	£19,069
Rate of hospitalisation and Length of stay			
Any ICD Field	£47,104	£52,767	£19,601
Summary Outcomes			
Case Fatality Ratio of Varicella			
Lower bound 90%C_rI^B	£104,077	£100,228	£28,177
Upper bound 90%C_rI^B	£21,325	£24,120	£10,443
Case Fatality Ratio of Zoster			
Lower bound 90%C_rI^B	£34,518	£39,992	£18,768
Upper bound 90%C_rI^B	£37,522	£43,500	£19,368
Costs			
Cost per vaccine course			
-25% Base Case	£25,109	£30,105	£12,488
+25% Base Case	£51,653	£58,397	£25,731
Cost per consultation			
-25% Base Case	£35,035	£41,428	£18,022
+25% Base Case	£41,728	£47,073	£20,197
Cost per inpatient day			
-25% Base Case	£38,254	£44,049	£19,467
+25% Base Case	£38,509	£44,453	£18,752
Prior History of Varicella			
Sensitivity: 90%	X	£44,445	£20,626
99%	X	£44,170	£12,085
Specificity: 50%	X	£50,253	£30,380
80%	X	£42,419	£15,670
Model and Methodological Assumption			
Duration of immunity to zoster after exposure to VZV			
7 years (lower bound 95% CI)	£21,927	£26,042	£16,553
11 years (lower bound 75% CI)	£28,575	£33,147	£17,857
41 years (upper bound 95% CI)	£47,380	£54,359	£19,896
Excluding indirect effects			
No Herd-immunity and Excluding Zoster	£22,856		
With Herd-immunity and Excluding Zoster	£18,158	£23,171	£16,423
Discount rate			
Benefits 6%, Costs 6%	£33,890	£44,586	£27,465
Benefits 3%, Costs 6%	£23,482	£32,174	£11,969
Benefits 0%, Costs 6%	£12,118	£18,290	£3,558
Benefits 0%, Costs 3%	£19,807	£25,155	£5,681
Benefits 0%, Costs 0%	£37,477	£39,563	£11,764
Time Scale			
30 years	£32,579	£34,407	£25,380

Table 5.8. Cost-Utility, sensitivity analysis - NHS perspective

	Infant	Catch-up	Adolescent
Base Case	QALY Loss[A]	QALY Loss	£17,673
Vaccine and epidemiological parameters			
Vaccine Efficacy			
Best case	QALY LOSS	QALY LOSS	£24,755
Worst case	£11,327	£10,181	£8,172
Vaccine Coverage			
50% infants, 50% children	QALY LOSS	QALY LOSS	£22,841
95% infants, 90% children	QALY LOSS	QALY LOSS	£16,837
Physician visits per case of varicella			
Lower bound 90%C_rI[B]	QALY LOSS	QALY LOSS	£19,566
Upper bound 90%C_rI[B]	QALY LOSS	QALY LOSS	£17,717
Rate of hospitalisation and Length of stay			
Any ICD Field	QALY LOSS	QALY LOSS	£18,021
Summary Outcomes			
Case Fatality Ratio of Varicella			
Lower bound 90%C_rI[B]	QALY LOSS	QALY LOSS	£21,126
Upper bound 90%C_rI[B]	QALY LOSS	QALY LOSS	£11,129
Case Fatality Ratio of Zoster			
Lower bound 90%C_rI[B]	QALY LOSS	QALY LOSS	£17,454
Upper bound 90%C_rI[B]	QALY LOSS	QALY LOSS	£17,801
QALY of Varicella			
Lower bound 90%C_rI[B]	QALY LOSS	QALY LOSS	£46,323
Upper bound 90%C_rI[B]	QALY LOSS	QALY LOSS	£9,582
QALY of Zoster			
Lower bound 90%C_rI[B]	QALY LOSS	QALY LOSS	£12,630
Upper bound 90%C_rI[B]	QALY LOSS	QALY LOSS	QALY LOSS
Costs			
Cost per vaccine course			
-25% Base Case	QALY LOSS	QALY LOSS	£13,081
+25% Base Case	QALY LOSS	QALY LOSS	£22,266
Cost per consultation			
-25% Base Case	QALY LOSS	QALY LOSS	£18,680
+25% Base Case	QALY LOSS	QALY LOSS	£16,667
Cost per inpatient day			
-25% Base Case	QALY LOSS	QALY LOSS	£18,004
+25% Base Case	QALY LOSS	QALY LOSS	£17,306
Prior History of Varicella			
Sensitivity: 90%	X	QALY LOSS	£19,047
99%	X	QALY LOSS	£11,048
Specificity: 50%	X	QALY LOSS	£28,058
80%	X	QALY LOSS	£14,463
Model and Methodological Assumption			
Duration of immunity to zoster after exposure to VZV			
7 years (lower bound 95% CI)	£9,396	£10,449	£7,679
11 years (lower bound 75% CI)	QALY LOSS	QALY LOSS	£11,421
41 years (upper bound 95% CI)	QALY LOSS	QALY LOSS	£31,258
Excluding indirect effects			
No Herd-immunity and Excluding Zoster	£4,199	X	X
With Herd-Immunity and Excluding Zoster	£3,256	£4,665	£6,667
Discount rate			
Benefits 6%, Costs 6%	QALY LOSS	QALY LOSS	£74,511
Benefits 3%, Costs 6%	QALY LOSS	QALY LOSS	£11,049
Benefits 0%, Costs 6%	£6,249	£16,933	£1,579
Benefits 0%, Costs 3%	£10,214	£23,289	£2,521
Benefits 0%, Costs 0%	£19,327	£16,511	£5,228
Time Scale			
30 years	QALY LOSS	QALY LOSS	£29,988

A. QALY Loss: Negative benefit of vaccination. B. 90% C_rI of distribution in Table 5.3.

Cost-Benefit. The base case Cost-Benefit ratios for the *infant* and *catch-up* strategies are 0.39 and 0.40 respectively. Hence, in contrast to Cost-Effectiveness and Cost-Utility analysis, Cost-Benefit analysis is deemed to be highly desirable from the NHS perspective.

5.1.6 SENSITIVITY ANALYSIS

5.1.6.1 Univariate Sensitivity Analysis.

The sensitivity of results to changes in the key parameters is shown in Tables 7-9.

Cost-Effectiveness. The cost-effectiveness of *infant* and *catch-up* vaccination is most sensitive to vaccine efficacy, vaccine coverage, the cost per vaccine course, the case-fatality ratios, and the duration of immunity to zoster after exposure to VZV (Table 5.7). However, using £20,000 per life-year gained as the criteria for an intervention to be considered cost-effective, infant vaccination (with or without catch-up) remains cost-*in*effective when varying these key parameters within their plausible ranges. Only when discount rates are set to 0% for benefits or the indirect effect of zoster is excluded from the analysis does the cost per life-years gained of infant varicella vaccination become lower than the £20,000 threshold.

The results of the *adolescent* programme are relatively insensitive to changes in parameter values and oscillate around £20,000 per life-year gained. Parameters with the greatest impact on results are the case-fatality ratio of varicella and accuracy of reported history of varicella.

Table 5.9. Cost-Benefit Analysis, sensitivity analysis - NHS perspective

	Infant	Catch-up
Base Case	0.39	0.40
Vaccine and epidemiological parameters		
Vaccine Efficacy		
Best case	0.34	0.33
Worst case	0.29	0.27
Vaccine Coverage		
50% infants, 50% children	0.56	0.56
95% infants, 90% children	0.38	0.39
Physician visits per case of varicella		
Lower bound 90%C_rI^B	0.45	0.44
Upper bound 90%C_rI^B	0.39	0.38
Rate of hospitalisation and Length of stay		
Any ICD Field	0.45	0.47
Summary Outcomes		
WTP for Varicella Vaccination/Treatment		
Lower bound 90%C_rI^B	0.50	0.51
Upper bound 90%C_rI^B	0.30	0.32
WTP for Zoster/Treatment		
Lower bound 90%C_rI^B	0.37	0.37
Upper bound 90%C_rI^B	0.42	0.43
Costs		
Cost per vaccine course		
-25% Base Case	0.21	0.24
+25% Base Case	0.57	0.56
Cost per consultation		
-25% Base Case	0.42	0.43
+25% Base Case	0.36	0.37
Cost per inpatient day		
-25% Base Case	0.39	0.39
+25% Base Case	0.39	0.41
Prior History of Varicella		
Sensitivity: 90%	X	0.40
99%	X	0.40
Specificity: 50%	X	0.40
80%	X	0.40
Model and Methodological Assumption		
Duration of immunity to zoster after exposure to VZV		
7 years (lower bound 95% CI)	0.24	0.20
11 years (lower bound 75% CI)	0.30	0.28
41 years (upper bound 95% CI)	0.47	0.51
Excluding indirect effects		
No Herd-immunity and Excluding Zoster	0.23	
With Herd-Immunity and Excluding Zoster	0.22	0.18
Discount rate		
Benefits 6%, Costs 6%	0.44	0.42
Benefits 3%, Costs 6%	0.24	0.24
Benefits 0%, Costs 6%	0.08	0.08
Benefits 0%, Costs 3%	0.13	0.14
Benefits 0%, Costs 0%	0.25	0.25
Time Scale		
30 years	0.51	0.53

Cost-Utility. The cost-utility of infant and catch-up vaccination is most sensitive to vaccine efficacy and the duration of immunity to zoster after exposure to VZV.

If vaccine efficacy is poor (worst case scenario), duration of immunity to zoster after exposure to VZV is 7 years (lower bound of the 95% CI see Chapter 2) or the impact of zoster is excluded from the analysis, then infant and catch-up vaccination are estimated to be highly cost-effective (i.e. cost per QALY gained is lower than £10,000). The cost-effectiveness of infant varicella vaccination is also sensitive to the choice of discount rate and time frame of the analysis. Because zoster morbidity will eventually decline after 60 years (once all cohorts are vaccinated (see Chapter 3)), lower discount rates for benefits and longer time frames of analysis will cause varicella vaccination to be more cost-effective (Table 5.8). Infant varicella vaccination remains highly cost-*in*effective for changes in all other key parameters (Table 5.8).

The results of the adolescent programme are sensitive to changes in parameter values. However, most scenarios cost less than £25,000 per QALY saved. Parameters with the greatest impact on results are the case-fatality ratio of varicella, QALY lost due to varicella and zoster and the discount rate.

Cost-Benefit. The cost-benefit of varicella vaccination is most sensitive to vaccine coverage, WTP for varicella vaccination, the cost of the vaccine and the impact of vaccination on zoster. However, varicella vaccination remains highly cost-beneficial for changes in all parameters. It should be stressed that this is the case despite reducing by 50% the WTP values elicited in Chapter 4. In fact, the WTP values elicited in Chapter 4 must be reduced by more than 80% for the CBR ratio to be greater than one.

5.1.6.2 Multivariate Sensitivity Analysis

The results of the multivariate analysis are shown in Figures 1-3. Unless stated otherwise, results are from the NHS perspective, and vaccine efficacy, vaccine coverage, duration of immunity to zoster WAIFW matrix, time frame of analysis and discount rates are held at base-case values. All other parameters are varied simultaneously according to their assigned probability distributions.

Cost-Effectiveness. For a given value along the x-axis, Figure 5.1 a and b show the proportion of simulations which result in a cost per life-year gained equal or less than that value. More loosely, for different programmes and epidemiological assumptions, these figures can be interpreted as showing the probability that varicella vaccination would be deemed cost-effective for alternative values of society's maximum willingness to pay for a life-year gained. The results suggest that infant vaccination (with and without catch-up) is unlikely to be cost-effective (Figure 5.1a, b). Using £20,000 per life-year gained as the CEA threshold, the probability that *infant* vaccination is cost-effective is 0% (95%CI 7-41 yrs immunity, 0-18%). The CEA threshold must be doubled for infant vaccination to have more than a 50% chance of being cost-effective. On the other hand, if the impact of zoster is ignored then varicella vaccination is cost-effective under many acceptable criteria. Consistent with the univariate sensitivity analysis, adolescent vaccination is the strategy, which is most likely to be cost- (Figure 5.1a).

Figure 5.1c presents the results of the probabilistic sensitivity analysis of infant vaccination on the cost-effectiveness (CE) plane. The continuous black line represents the CEA threshold (assumed at £20,000 per life-year gained) and each point on the CE plane represents the results of one realisation of the probability sensitivity analysis. Under the NHS perspective, more than half of simulations are

deemed cost-effective (left of the continuous line) when the impact of zoster is excluded. However, if zoster is included, very few simulations produce results that are cost-effective. On the other hand, most simulations are cost-saving under the societal perspective (with or without the zoster externality). It should be stressed that including indirect costs due to zoster increases greatly the variability of results, which represents the high level of uncertainty concerning the cost of productivity loss due to shingles.

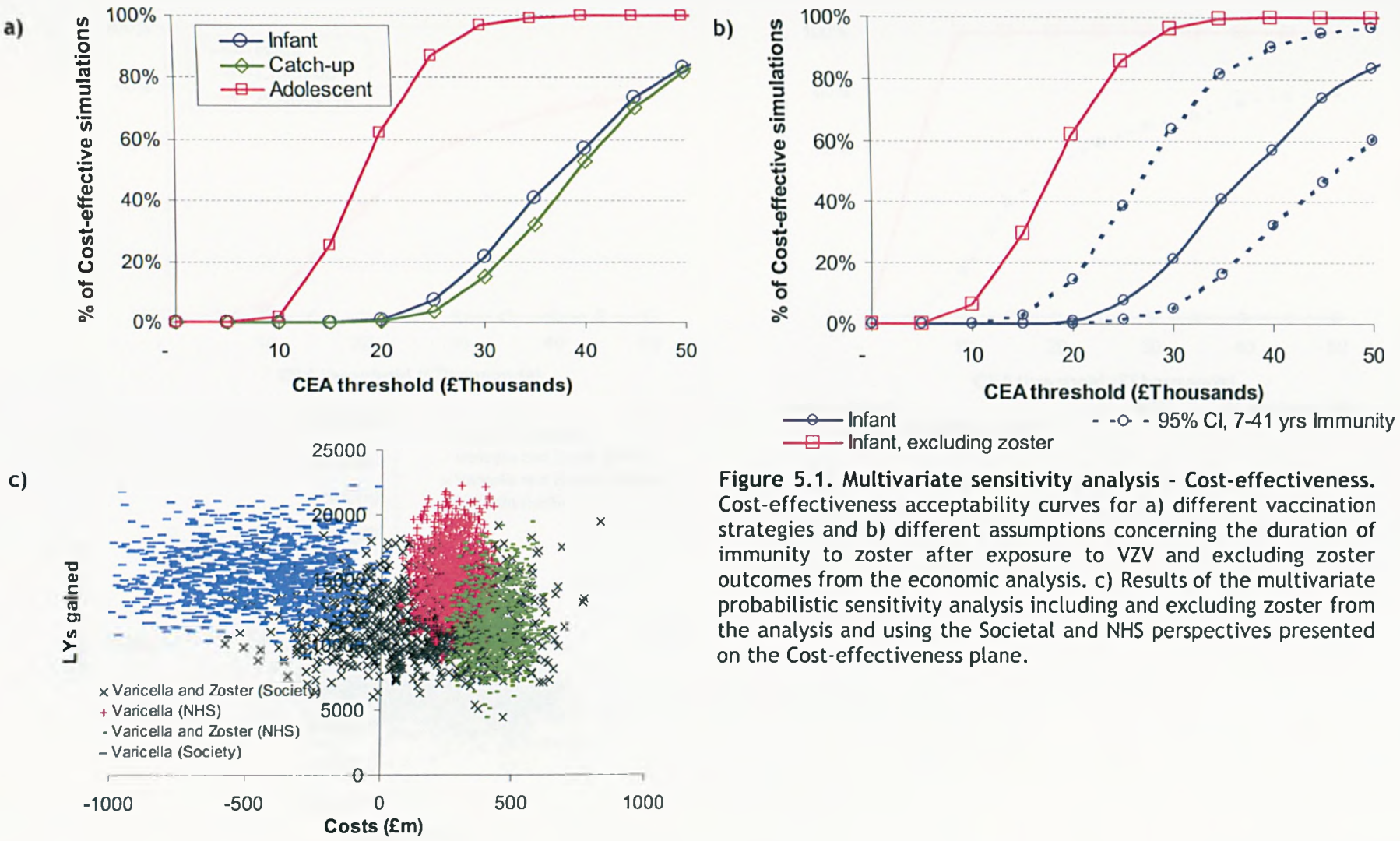


Figure 5.1. Multivariate sensitivity analysis - Cost-effectiveness. Cost-effectiveness acceptability curves for a) different vaccination strategies and b) different assumptions concerning the duration of immunity to zoster after exposure to VZV and excluding zoster outcomes from the economic analysis. c) Results of the multivariate probabilistic sensitivity analysis including and excluding zoster from the analysis and using the Societal and NHS perspectives presented on the Cost-effectiveness plane.

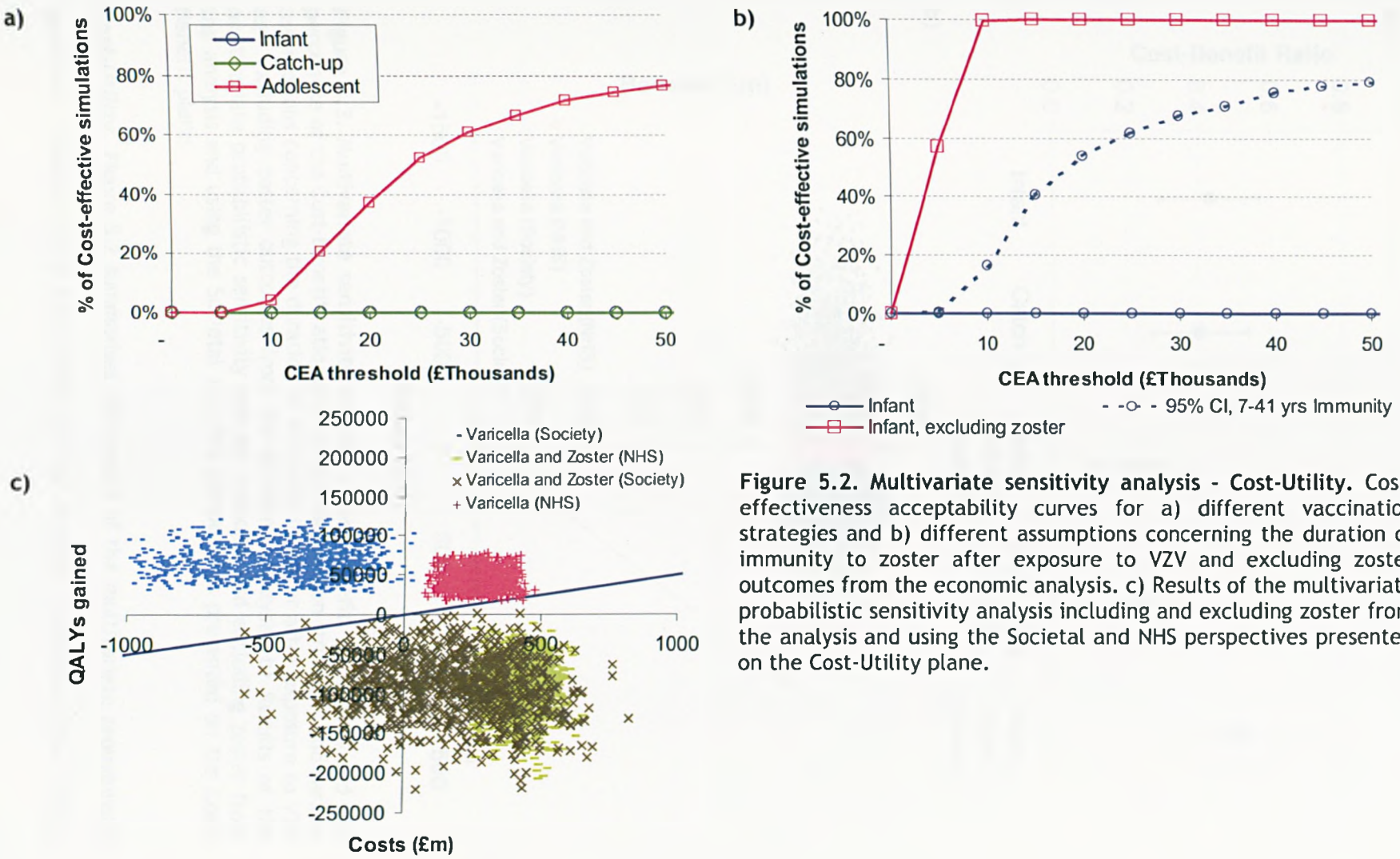


Figure 5.2. Multivariate sensitivity analysis - Cost-Utility. Cost-effectiveness acceptability curves for a) different vaccination strategies and b) different assumptions concerning the duration of immunity to zoster after exposure to VZV and excluding zoster outcomes from the economic analysis. c) Results of the multivariate probabilistic sensitivity analysis including and excluding zoster from the analysis and using the Societal and NHS perspectives presented on the Cost-Utility plane.

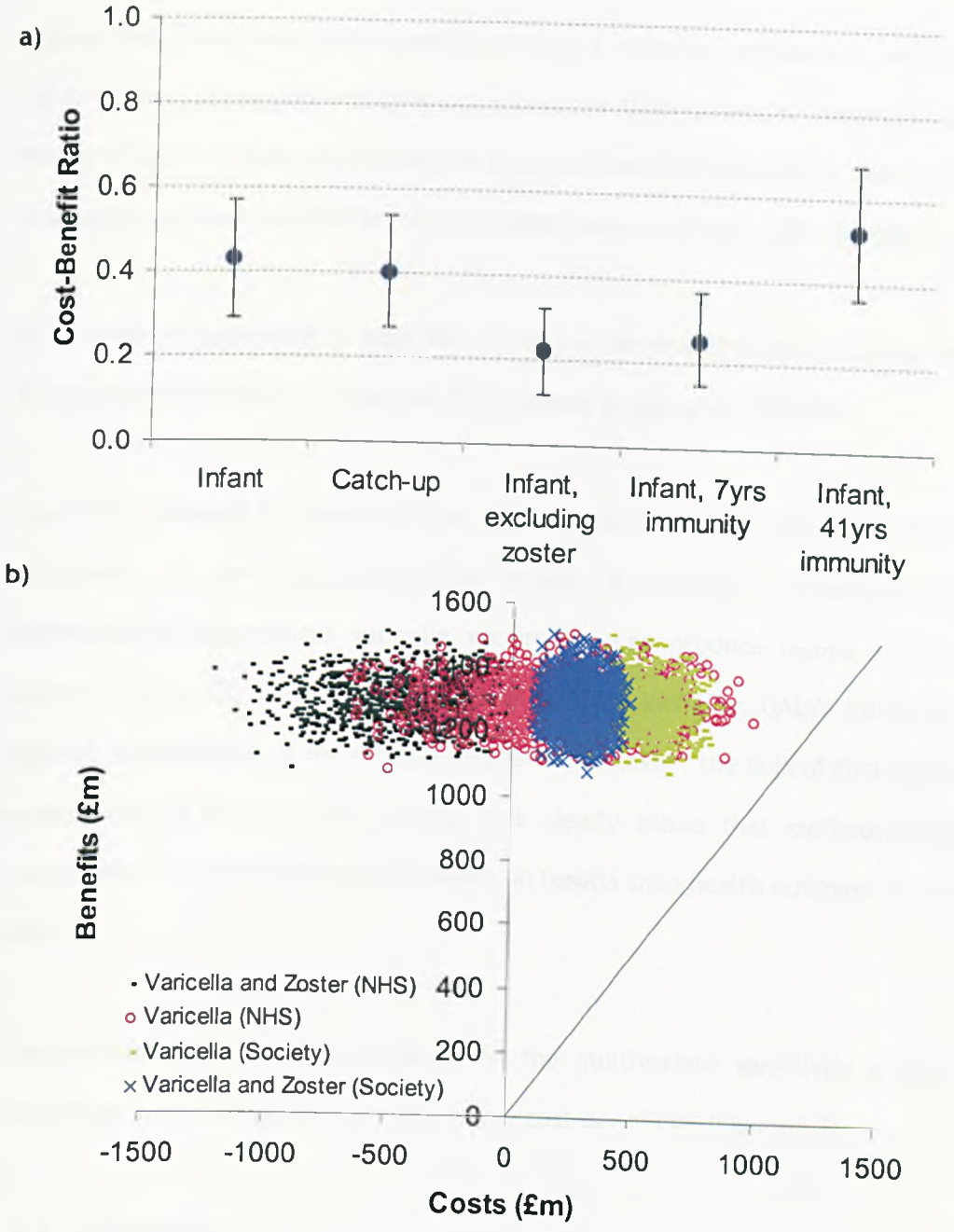


Figure 5.3. Multivariate sensitivity analysis - Cost-Benefit. a) 5%, 50% and 95% percentile of the Cost-Benefit ratio for different vaccination strategies and various assumptions concerning the duration of immunity to zoster after exposure to VZV and excluding zoster outcomes from the economic analysis. b) Results of the multivariate probabilistic sensitivity analysis including and excluding zoster from the analysis and using the Societal and NHS perspectives presented on the Cost-Benefit plane.

Cost-Utility. Figure 5.2 summarises the results of the multivariate probabilistic sensitivity analyses using Cost-Utility as the analytic technique. The results

suggest that, infant vaccination (with or without a catch-up programme) would be highly unlikely to be cost-effective using cost per QALY gained. However, if the impact of zoster is excluded from the analysis, then the probability that infant vaccination will be cost-effective is 100% under many acceptable CEA thresholds.

Vaccination of susceptible 11 year olds is likely to be cost-effective (close to half of the simulations result in a cost per QALY gained of less than £20,000).

Figure 5.2c presents the results of the probabilistic sensitivity analysis of infant vaccination on the cost-utility (CU) plane. Interestingly, dependant on methodological assumptions varicella vaccination can produce results in all 4 quadrants of the CU plane. If the impact of zoster is included, QALYs gained are negative. Furthermore, if the societal perspective is taken, the bulk of simulations produce results that are cost saving. This clearly shows that methodological assumptions can have a far greater impact on results than health outcome or cost parameters.

Cost-Benefit. All simulations/scenarios in the multivariate sensitivity analysis show infant varicella vaccination to be highly cost-beneficial (Figure 5.3).

5.1.7 DISCUSSION

Conclusions regarding the economic desirability of infant varicella vaccination (with and without catch-up) is largely dependant on the choice of analytical technique.

Cost-Effectiveness and Cost-Utility analysis. The Cost-Effectiveness and Cost-Utility analyses produce similar conclusions. First, the "cost-effectiveness" of

infant varicella vaccination rests heavily on the impact it will have on the incidence of zoster (Table 5.10). In Chapter 3, we show that the increase in zoster following vaccination is dependant on vaccine effectiveness at preventing varicella and the length of time exposure to VZV protects against zoster. If duration of immunity to zoster after exposure to VZV is more than 10 years (lower bound of the 85% CI) and vaccination is effective (as it has been proven to be in the US (Seward et al., 2002, Vazquez et al., 2001) then universal infant strategies are unlikely to be cost-effective and, using QALYs as a measure of overall morbidity, are likely to produce more harm than good. This conclusion is robust to changes in all other health outcome and cost estimates investigated here. Secondly, if the discount rate for benefits is very low (i.e. if time preference is such that short and long term benefits are valued equally), then infant varicella vaccination would be worthwhile since after 60 years a reduction in zoster cases will occur provided vaccine recipients are less likely to develop zoster than individuals who have acquire natural infection (Garnett et al., 1992a,b).

Under all scenarios investigated, *adolescent* vaccination is the most cost-effective option from the health provider's perspective because, per vaccinee, there is a larger reduction of serious disease than for the infant programs. Furthermore, it is the safest option since it has little effect on the age at infection and incidence of zoster. However, the cost-effectiveness of this strategy depends on the accuracy of the QALY measures for varicella and zoster.

Cost-Benefit analysis. Cost-benefits analysis results predict that infant varicella vaccination is highly desirable. This conclusion is robust to methodological (e.g. discount rate, time horizon of analysis) and modelling assumptions (i.e. including/excluding herd-immunity and zoster) as well as changes in all

parameters investigated here (Table 5.10). In fact, the WTP for varicella vaccination or avoidance of varicella must be reduced by an additional 20% (the elicited values have already been halved) or the WTP for zoster must be increased by 300% (or elicited WTP be increased by 150%) for the cost-benefit ratio to exceed unity.

Strengths and limitations of the analysis. The analysis presented here expands on previous analyses in four major areas. Most importantly we include the possible effect of zoster on the economic desirability of varicella vaccination using a dynamic mathematical model parameterised from recent data. Secondly, we use other outcome measures than life-years gained. Using QALY or £, instead of life-years gained as previous studies have done (see Table 5.1), is arguably more appropriate since the main aim of varicella vaccination is to reduce VZV morbidity (because VZV causes little mortality). Thirdly, like Lieu *et al.* and Brisson et *al.* we take into account herd-immunity effects when assessing cost-effectiveness. Finally, we performed extensive univariate and multivariate sensitivity analysis, not only on the parameters used, but also on methodology.

The two main limitations of the economic analysis presented here are the lack of data on the indirect costs due to zoster and uncertainty surrounding the WTP to prevent zoster and PHN since values were taken from a convenient sample not representative of the UK population. Furthermore, the mathematical model has two main limitations. First, it has a simplified age structure in the elderly, which results in an underestimate of the overall burden of zoster in this age group (Edmunds *et al.*, 2001). Hence, results may overestimate the cost-effectiveness of varicella vaccination. Finally, a better understanding of the mechanisms that lead

to the development of shingles is needed to improve accuracy of model predictions.

Impact of model and methodological assumptions on results. In this section we show that model and methodological assumptions can have greater impact on results than parameter estimates. More particularly, we illustrate that the economic analysis can produce opposite conclusions depending on the choice of 1) outcome measure, 2) model (including or not herd-immunity and zoster) and 3) discount rate. Our analysis predicts that, while varicella vaccination is expected to increase morbidity using QALYs, it is deemed highly beneficial using WTP. As discussed in Chapter 4, this is because the average WTP per QALYs gained is higher for interventions that prevent acute mild disease (e.g. varicella) than severe long-term disease (e.g. zoster). Hence, basing policy decisions on Cost-benefit (Cost per WTP) or Cost-Effectiveness (Cost-Utility) analysis will lead to very different resource allocation decisions.

Vaccination is a preventive intervention hence benefits can occur in the short to long term. Hence, the choice of discount rate can greatly influence results (has a greater impact on results than curative interventions). This is illustrated in our results: varicella vaccination is cost-effective when discounting is very low because the long-term benefits on zoster become significant.

These results reinforce the importance of not only clearly stating methodological and model assumptions, but also justifying the choices made and discussing their impact. Complexity of methodology or modelling technique should not be an acceptable justification for simplicity if the technique used has been proven to be inadequate (e.g. excluding herd-immunity when it can produce negative effects -

see Discussion, Section 2, Chapter 3). Further research is needed to better understand the impact of the different methodological assumptions on results and resource allocation decisions, more particularly on the effects of the choice of outcome measure and elicitation technique. In the meantime, although this may be resource intensive, sensitivity analysis should be performed on key model and methodological assumptions.

5.2 SUMMARY

In this section we assessed the cost-effectiveness, cost-utility and cost-benefit of varicella vaccination taking into account its impact on zoster. Furthermore, results from the different economic evaluation techniques, were compared to illustrate the importance of model and methodological assumptions on results and thus potentially on resource allocation. To do so, the age-structured transmission dynamic model, described in Chapter 3, was used to predict the future incidence of varicella and zoster. Data from national and sentinel surveillance systems were used to estimate age-specific physician consultation, hospitalisation and mortality rates. Unit costs, taken from standard sources, were applied to the predicted health outcomes.

The WTP and QALY outcome measures elicited in Chapter 4 where used. Using cost-utility and cost-effectiveness analysis, we predict that routine infant varicella vaccination is unlikely to be ''cost-effective''. Furthermore, that adolescent vaccination is the safest and most ''cost-effective'' strategy but has the least overall impact on varicella. On the other hand, varicella is highly cost-beneficial when using £ as the outcome measure.

In this Chapter we show that results are less sensitive to parameter estimates than model and methodological assumptions. Results were most sensitive to the inclusion/exclusion of externalities (impact on zoster and herd-immunity), the outcome measure, analytical perspective and discount rate.

The research in this chapter has been published in part in the following peer reviewed journals:

- **Brisson M,** Edmunds WJ. Varicella Vaccination in England and Wales: Cost-utility analysis. Arch Dis Child 2003; 88:862-9.
- **Brisson M,** Edmunds WJ. The cost-effectiveness of varicella vaccination in Canada. Vaccine 2002; 20: 1113-1125.

Chapter 6
Summary findings and guidelines for the economic evaluation of vaccination programmes

6.0 GENERAL INTRODUCTION

This thesis has two broad aims, which are to: 1) assess the effectiveness and "cost-effectiveness" of introducing routine childhood varicella vaccination in the UK, and 2) investigate the methodological challenges related to the economic evaluation of vaccination programmes. In this chapter we give a brief overview of the findings which relate to these objectives and highlight where future work should be focussed. Further discussion is presented within each of the previous Chapters.

6.1 SUMMARY OF EMPIRICAL FINDINGS

Two main concerns have limited the widespread acceptance of varicella vaccination: 1) it could increase the number of varicella cases in adults, where severity is greater, and 2) increase cases of zoster. To study these concerns, a deterministic realistic age-structured (RAS) model of varicella and zoster was built. The main findings from the modelling study were as follows:

- **The overall varicella incidence and morbidity is likely to decrease following mass infant vaccination.** The model, presented in Chapter 3, predicts that mass vaccination of children in England and Wale will reduce both varicella incidence and morbidity. That is, it is unlikely that infant vaccination will shift the average age at infection to such an extent that morbidity due to varicella is worse than the pre-vaccination state. However, the overall level of effectiveness of routine immunisation depends highly on the level of coverage and the efficacy of the vaccine. Lower efficacy vaccines produce more cases in both vaccinated and unvaccinated individuals than better vaccines but paradoxically, may reduce morbidity more than better vaccines. Finally, while not increasing overall morbidity, there are many scenarios in which vaccination at intermediate levels of coverage results in only marginal long-term benefits.

- **Cases of zoster are likely to significantly increase in the first 30 to 50 years following infant vaccination, but will decrease rapidly thereafter.** In Chapter 3 we predict that, if vaccination is highly effective against varicella (Chapter 3 section 1) and exposure to varicella is protective against zoster (Chapter 2 section 2), then an increase in zoster will occur following mass infant vaccination. These predictions depend on one main assumption. That exposure to varicella boosts against zoster. However, we estimate that the duration of immunity is likely to be long enough to produce a significant increase in zoster after vaccination. It should be noted that, in the long-term a reduction of zoster cases will occur provided vaccine recipients are less likely to develop zoster than individuals who acquire natural infection.

In Chapter 4, we estimated, using electronic questionnaires, parents willingness to pay for varicella vaccination and the QALYs lost due to chickenpox using various elicitation techniques and aggregated these results to the population level using the model developed in Chapter 3. The key findings of Chapter 4 are:

- **The estimated WTP for varicella vaccination and QALY lost due to chickenpox** (see Table 4.10, 4.16 and 4.23 for values).

- **Vaccination possesses measurable non-health attributes: insurance type benefits and prevention of work loss.** Using the CV method we demonstrate, for the first time, that vaccination possesses different non-health attributes such as *insurance type benefits* (i.e. WTP for vaccination was greater than for treatment). Furthermore, we show that prevention of *work loss* is an important intervention attribute for parents. Altruism was not found to be a significant attribute of parents' willingness to pay. However, this may have been due to insufficient sample size. QALYs did not capture non-health benefits.

- **WTP and QALY analysis produced conflicting results when all benefits were aggregated to the population level taking into account externalities.** In Chapter 4, we illustrate formally, for the first time, how individual preferences can be aggregated to estimate the overall benefit of vaccination at the population level taking into account externalities and non-health benefits. Results suggest that WTP and QALYs are not interchangeable and that this can produce conflicting results when all benefits are aggregated to the population level.

In Chapter 5, we used the dynamic mathematical model of VZV transmission developed and presented in Chapter 3 to explore the possible economic desirability of mass varicella vaccination taking into account the external effects of herd-immunity and increase in zoster. To do so, we performed the three major types of economic evaluation techniques (cost-effectiveness, cost-utility and cost-benefit analyses) using the outcomes valued in Chapter 4. Data from national and sentinel surveillance systems were used to estimate age specific consultation, hospitalisation and mortality rates. Average unit costs, taken from standard sources, were applied to the predicted health outcomes. Univariate and multivariate sensitivity analyses were used to assess robustness of results/conclusions. The main results of the analysis are:

- **Adolescent vaccination is the only programme estimated to be cost saving from the societal perspective.**

- **Cost-Effectiveness and Cost-Utility of infant varicella vaccination rests heavily on the impact it will have on the incidence of zoster.** If, as expected, zoster increases after mass infant varicella vaccination (see Chapter 3), then it is unlikely to be cost-effective and may produce an increase in overall morbidity (i.e. QALYs lost). These results are robust to changes in all other health outcome and cost estimates investigated in the thesis. If zoster does not increase, varicella vaccination is likely to be cost-effective from the NHS perspective (£18,158 and £3,256 per Life-year saved and QALY saved respectively).

- **Cost-benefit analysis results predict that infant varicella vaccination is highly desirable.** This conclusion is robust to methodological and modelling

assumptions as well as changes in all parameters investigated here.

Many economic evaluations of routine childhood varicella vaccination have been published (see Chapter 5, Table 1). However, we are the first to include the impact of varicella vaccination on zoster. Furthermore, all previous economic evaluations of varicella vaccination have used either direct cost, cost-consequence and/or cost-effectiveness analysis (Chapter 5, Table 1). That is, no cost-benefit or cost-utility analysis has been performed for varicella vaccination. As shown in Chapter 5, these are important omissions since the economic desirability of varicella vaccination is dependent on the impact it will have on zoster and the choice of analytic technique.

6.2 GUIDELINES FOR THE ECONOMIC EVALUATION OF VACCINATION PROGRAMMES

Recently, Beutels *et al.* (2002) proposed specific guidelines for the economic evaluation of vaccination programmes, due to inconsistencies in the methods used to estimate the future benefit of immunisation programmes. In this section we discuss the challenges related to the economic evaluation of vaccination programmes and propose additions to the guidelines proposed by Beutels *et al.* (2002).

The important methodological components that must be considered when performing or judging the quality of an economic evaluation of a vaccination programme can be separated into 4 categories: 1) Model Structure, 2) Outcome measure and valuation technique, 3) Study design, and 4) Sensitivity analysis. Here, varicella vaccination is used as an example to illustrate and support recommendations.

1. Model Structure

As discussed in Chapter 1, there are two general types of models that are used to estimate the effectiveness of vaccination programmes: static and dynamic. Presently, the majority of economic analyses use static models due to their relative simplicity compared to dynamic models. Here, we propose guidelines (similar to those of Beutels *et al.* (2002)) for judging which type of model should be used (Table 6.1) and what should be included in the model. The guidelines are as follows:

- **Static model can be used 1) if vaccination is unlikely to change the force of infection or, 2) to estimate the worst-case scenario when herd-immunity cannot produce negative effects.** The difference between static and dynamic models is that static models cannot take into account herd-immunity effects. Hence, when the force of infection is unlikely to change following vaccination (i.e. herd-immunity effects are unlikely to occur) then static models can adequately predict effectiveness. In Chapter 3, we show that if coverage is low or vaccination is targeted at groups that do not have an impact on overall transmission then static and dynamic models produce similar results. Although not shown in the thesis, results are also similar for vaccines that do not prevent the circulation of the pathogen (e.g. rotavirus vaccine) since herd-immunity effects are negligible.

- **Dynamic models should be used if vaccination is likely to change the force of infection.** In Chapter 3, we illustrate the importance of incorporating herd-immunity externalities when assessing the effectiveness of vaccination programmes. To do this, we compare a dynamical model, in which the force of infection is an endogenous time-dependant variable, with a static model in

which the force of infection is treated as a time-independent exogenous variable. We show that, by taking into account the changes in the rate of infection following vaccination, dynamic models can 1) produce non-linear dynamics, 2) predict a higher number of cases prevented and 3) predict either increases or decreases in morbidity and mortality due to shifts in the age at infection. We further show that, contrary to what is generally assumed in the literature, using static models does not always produce conservative results. In fact the use of static models may grossly overestimate the effectiveness of mass vaccination at preventing serious disease since they cannot capture possible increases in morbidity due to shifts in the age at infection.

- **Externalities related to vaccination should be included in the model. If spill over effects are not included, their likely impact should be discussed. The possible equity implications should also be discussed** In Chapters 3 to 5 we show that the conclusions regarding the effectiveness and cost-effectiveness of varicella immunisation rest heavily on the indirect effect it will have on zoster. Due to it's importance, omitting zoster from the economic analysis of varicella vaccination because "no long term data exist on this question (Lieu et al., 1994)" or because "the relationship between varicella and zoster incidence is not completely investigated (Banz *et al.*, 2002)" is unjustified and can mislead public health decision makers. There are many other types of positive and negative spill over effects that can be produced by vaccination (e.g. serotype replacement, vaccine cross protection), which can have an impact on economic evaluation. It is important that externalities be identified and if not incorporated into the model, their likely impact should be discussed. Furthermore, the distributional impact of externalities on the

health of the population should be discussed (i.e. discuss the possible equity considerations related to vaccination).

2. Intervention outcome and valuation technique

There are different methods of assigning values to intervention outcomes (monetary, natural units and Quality of life). We propose guidelines for the choice of valuation technique, outcome measure and type of economic analysis. Here, we do not use theoretical foundation but rather empirical evidence and the possible implications the choice of outcome measure can have on resource allocation decisions as our primary basis for evaluation.

- **QALYs estimated from Multi-Attribute Utility Scale (MAUS) should be considered the preferred type of analysis. CV (WTP) should be considered as an additional type of measure to understand the value and relative importance of the different non-health attributes of vaccination.**
  - ***Practicality***: Concurrent with the literature (Table 1.2 and Table 1.5) we found CV and HUI2 to be practical, interviews were conducted rapidly and completion rates were 100%. On the other hand, we encountered a number of difficulties with the SG. First, we had difficulty getting ethical approval. Ethics committees were reluctant to approve the SG questionnaire, as they were worried that presenting to parents of very young children scenarios in which their child could die from vaccination could adversely affect vaccine coverage rates. Second, the SG demanded more explanation and parents were uncomfortable/reluctant to accept risk of death for their children for treatment.
  - ***Content Validity***: It has been argued that, contrary to HR-QoL techniques, CV can capture non-health benefits as it imposes no restrictions on which

dimensions of a programme people are allowed to express a value for (Olsen *et al.*, 2001; Bala *et al.*, 1998; O'Brien and Viramontes, 1994; O'Brien and Gafni, 1996). This was tested in Chapter 4. We found that CV can measure *insurance type benefits* (WTP was greater for varicella vaccination than varicella treatment) and the added benefit of preventing parental *work loss* (controlling for other factors WTP was greater for parents who must take time off work when their child is sick). However, their was no evidence that *caring* was an attribute of vaccination, perhaps due to lack of power to measure very small differences in WTP. These non-health attributes represented 20% of the overall WTP for vaccination (i.e. 80% of the overall value were direct health benefits). On the other hand, consistent with general belief, SG and HUI2 did not capture non-health attributes.

- ***Empirical Validity:*** In the literature, hypothetical WTP (using CV) has been demonstrated to be greater than observed WTP (NOAA, 1993). Furthermore, there is, little empirical evidence concerning the *criterion validity* of SG and HUI2 (or other MAUS). On the other hand all three valuation techniques have demonstrated *construct validity* and *convergent validity (*see Table 1.2 and 1.5*)*. In Chapter 4, we demonstrate *construct validity* and *convergent validity* for HUI2 and CV. However, we found discrepancy between the QALY-weight elicited from HUI2-CV (HUI2 within the CV questionnaire in which the chickenpox lasted 1 week) and the SG questionnaire (in which the health state was described as lasting 15 years). SG produced a QALY weight of 56%, which seems unrealistic for varicella and is significantly lower than the HUI2 estimate (76%). We believe this highlights the difficulty of using SG for acute diseases as the risk of death individuals must trade-off in such circumstances are too small for them to

comprehend. Furthermore, this raises issues regarding the theoretical basis of QALYs. That is, whether the proportional trade-off assumption holds. It should be pointed out that chained methods were not used in Chapter 4 although they have previously been used to address the problem of assessing QALYs for temporary health states within the SG framework (Jansen et al., 1998). To our knowledge none have been used for health states that are as short and as mild as chickenpox. Furthermore, for durations as short as varicella, chaining will be difficult (e.g. use of many anchor levels) and the opportunity of including bias will be large. Nevertheless, in future work chained procedures should be considered as an alternative to the method chosen here and may prove to produce greater empirical validity.

- ***Sensitivity***: As mentioned above, SG could not capture small changes in Quality of Life (i.e. low morbidity or very acute disease) because risks of death that would rationally be taken are too small for individuals to comprehend. Some evidence suggests that CV can be oversensitive to small changes in well being (Clarke, 2002; Seip and Strand, 1992; Duffield and Patterson, 1991) or that it is limited by ability to pay. In Chapter 4, we show that, WTP is less sensitive to large increases in severity of disease than QALYs (based on HUI2). The fact that WTP is capped by ability to pay seems to explain results showing that WTP increases as QALYs increase but at a decreasing rate. This has been previously observed by Bala *et al.* (1998) and has produced concern about using the welfarist framework as a basis for the allocation of health care resources (Weinstein and Manning, 1997). If we assume QALYs adequately measure disease severity, our results suggest that using WTP as the outcome measure may bias resource allocation towards less severe diseases, which may, as illustrated in

Chapters 4 and 5, lead to reduction in overall quality of life thus justifying extra-welfarists' concerns.

- ***Conclusion***: Of the valuation techniques investigated, the CV and HUI2 are best suited for the economic evaluation of vaccination programmes. The advantage of MAUS, compared to SG and TTO, is its practicality and its capacity to measure small changes in well being (see Chapter 1 and Chapter 4). More work is however required to assess whether SG and TTO are indeed incapable of valuing short and mild health states such as varicella. Although, CV possesses the same advantages as HUI2 (or other MAUS) our results raise concerns about its capacity to produce resource allocation decisions that will improve the overall health of a population. On the other hand, CV can be useful to better understand the non-health attributes related to vaccination and their relative importance compared to health gains. Hence, we prefer MAUS as valuation technique and thus QALY as outcome measure and Cost-Utility as type of analysis. We however believe CV (WTP) could be considered as an additional type of measure to understand the value and relative importance of the different non-health attributes of vaccination.

3. **Study Design**

- **The time span must be long enough to capture all relevant positive and negative effects.** The introduction of routine infant mass vaccination typically produces dynamical effect, which are composed of three phases (see Chapter 3 for description): 1) Honeymoon period, 2) Post-honeymoon epidemic, and 3) Post-vaccination endemic equilibrium. Furthermore, vaccination may produce external effects. In Chapter 3, we show that varicella vaccination can produce a short to medium term increase in zoster. Analyses should capture all of these

effects. To assure this, as Beutels *et al.* (2002) suggest, the appropriate time span of analysis should be determined during the analysis and not prior.

- **Both discounted and non-discounted values should be presented.** Vaccination is a preventive intervention thus costs of the programme are incurred at the moment of vaccination while benefits can occur in the short to long term. Hence, the choice of discount rate can greatly influence results (has a greater impact on results than curative interventions). This is illustrated in Chapter 5 where varicella vaccination is cost-effective when discounting is very low because the long-term benefits on zoster become significant. Another example where discounting will have an impact is with the Human Papillomavirus (HPV) vaccine. The vaccine will most probably be given to pre-adolescents to prevent cervical cancer 20 to 30 years later. In cases like these, where benefits occur in the medium to long term, higher discount rates bias against preventive measures. It should however be noted that a zero discount rate for health effects could lead to undesirable implications, such as infinite benefits arising from successful eradication programs (Edmunds et al., 1999; Beutels et al., 2002). As recommended by the US panel on cost-effectiveness we believe that that costs and benefits should be discounted at the same rate (Weinsten *et al.*, 1996) and that discounting should be subject to thorough sensitivity analysis (Beutels *et al.*, 2002).

4. **Sensitivity Analysis**

- **Multivariate and univariate sensitivity analysis should be performed in addition to an exploration of the impact of model/methodological choices.** Because of the complex nature of infectious disease control, economic analysis of vaccination programmes is based on numerous uncertain parameter values

and model and methodological assumptions. Because of this, ideally a probabilistic multivariate sensitivity analysis (uncertainty analysis) should be performed. However, this should be extended to account for methodological uncertainties as well as parameter uncertainties. In Chapter 5 we show that model and methodological assumptions can have greater impact on results than parameter estimates. More particularly, we illustrate that the economic analysis can produce opposite conclusions depending on the choice of 1) analytic technique, 2) model (including or not herd-immunity and zoster) and 3) discount rate. Hence, it is essential that sensitivity analysis of model and methodological assumptions be performed in addition to parameter values.

Table 6.1. Guidelines for the Economic Evaluation of Vaccination programmes (adapted from Beutels *et al.*, 2002) [&]

1. Model Structure

- ☐ The mathematical model should be:
  - Static, if vaccination is unlikely to change the rate of infection in susceptibles (force of infection) or as an estimate of the worst-case scenario when herd-immunity externalities cannot produce negative effects.
  - Dynamic, if vaccination is likely to change the rate of infection in susceptibles (force of infection)
- ☐ Externalities related to vaccination should be included in the model.
  - If externalities are not included, their likely impact should be discussed.
  - The possible equity implications should also be discussed.

2. Outcome and Valuation technique

- ☐ QALYs estimated from Multi-Attribute Utility Scales (MAUS) should be considered the preferred outcome measure.
  - WTP (measured from CV) should be considered as an additional type of measure to understand the value and relative importance of the different non-health attributes of vaccination.
  - If life-years gained is used, the likely impact of doing so should be discussed.

3. Study Design

- ☐ **Time Span:** The time span must be long enough to capture all relevant positive and negative effects.
- ☐ **Discounting:** Both discounted and non-discounted values should be presented.

4. Sensitivity analysis

- ☐ Multivariate and Univariate sensitivity analysis should be performed in addition to an exploration of the impact of model/methodological choice.

& Here, we discuss the methodological components of economic evaluation that have been covered in the thesis.

The guidelines presented above are meant to add to the previous recommendations made by Beutels *et al.* (2002) and to highlight important methodological components that must be considered when performing or judging the merit of economic analysis of vaccination programmes. Analysts, who ignore these methodological issues because of complexity, risk producing erroneous conclusions, which can have important detrimental public health consequences and thus adversely affect the credibility of economic analysis and modelling as decision making tools.

6.3 FUTURE DIRECTIONS

Any thesis is necessarily limited in scope. In this final section highlight themes that the thesis has touched upon that may warrant further research.

6.3.1 EFFECTIVENESS AND COST-EFFECTIVENESS OF VARICELLA VACCINATION

As shown in the thesis the effectiveness and cost-effectiveness of varicella vaccination is dependent on the impact of vaccination on zoster. Hence, more work is needed to understand the relationship between varicella and zoster. More precisely, studies are needed to confirm whether exposure to varicella does protect against zoster. Currently, a large clinical trial is underway to determine whether varicella vaccination can protect against zoster through boosting cell-mediated immunity to VZV (Oxman, 1995). If vaccination prevents zoster, then it is likely that exposure to the wild virus would perform a similar function. Furthermore, active surveillance is underway in the US (Seward *et al.*, 2002b), which should demonstrate within the next few years whether varicella vaccination produces an increase in zoster cases. Studies should also be aimed at determining the duration of protection following exposure to varicella to better predict the magnitude and duration of the increase in zoster cases.

6.3.2 METHODOLOGICAL ISSUES RELATED TO THE ECONOMIC EVALUATION OF VACCINATION

There are three main topics that have not been explored, which are important issues in the evaluation of the benefit of vaccination programmes. The first is the impact of vaccine side-effects and risk of disease on the demand and uptake of vaccines. It has been shown that the decision to vaccinate (or the WTP for a vaccine) is influenced by the probability of side effects, the severity of disease and perceived risk of disease (Hall *et al.*, 2002; Sansom, 2001; Geoffard &

Philipson, 1996; Geoffard & Philipson, 1997; Philipson, 2000). In the thesis, we could not, because of ethical considerations, measure the impact of the risk of side-effects on vaccine uptake and WTP for vaccination. Furthermore, it was beyond the scope of the thesis to evaluate whether perceived risk of disease could influence the demand for vaccine. However, we show historical vaccine coverage data from the UK, which clearly shows that vaccine coverage is relatively insensitive to prevalence of disease (see Figure 4.5). Clearly, further research is needed in this area to understand what really influences drops and increases in vaccine coverage and how we can incorporate this into the social welfare function. The second issue that was not investigated is the methodological challenges related to eliciting the Health State of children. This is an important topic for vaccination as many vaccine programmes involve children. In his recent paper, Petrou (2003) identifies and discusses a number of methodological issues, which should be further investigated. These are, 1) who should be the respondent of questionnaires (the child, parent, physician or sample of the population), 2) what health dimensions should be valued, 3) what is the psychometric integrity of alternative measurement approaches, 4) what are the potential biases in the description and valuation process. To ensure the appropriate distribution of health care resources more research is clearly needed in this area. The third issue that has not been explored is the impact of externalities resulting from mass vaccination on the distribution of health in the population. As shown in Chapter 3, vaccinating a proportion of the population against an infectious disease affects the risk of disease in those in the population that are not immunised. Future research should explore these equity issues.

The research produced in the thesis has raised many questions on which future work can be performed. First, we show that CV can capture different non-health attributes of vaccination. Future work can be directed towards estimating the relative importance of non-health attributes for various vaccines (e.g. pneumoccocal and meningococcal vaccines). This to better understand the relationship between the severity of the disease being prevented and non-health benefits such as altruism and insurance type benefits. In the thesis we also show evidence that the relationship between WTP and QALYs is non-linear and that this may be due to the fact that WTP is limited by ability to pay. Future research should be aimed at eliciting WTP and QALYs for diseases with varying severity and duration to test this relationship and to investigate the potential impact of this on resource allocation. Finally, we show that for varicella vaccination, the economic desirability is most sensitive to model and methodological assumptions. More research is needed to understand the impact of model and methodological assumptions (e.g. choice of elicitation technique, discounting and time frame of analysis) on results of economic analyses of vaccination, and other health care, programmes.

6.4 GENERAL CONCLUSION

The thesis has two objectives. The first aim is to evaluate the effectiveness and "cost-effectiveness" of routine childhood varicella vaccination in the UK. The findings presented here have major public health implications. We show, using a dynamic model parameterised from population data, that varicella vaccination is likely to provoke an increase in zoster cases, which would produce an overall increase in morbidity. These results strongly support that, before introducing varicella vaccination public health take careful consideration of the potential detrimental external effect of vaccination on zoster and support the need of sensitive zoster surveillance where immunisation is underway. These results were requested and discussed at various meetings meant to establish recommendations for the routine administration of varicella vaccination: the Canadian National Varicella Consensus Conference (Canada, 1999), the Joint Committee on Vaccination and Immunisation (England and Wales, 2002) and, the Advisory Committee on Immunization Practice (United-States, 2003). This demonstrates the willingness of public health officials to use dynamic mathematical modelling (which take into account externalities such as herd-immunity) and cost-effectiveness studies as an aid in policy decision making.

The second aim of the thesis is to address the major methodological issues related to the economic evaluation of vaccination programs. We compared results from a dynamic model with those of a static model to illustrate the impact of including herd-immunity and to help provide guidance on which model should be used when assessing the impact of vaccination. Secondly, we assessed the average willingness to pay for varicella vaccination and the QALY lost due to chickenpox using various elicitation techniques. We then identified important attributes of vaccination and what elicitation techniques can capture these components. Results were

compared to investigate what valuation techniques should be used in the economic evaluation of vaccine programmes. Thirdly, we assessed the sensitivity of economic analysis to the choice of model, methodological assumptions and parameter estimates. In order to improve/maintain the credibility and usefulness of economic evaluation for decision-makers, it is important that further research investigates the impact of methods on results of economic analysis and that specific guidelines such as those presented here be followed.

REFERENCES

1. Altonji JG, Hayashi F, Kotlikoff LJ. Parental altruism and inter vivos transfers: theory and evidence. J Polit Econ 1997; 105:1,121-66.
2. American Academy of Pediatrics, Committee on Infectious Disease. Varicella Vaccine Update. Pediatrics 2000; 105:136-141.
3. Anderson RM, May RM (1991). Infectious Diseases of Humans: Dynamics and Control. Oxford: Oxford University Press, 757 pp.
4. Andreoni J. Impure altruism and donation to public goods: A theory of warming glow giving. Economic Journal 1990; 10:464-477.
5. Appel LJ, Steinberg EP, Powe NR, Anderson GF, Dwyer SA, Faden RR. Risk reduction from low osmolality contrast media. What do patients think it is worth? Med Care 1990; 28:324-37.
6. Arana J, Leon CJ. Willingness to pay for health risk reduction in the context of altruism. Health Economics 2002;11:623-35.
7. Arbeter AM, Starr SE, Plotkin SA. Varicella vaccine studies in healthy children and adults. Pediatrics 1986; 78(4 Pt 2):748-56.
8. Arbeter AM, Starr SE, Preblud SR *et al.* Varicella vaccine trials in healthy children. A summary of comparative and follow-up studies. Am J Dis Child 1984; 138:434-8.
9. Arbeter AM, Starr SE, Weibel RE, Plotkin SA. Live attenuated varicella vaccine: immunization of healthy children with the OKA strain. J Pediatr 1982; 100:886-93.
10. Arvin AM, Celine MK, Wittek AE. Immunologic evidence of reinfection with varicella zoster virus. J Infect Dis 1983; 148:200-5.

11. Asano Y, Suga S, Yoshikawa T, et al. Experience and Reason: Twenty-year follow-up of protective immunity of the Oka strain live varicella vaccine. Pediatrics 1994; 94:524-526.

12. Ashby J, O'Hanlon M, Buxton MJ. The time trade-off technique: how do the valuations of breast cancer patients compare to those of other groups? Qual Life Res 1994; 3:257-65.

13. Atkinson WL, Orenstein WA, Krugman S. The resurgence of measles in the United States, 1989-1990. Annu Rev Med 1992; 43:451-63

14. Babad HR, Nokes DJ, Gay NJ *et al.* Predicting the impact of measles vaccination in England and Wales: model validation and analysis of policy options. Epidemiol Infect. 1995;114:319-44.

15. Bakker C, Rutten M, van Doorslaer E, Bennett K, van der Linden S. Feasibility of utility assessment by rating scale and standard gamble in patients with ankylosing spondylitis or fibromyalgia. J Rheumatol 1994; 21:269-74.

16. Bala MV, Mauskopf JA, Wood LL. Willingness to pay as a measure of health benefits. Pharmacoeconomics 1999; 15:9-18.

17. Bala MV, Wood LL, Zarkin GA, Norton EC, Gafni A, O'Brien B. Valuing outcomes in health care: a comparison of willingness to pay and quality-adjusted life-years. Clin Epidemiol 1998; 51: 667-76.

18. Bala MV, Wood LL, Zarkin GA, Norton EC, Gafni A, O'Brien BJ. Are health states "timeless"? The case of the standard gamble method. J Clin Epidemiol 1999; 52:1047-53.

19. Bala MV, Zarkin GA. Are QALYs an appropriate measure for valuing morbidity in acute diseases? Health Econ 2000; 9:177-80.

20. Banz K, Wagenpfeil, Neiss A, Goertz A, Staginnus U, Vollmar J, Wutzler P. The cost-effectiveness of routine childhood varicella vaccination in Germany. Vaccine 2003; 21: 1256-67.

21. Barr RD, Furlong W, Dawson S, Whitton AC, Strautmanis I, Pai M, Feeny D, Torrance GW. An assessment of global health status in survivors of acute lymphoblastic leukemia in childhood. Am J Pediatr Hematol Oncol 1993;15:284-90.

22. Becker Gs. Human Capital. New York: Columbia University Press. 1964.

23. Beneson AS. Control of Communicable Disease Manual. American Public Health Association 1995. Washington. 575 pp.

24. Bergson A. A reformulation of certain aspects of welfare economics. Q J Econ 1938; 52: 310-334.

25. Bernstein HH, Rothstein EP et al. Clinical Survey of Natural Varicella Compared With Breakthrough Varicella After Immunization With Live Attenuated Oka/Merck Varicella Vaccine. Pediatrics 1993; 92:833-837.

26. Beutels P, Clara R, Tormans G, Van Doorslaer E, Van Damme P. Costs and Benefits of routine varicella vaccination in Geman children. JID 1996; 174(Suppl 3):S335-41.

27. Beutels P, Edmunds WJ, Antonanzas F, de Wit GA, Evans D, Feilden R, Fendrick AM, Ginsberg GM, Glick HA, Mast E, Pechevis M, Van Doorslaer EK, van Hout BA. Economic evaluation of vaccination programmes: a consensus statement focusing on viral hepatitis. Pharmacoeconomics 2002; 20:1-7.

28. Birch S, Gafni A, O'Brien B. Willingness to pay and the valuation of programmes for the prevention and control of influenza. Pharmacoeconomics 1999;16 Suppl 1:55-61.

29. Black S, Shinefield H, Ray P, Lewis E, Hansen J, Schwalbe J, Coplan P, Sharrar R, Guess H. 1999. Postmarketing evaluation of the safety and effectiveness of varicella vaccine. Pediatr Infect Dis J 18:1041-6.

30. Bleichrodt H, Johannesson M. The validity of QALYs: an experimental test of constant proportional tradeoff and utility independence. Med Decis Making. 1997; 17:21-32.

31. Bleichrodt H, Quiggin J. Life-cycle preferences over consumption and health: when is cost-effectiveness analysis equivalent to cost-benefit analysis? J Health Econ 1999; 18:681-708.

32. Blomqvist A. QALYs, standard gambles, and the expected budget constraint. J Health Econ 2002; 21:181-95.

33. Bolker BM, Grenfell BT, Chaos and biological complexity in measles dynamics. Proc R Soc Lond B Biol Sci 1993 Jan 22; 251:75-81.

34. Bond L, Nolan T, Pattison P, Carlin J. Vaccine preventable diseases and immunisations: a qualitative study of mothers' perceptions of severity, susceptibility, benefits and barriers. Aust N Z J Public Health 1998; 22:441-6.

35. Boyle KJ, Bishop RC, Welsh MP. Starting point bias in contingent valuation bidding games. Land economics 1985; 61:188-194.

36. Bramley JC, Jones IG. Epidemiology of chickenpox in Scotland: 1981 to 1998. Commun Dis Public Health 2000;3:282-7.

37. Brazier J, Deverill M, Green C, Harper R, Booth A. A review of the use of health status measures in economic evaluation. Health Technol Assess 1999; 3:i-iv, 1-164.

38. Brazier J, Deverill M. A checklist for judging preference-based measures of health related quality of life: learning from psychometrics. Health Econ 1999; 8:41-51.

39. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. J Health Econ 2002; 21: 271-292.

40. Brisson M, Edmunds WJ, Gay NJ, Law B, De Serres G. Modelling the impact of immunisation on the epidemiology of varicella zoster virus. Epidemiol Infect 2000; 125:651-669.

41. Brisson M, Edmunds WJ, Law B, Gay NJ, Walld R, Brownell M, Roos L, De Serres G. Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. Epidemiol Infect 2001; 127:305-14.

42. Brisson M, Edmunds WJ. The cost-effectiveness of varicella zoster virus (VZV) vaccination in Canada. Vaccine 2002; 20: 1113-1125.

43. British Medical Association and the Royal Pharmaceutical Society of Great Britain. British National Formulary: BNF-37. London, British Medical Association and the Royal Pharmaceutical Society of Great Britain, 1999:279-80.

44. Brookshire DS, Randall A, Stoll JR. Valuing increments and decrements of natural resource servoice flows. American Journal of Agricultural Economics 1980; 62:478-488.

45. Brouwer W, Koopmanschap M. On the economic foundations of CEA: Ladies and gentlemen, take your positions! Journal of Health Economics 2000;19:439-59.

46. Busschbach JJ, Horikx PE, van den Bosch JM, Brutel de la Riviere A, de Charro FT. Measuring the quality of life before and after bilateral lung transplantation in patients with cystic fibrosis. Chest 1994; 105:911-7.

47. Cameron TA, Quiggen J. Esimation using conjoint valuation data from 'Dichotomous choice with follow-up' questionnaire. J Environ Econ Manag 1994; 27: 218-234.

48. Canadian Coordinating Office for Health Technology Assessment. Guidelines for economic evaluation of pharmaceuticals: Canada. 2nded. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 1997.

49. Caro Research Inc. Varicella Vaccination: Economic Evaluation of Possible Canadian Programs. Final Report. Ottawa (ON): Health Canada; 1999, Nov.

50. Carson RT. Construct markets. In Braden JB, Kolstad. Measuring the demand for environmental quality. Amsterdam, Elsevier/North Holland, 1991.

51. Chen RT, Weierbach R, Bisoff Z et al. A 'post-honeymoon period' measles outbreak in Muyinga sector, Burundi. Int J Epidemiol 1994; 23:185-93.

52. Cher DJ, Miyamoto J, Lenert LA. Incorporating risk attitude into Markov-process Decision Models. Medical Decision Making 1997;17:340-350.

53. Choo PW, Donahue JG, Manson JE, Platt R. The Epidemiology of varicella and its complications. J Infect Dis 1995; 172:706-12.

54. Clarke AE, Goldstein MK, Michelson D, Garber AM, Lenert LA. The effect of assessment method and respondent population on utilities elicited for Gaucher disease. Qual Life Res 1997; 6:169-84.

55. Clarke PM. Testing the convergent validity of the contingent valuation and travel cost methods in valuing the benefits of health care. Health Econ 2002; 11:117-27.

56. Clements DA, Armstrong CB, Ursano AM *et al.* Over five-year follow-up of Oka/Merck varicella vaccine recipients in 465 infants and adolescents. Pediatr Infect Dis J 1995; 14:874-9.

57. Clements DA, Zaref JI, Bland CL, Walter EB, Coplan PM. Partial uptake of varicella vaccine and the epidemiological effect on varicella disease in 11 day-care centers in North Carolina. Arch Pediatr Adolesc Med 2001; 155:455-61.

58. Cochi SL, Preblud SR, Orenstein WA. Perspectives on the relative resurgence of mumps in the United-States. Am J Dis Child 1988; 142:499-507.

59. Committee on Infectious Diseases. Live attenuated varicella vaccine. Pediatrics 1995; 95:791-796.

60. Commonwealth of Australia. Guidelines for pharmaceutical industry and preperation of submissions to the Pharmaceutical Benefits Advisory Committee: including economic analyses. Canberra: Department of Health and Community Services, 1995.

61. Coplan P, Black S, Rojas C, Shinefield H, Ray P, Lewis E, Guess H. Incidence and hospitalisation rates of varicella and herpes zoster before varicella vaccine introduction: a baseline assessment of the shifting epidemiology of varicella disease. Pediatr Infect Dis J 2001; 20:641-5.

62. Coudeville L, Paree F, Lebrun T, Sailly JC. The value of varicella vaccination in healthy children: cost-benefit analysis of the situation in France. Vaccine 1999; 17:142-151

63. Culyer A. The normative economics of health care finance and provision. In: McGuire A, Fenn A, Mayhew K. Providing health care, Oxford, OUP; 1990.

64. Dalmau-Matarrodona E. Alternative approaches to obtain optimal bid values in contingent valuation studies and to model protest zeros. Estimating the determinants of individuals' willingness to pay for home care services in day case surgery. Health Econ 2001; 10:101-18.

65. Davies L, Cossins L, Bowsher D, Drummond M. The cost of treatment for post-herpetic neuralgia in the UK. PharmacoEconomics 1994; 6:142-8.

66. de Moragas JM, Kierland RR. The outcome of patients with herpes zoster. AMA Arch of Derm 1957; 7: 193-6.

67. de Vries SO, Kuipers WD, Hunink MG. Intermittent claudication: symptom severity versus health values. J Vasc Surg 1998; 27:422-30.

68. De Wals P, Blackburn M, Guay M, Bravo G, Blanchette D, Douville-Fradet. Burden of chickenpox on families: A study in Quebec. Can J Infect Dis 2001; 12: 27-32.

69. De Wit GA, Busschbach JJ, De Charro FT. Sensitivity and perspective in the valuation of health status: whose values count? Health Econ 2000; 9:109-26.

70. Deguen S, Chau NP, Flahaut A. Epidemiology of Chickenpox in France (1991-1995). J Epidemiol Community Health 1998; 52(Suppl 1):46S-49S.

71. Dennett P, Smith C. Parents attitudinal and social influences on childhood vaccination. Health Educ Res. 1992 Sep;7:341-8.

72. Departement of Education and Science. Statistical bulletin, 1982-91. London: Government Statistical Service, 1992.

73. Department of Health Statistics Division. Prescription Cost Analysis 1998: England. London, HMSO, 1999: 165

74. Department of Health. Policy Appraisal and Health. London: Department of Health, 1995.

75. Diamond PA, Hausman JA, Leonard GK, Denning MA. Does Contingent Valuation measure preferences? Experimental Evidence. Paper presented at the Cambridge Economics, Inc. Symposium, Contingent Valuation: A critical Assessment; Washington D.C., April 1992.

76. Dickie M, Fisher A, Gerking S. Market transactions and hypothetical demand data: A comparative study. J Am Stat Ass 1987; 82: 69-75.

77. Diener A, O'Brien B, Gafni A. Health care contingent valuation studies: a review and classification of the literature. Health Econ 1998; 7:313-26.

78. Dolan P, Edlin R. Is it really possible to build a bridge between cost-benefit analysis and cost-effectiveness analysis? J Health Econ 2002; 21:827-43.

79. Dolan P, Gudex C, Kind P, Williams A. The time trade-off method: results from a general population study. Health Econ 1996; 5:141-54.

80. Dolan P, Gudex C. Time preference, duration and health state valuations. Health Econ 1995; 4:289-99.

81. Dolan P, Stalmeier P. The validity of time-trade off values in calculating QALYs: constant proportional time trade-off versus the proportional heuristic. J Health Econ 2003; 22:445-458.

82. Dolan P. Output measures and valuation of health. In: Drummond MF, McGuire A. Economic evaluation in health care: Merging theory with practice. Oxford, Oxford University Press; 2001.

83. Dolan P. The measurment of health-related quality of life for use in resource allocation decisions in health care. In: Culyer AJ, Newhouse JP. Handbook of Health Economics, Volume I. Elsevier Science B.V.; 2000.

84. Domingo JD, Ridao M, Latour J, Ballester A, Morant A. A cost benefit analysis of routine varicella vaccination in Spain. Vaccine 1999; 17:1306-1311.

85. Donaldson C, Birch S, Gafni A. The distribution problem in economic evaluation: income and the valuation of costs and consequences of health care programmes. Health Econ 2002; 11:55-70.

86. Donaldson C, Farrar S, Mapp T, Walker A, Macphee S. Assessing community values in health care: is the 'willingness to pay' method feasible? Health Care Anal 1997;5:7-29.

87. Donaldson C, Shackley P, Abdalla M, Miedzybrodzka Z. Willingness to pay for antenatal carrier screening for cystic fibrosis. Health Econ 1995; 4:439-52.

88. Donaldson C, Shackley P. Does "process utility" exist? A case study of willingness to pay for laparoscopic cholecystectomy. Soc Sci Med. 1997; 44:699-707.

89. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. BMJ 1996; 313: 275-83.

90. Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Methods for the evaluation of health care programmes New York: Oxford University Press; 1997.

91. Duffield JW, Patterson DA. Field testing existence values: an instream flow trust fund for Montana rivers. Paper presented at the annual meeting of the American Economics Association, New Orleans, 1991.

92. Dworkin RH, Boon RJ, Griffin DRG, Phung D. Postherpetic neuralgia: impact of famciclovir, age, rash severity, and acute pain in herpes zoster patients. J Infect Dis 1998; 178(Suppl 1): S276-80.

93. Dworkin RH, Portenoy RK. Pain and its presence in herpes zoster. Pain 1996; 67: 241-51

94. Eastaugh SR. Willingness to pay in treatment of bleeding disorders. Int J Technol Assess Health Care 2000; 16:706-10.

95. Edmunds WJ, Brisson M, Rose JD The epidemiology of herpes zoster and potential cost-effectiveness of vaccination in England and Wales. Vaccine 2001;19:3076-3090.

96. Edmunds WJ, Gay NJ, Kretzschmar M, Pebody RG, Wachmann H. The pre-vaccination epidemiology of measles, mumps and rubella in Europe: implications from modelling studies. Epidemiol Infect. 2000; 125:635-50.

97. Edmunds WJ, Medley GF, Nokes DJ. Evaluating the cost-effectiveness of vaccination programmes: a dynamic perspective. Stat Med 1999; 18:3263-82.

98. Edmunds WJ, O'Callaghan CJ, Nokes DJ. Who mixes with whom? A method to determine the contact patterns of adults that may lead to the spread of airborne infections. Proc R Soc Lond B Biol Sci 1997; 264:949-57.

99. Eiser C, Morse R. Quality-of-life measures in chronic diseases of childhood. HTA publications 2001;

100. Elixhauser A, Halpern M, Schmier J, Luce BR. Health care CBA and CEA from 1991 to 1996: an updated bibliography. Med Care 1998;36(5 Suppl):MS1-9, MS18-147.

101. Ellis ME, Neal KR, Webb AK. Is smoking a risk factor for pneumonia in adults with chickenpox? BMJ 1987; 294:1002.

102. Ennett ST, DeVellis BM, Earp JA, Kredich D, Warren RW, Wilhelm CL. Disease experience and psychosocial adjustments in children with juvenile rheumatoid arthritis: children's versus mother's reports. J Pediatr Psychol 1991;16:557-68.

103. Fairley CK, Miller E. Varicella-Zoster Virus Epidemiology - A Changing Scene? J Infect Dis 1996; 174(Suppl 3):S314-9.

104. Farrington CP. Modeling forces of infection for measles, mumps and rubella. Stat Med 1990; 9:953-67.

105. Fedson DS, Wadja A, Nicol JP, Roos LL. Disparity between influenza vaccination rates and risks for influenza-associated hospital discharge and death in Manitoba in 1982-1983. Ann Intern Med 1992; 116: 550-5.

106. Fedson DS. Pneumococcal vaccination in the United States and 20 other developed countries, 1981-96. Clin Infect Dis 1998; 26: 1117-23.

107. Ferguson NM, Anderson RM, Garnett GP. Mass Vaccination to control chickenpox: The influence of zoster. Proc Natl Acad Sci USA. 1996; 93:7231-7235.

108. Finger R, Hughes JP, Meade BJ, *et al.* Age-specific incidence of chickenpox. Public Health Rep 1994; 109:750-755.

109. Fleming DM, Norbury CA, Crombie DL. Annual and seasonal variation in the incidence of common diseases. Twenty-three years' experience of the weekly Returns service of the Royal College of General Practitioners. Occasional paper 53. London: Royal College of General Practitioners, 1991.

110. Fleming DM. Weekly returns service of the Royal College of General Practitioners. Communicable Disease and Public Health 1999; 2:96-100.

111. Fornaro P, Gandini F, Marin M, Pedrazzi C et al. Epidemiology and cost analysis of varicella in Italy: results of a sentinel study in the pediatric practice. Pediatr Infect Dis J 1999; 18:414-9.

112. Francis B, Green M, Payne C. The GLIM System Release 4 manual, 1994 reprint, Clarendon Press Oxford.

113. Friedman WJ. Children's representaion of the pattern of daily activities. Child Dev 1990; 61:1399-412.

114. Froberg DG, Kane RL. Methodology for measuring health-state preferences--II: Scaling methods. J Clin Epidemiol 1989; 42:459-71.

115. Froberg DG, Kane RL. Methodology for measuring health-state preferences--I: Measurement strategies. J Clin Epidemiol 1989;42:345-54.

116. Froberg DG, Kane RL. Methodology for measuring health-state preferences--IV: Progress and a research agenda. J Clin Epidemiol 1989; 2:675-85.

117. Froberg DG, Kane RL. Methodology for measuring health-state preferences--III: Population and context effects. J Clin Epidemiol 1989; 2:585-92.

118. Fryback DG, Dasbach EJ, Klein R, Klein BE, Dorn N, Peterson K, Martin PA. The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors. Med Decis Making 1993; 13:89-102.

119. Gafni A. The standard gamble method: what is being measured and how it is interpreted. Health Serv Res 1994; 29:207-24.

120. Gage BF, Cardinalli AB, Owens DK. The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. Arch Intern Med 1996; 156:1829-36.

121. Galil K, Choo PW, Donahue JG, Platt R. The sequelae of herpes zoster. Arch Intern Med 1997; 157: 1209-13.

122. Garber AM, Phelps CE. Economic foundations of cost-effectiveness analysis. J Health Econ 1997;16:1-31.

123. Garnett GP, Ferguson NM. Predicting the effect of varicella vaccine on subsequent cases of zoster and varicella. Rev Med Virol 1996; 6:151-161.

124. Garnett GP, Grenfell BT. The epidemiology of varicella-zoster virus infections: a mathematical model. Epidemiol Infect 1992; 108:495-511.

125. Garnett GP, Grenfell BT. The epidemiology of varicella-zoster virus infections: the influence of varicella on the prevalence of herpes-zoster. Epidemiol Infect 1992; 108:513-528.

126. Gershon AA, LaRussa P, Steinberg S, Mervish N, Lo SH, Meier P. The protective effect of immunologic boosting against zoster: an analysis in leukemic children who were vaccinated against chickenpox. J Infect Dis 1996; 173: 450-3.

127. Gershon AA, Takahashi M , White CJ. Varicella vaccine, in Vaccines, 3rd Edition, Ed Plotkin SA and Orenstein WA. W.B. Saunders Co. 1999, 475-507.

128. Getsios BA, Caro JJ, Caro G, De Wals P, Law BJ, Robert Y, Lance JMR. Instituting a routine varicella vaccination program in Canada: an economic evaluation. Ped Infect Dis J 2002; 21: 542-.

129. Gold MR, Siegel JE, Russell LB, Weinstein MC, editors. Cost-effectiveness in health and medicine New York: Oxford University Press; 1996.

130. Goodwin DA, Boggs SR, Graham-Pole J. Development and validation of the Pediatric Oncology Quality of Life Scale. Psychol Assess 1994; 6:321-8.

131. Graham P, Stevenson J, Flynn D. A new measure of health-related quality of life for children: preliminary findings. Psychol Health 1997; 12:655-65.

132. Gray AM, Fenn P, Weinberg J, Miller E, McGuire A. An economic analysis of varicella vaccination for health care workers. Epidemiol Infect 1997;119:209-20.

133. Green C, Brazier J, Deverill M. Valuing health-related quality of life. A review of health state valuation techniques. Pharmacoeconomics 2000; 17:151-65.

134. Grenfell BT, Anderson RM. The estimation of age related rates of infection from case notifications and serological data. J Hyg Camb 1985; 95:419-36.

135. Gudex C, Dolan P, Kind P, Williams A. Health state valuations from the general public using the visual analogue scale. Qual Life Res 1996; 5:521-31.

136. Guess HA, Broughton DD, Melton LJ, Kurland LT. Chickenpox hospitalisations among residents of Olmsted Country, Minnesota, 1962 through 1981. American Journal of Diseases in Children 1984; 138:1055-557.

137. Guess HA, Broughton DD, Melton LJ, Kurland LT. Population-based studies of varicella complications. Pediatrics 1986; 78(suppl)723-27.

138. Haake DA, Zakowski PC, Haake DL, Bryson YJ. Early treatment with acyclovir for varicella pneumonia in otherwise healthy adults: retrospective controlled study and review. Rev Inf Dis 1990; 12:788-798.

139. Hall J, Kenny P, King M, Louviere J, Viney R, Yeoh A. Using stated preference discrete choice modelling to evaluate the introduction of varicella vaccination. Health Econ 2002;11:457-65.

140. Halloran ME, Cochi SL, Lieu TA, Wharton M, Fehrs L. Theoretical Epidemiologic and Morbidity Effects of Routine Varicella Immunization of Preschool Children in the United States. Am J Epidemiol 1994; 140: 81-104.

141. Halloran ME, Struchiner CJ, Longini IM Jr. Study designs for evaluating different efficacy and effectiveness aspects of vaccines. Am J Epidemiol 1997; 146: 789-803

142. Halloran ME. Concepts of Infectious Disease Epidemiology. In: Rothman KJ, Greenland S. Modern Epidemiology. Lippincott-Raven Publishers, Maple Press; 1998.

143. Health Canada Proceedings of the National Varicella Consensus Conference, Canada Communicable Disease Report 1999; 25(supplement): 1-29.

144. Health Education Authority (1999) Childhood Immunisation Wave 15. Report on the tracking survey October 1991-October 1998.

145. Hicks JR. The foundation of welfare economics. Economic Journal 1939; 49:696-712.

146. Hope-Simpson RE. Postherpetic neuralgia. J R Coll Gen Pract 1975; 25: 571-75.

147. Hope-Simpson RE. The Nature of Herpes Zoster: A Long-term Study and a New Hypothesis. Proc R Soc Med 1965; 58: 9-12.

148. Hornberger JC, Redelmeier DA, Petersen J. Variability among methods to assess patients' well-being and consequent effect on a cost-effectiveness analysis. J Clin Epidemiol 1992; 45:505-12.

149. Huse DM, Meissner HC, Lacey MJ, Oster G. Childhood vaccination against chickenpox: An analysis of benefits and costs. J Pediatr 1994; 124:869-74.

150. Ikada J, Kayami K, Yamamoto Y. Varicella may protect against zoster. Lancet 1973: ii: 1276.

151. Izurieta HS, Strebel PM, Blake PA. Postlicensure effectiveness of varicella vaccine during an outbreak in a child care center. JAMA 1997; 278:1495-9.

152. Jacobs RJ, Moleski RJ, Meyerhoff AS. Valuation of symptomatic hepatitis a in adults: estimates based on time trade-off and willingness-to-pay measurement. Pharmacoeconomics 2002; 20:739-47.

153. Jansen SJ, Stiggelbout AM, Wakker PP, Vliet Vlieland TP, Leer JW, Nooy MA, Kievit J. Patients' utilities for cancer treatments: a study of the chained procedure for the standard gamble and time tradeoff. Med Decis Making 1998;18:391-9.

154. Johannesson M and Weinstein MC. Designing and Conducting Cost-Benefit Analyses. In: Spiker B. Quality of Lige and Pharmaeconomics in Clinical Trials. Lippincott-Raven Publishers, Philadelphia; 1996.

155. Johannesson M, Johansson PO, Kristrom B, Gerdtham UG. Willingness to pay for antihypertensive therapy--further results. J Health Econ 1993; 12:95-108.

156. Johannesson M. A note on the relationship between ex ante and expected willingness to pay for health care. Soc Sci Med 1996a; 42:305-11.

157. Johannesson M. The relationship between cost-effectiveness analysis and cost-benefit analysis. Soc Sci Med 1995; 41:483-9.

158. Johannesson M. Theory and methods of economic evaluation of health care Dordrecht/Boston/London: Kluwer Academic Publishers; 1996b.

159. Johansson PO. Altruism and the value of statistical life: empirical implications. J Health Econ 1994; 13:111-8.

160. Johansson PO. An introduction to modern welfare economics. Cambridge University Press, Cambridge; 1991

161. Johnson C, Rome LP, Stancin T, Kumar ML. Humoral immunity and clinical reinfections following varicella vaccine in healthy children. Pediatrics 1989; 84:418-21.

162. Johnson CE, Stancin T, Fattlar D, Rome LP, Kumar ML. A long-term prospective study of varicella vaccine in healthy children. Pediatrics 1997;100:761-6.

163. Johnson ES, Sullivan SD, Mozaffari E, Langley PC, Bodsworth NJ. A utility assessment of oral and intravenous ganciclovir for the maintenance treatment of AIDS-related cytomegalovirus retinitis. Pharmacoeconomics 1996; 10:623-9.

164. Jones SE, Armstrong CB, Bland C, Walter EB, Clements DA. Varicella prevalaence in day-care centers. Pediatr Infect Dis J 1995; 14:404-5

165. Juniper EF, Thompson AK, Roberts JN. Can the standard gamble and rating scale be used to measure quality of life in rhinoconjunctivitis? Comparison with the RQLQ and SF-36. Allergy 2002; 57:201-6.

166. Kaldor N. Welfare propositions of economic and interpersonal comparisons of utility. Economic Journal 1939; 49:549-52.

167. Kaplan RM, Feeny D, Revicki DA. Methods for assessing relative importance in preference based outcome measures. Qual Life Res 1993; 2:467-75.

168. Kartman B, Stalhammar NO, Johannesson M. Valuation of health changes with the contingent valuation method: a test of scope and question order effects. Health Econ 1996; 5:531-41.

169. Keeney R and Raiffa H. Decisions with multiple objectives: preferences and value tradeoffs. New York, Wiley; 1976.

170. Klose T. The contingent valuation method in health care. Health Policy. 1999; 47:97-123

171. Krabbe PF, Essink-Bot ML, Bonsel GJ. The comparability and reliability of five health-state valuation methods. Soc Sci Med 1997; 45:1641-52.

172. Krause PR, Klinman DM. Efficacy, immunogenicity, safety, and use of live attenuated chickenpox vaccine. J Pediatr 1995; 127:518-525.

173. Krause PR, Klinman DM. Varicella vaccination: evidence for frequent reactivation of the vaccine strain in healthy children. Nat Med 2000; 6:451-4.

174. Krause PR, Straus MD. Herpesvirus vaccines. Development, controversies, and applications. Infect Dis Clin North Am 1999; 13: 61-81.

175. Kuter BJ, Weibel RE, Guess HA *et al.* Oka/Merck varicella vaccine in healthy children: final report of a 2- year efficacy study and 7-year follow-up studies. Vaccine 1991; 9:643-7.

176. Laupacis A, Feeney D, Detsky AS, Tugwell P. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. CMAJ 1992; 146:473-481.

177. Law B, Fitzsimon C, Ford-Jones L, MacDonald N, Dery P, Vaudry W, Mills E, Halperin S, Michaliszyn A, Riviere M. Cost of chickenpox in Canada: part I. Cost of uncomplicated cases. Pediatrics 1999;104:1-6.

178. Law B, Fitzsimon C, Ford-Jones L, McCormick J, Riviere M. Cost of chickenpox in Canada: part II. Cost of complicated cases and total economic impact. The Immunization Monitoring Program-Active (IMPACT). Pediatrics 1999; 104:7-14.

179. Law B, Scheifele D, MacDonald N et al. The immunization monitoring program-active (IMPACT) prospective surveillance of varicella zoster infections among hospitalised Canadian children: 1991-1996. Canada Communicable Disease Report 2000b; 26:125-131.

180. Law BJ, Brownell MD, Walld R, Roos LL. Chickenpox in Manitoba: A population-based assessment using the Manitoba Health Services Commission Database.

Poster presentation at the Canadian National immunization Conference, Partnerships for Health through Immunization. Dec 6-9, 1998, Calgary, Alberta.

181. Lenert LA, Morss S, Goldstein MK, Bergen MR, Faustman WO, Garber AM. Measurement of the validity of utility elicitations performed by computerized interview. Med Care 1997; 35:915-20.

182. Lenert LA, Sturley AE. Acceptability of computerized visual analog scale, time trade-off and standard gamble rating methods in patients and the public. Proc AMIA Symp 2001; 364-8.

183. Levin MJ, Barber D, Goldblatt E *et al.* Use of a live attenuated varicella vaccine to boost varicella-specific immune responses in seropositive people 55 years of age and older: duration of booster effect. J Infect Dis 1998; 178(Suppl 1):S109-S112.

184. Levin MJ, Hayward AR. Prevention of Herpes Zoster. Infect Dis Clin North Am 1996; 10: 657-75.

185. Levin MJ, Murray M, Zerbe GO, White CJ, Hayward AR. Immune response of elderly persons 4 years after receiving a live attenuated varicella vaccine. J infect Dis 1994; 170:522-6.

186. Levine MJ, Ellison MC, Zerbe GO, *et al.* Comparison of a live attenuated and an inactivated varicella vaccine to boost the varicella-specific immune response in seropositive people 55 years of age and older. Vaccine 2000; 18: 2915-20

187. Lieu TA, Black SB, Rieser N, Ray P, Lewis EM, Shinefield HR. The cost of childhood chickenpox: parents' perspective. Pediatr Infect Dis J 1994; 13:173-7.

188. Lieu TA, Cochi SL, Black SB, et al. Cost-effectiveness of a routine varicella vaccination program for US children. JAMA 1994; 271:375-81.

189. Lin F, Hadler JL. Epidemiology of primary varicella and herpes zoster hospitalizations: the pre-varicella vaccine era. J Infect Dis 2000; 181:1897-905.

190. Longworth L, Bryan S. An empirical comparison of EQ-5D and the SF-6D in liver transplant patients. Health Econ 2003;12:1061-7.

191. Lovatt B. The United Kingdom guidelines for the economic evaluation of medicines. Med Care 1996; 34(Suppl):DS179-81.

192. Marin A, Psacharopoulos G. The reward for risk in the labor market: evidence from the United Kingdom and reconciliation with other studies. J Polit Econ 1982; 90: 827-53.

193. Mauskopf J, Austin R, Dix L, Berzon R. The Nottingham Health Profile as a measure of quality of life in zoster patients: convergent and discriminant validity. Qual Life Res 1994; 3: 431-5.

194. McCormick A, Fleming DM, Charlton J. Morbidity Statistics from General Practice, Fourth national study 1991-1992: MSGP4. Series MB5:3. London, HMSO, 1995: 1-365.

195. McCullagh P, Nelder JA. Generalized Linear Models London: Chapman and Hall; 1989.

196. McGuire A. Theoretical concepts in the economic evaluation of health care. In: Drummond MF, McGuire A. Economic evaluation in health care: Merging theory with practice. Oxford, Oxford University Press; 2001.

197. McLean AR, Blower SM. Imperfect vaccines and herd immunity to HIV. Proc R Soc Lond B 1993; 253:9-13.

198. Mehrez A, Gafni A. Quality-adjusted life years, utility theory, and healthy-years equivalents. Med Decis Making 1989; 9:142-9.

199. Mehrez A. Gafni A. The Healthy-years equivalents: How to measure them using the Standard-Gamble approach. Med Decis Making 1992; 11:140-6.

200. Meyer PA, Seward JF, Jumaan AO, Wharton M. Varicella mortality: trends before vaccine licensure in the United States, 1970-1994. J Infect Dis 2000; 182: 383-90.

201. Miller E, Marshall R, Vurdien J. Epidemiology, outcome and control of varicella-zoster infection. Reviews in Medical Microbiology 1993; 4:222-230.

202. Mitchell RC, Carson RT. Using Surveys to value public goods: the contingent valuation method. Washington D.C.: Resources for the Future, 1989.

203. Mooney G. What else do we want from our health services? Social Science and Medecine 1994; 39:151-154.

204. Muirhead N, Cattran DC, Zaltzman J, Jindal K, First MR, Boucher A, Keown PA, Munch LC, Wong C. Safety and efficacy of recombinant human erythropoietin in correcting the anemia of patients with chronic renal allograft dysfunction. J Am Soc Nephrol 1994; 5:1216-22.

205. Mullins CD, Ogilvie S. Emerging standardization in pharmacoeconomics. Clin Ther. 1998; 20:1194-202.

206. National Oceanic and Atmospheric Administration. Natural resource damage assessments under the oil pollution act of 1990. Notice of proposed rules. Federal Register 1993; 58:4612.

207. Netten A, Curtis L. Unit costs of health and social care. Canterbury, PSSRU, 2001.

208. Netten A, Dennet J. Unit costs of health and social care. Canterbury, PSSRU, 1996.

209. Nettleman MD, Schmid M. Controlling varicella in the healthcare setting: the cost effectiveness of using varicella vaccine in healthcare workers. Infect Control Hosp Epidemiol 1997;18:504-8.

210. Neumann PJ, Johannesson M. The willingness to pay for in vitro fertilization: a pilot study using contingent valuation. Med Care 1994;32:686-99.

211. NHS Executive. NHS Finance Manual. Appendix 1. Health Service Cost Index. London, Department of Health, 1999.

212. NICE. Guidance on the use of Orlistat for the treatment of Obesity in adults. Technology Appraisal Guidance No. 22. 2002.

213. Nokes DJ, Anderson RM. The use of mathematical models in the epidemiological study of infectious diseases and in the design of mass immunization programmes. Epidemiol Infect 1988; 101:1-20.

214. Nord E. An alternative to QALYs: the saved young life equivalents (SAVE). BMJ 1992a; 305:875-7.

215. Nord E. Methods for quality adjustment of life years. Soc Sci Med 1992b; 34:559-69.

216. Nord E. The validity of a visual analogue scale in determining social utility weights for health states. Int J Health Plann Manage 1991; 6:234-42.

217. Nowgesic E, Skowronski D, King A, Hockin J. Direct costs attributed to chickenpox and herpes zoster in British Columbia--1992 to 1996. Can Commun Dis Rep. 1999; 25:100-4.

218. O'Brien B, Gafni A. When do dollars make sense? Toward a conceptual framework for contingent valuation studies in health care. Med Decis Making 1996; 16: 288-299.

219. O'Brien B, Spath M, Blackhouse G, Severens JL, Dorian P, Brazier J. A view from the bridge: Agreement between the SF-6D utility algorithm and the Health Utilities Index. Health Econ (In press).

220. O'Brien B, Viramontes JL. Willingness-to-pay: A valid and reliable measure of health state preference? Med Decis Making 1994; 14:289-97.

221. O'Brien BJ, Goeree R, Gafni A, Torrance GW, Pauly MV, Erder H, Rusthoven J, Weeks J, Cahill M, LaMont B. Assessing the value of a new pharmaceutical. A feasibility study of contingent valuation in managed care. Med Care 1998; 36:370-84

222. O'Connor AM, Pennie RA. Reliability and validity of measures used to elicit health expectations, values, tradeoffs and intentions to be immunized for hepatitis B. J Clin Epidemiol 1995; 48:255-62.

223. Office for National Statistics. 1998 Mortality Statistic: Cause, England and Wales Series DH2 No 25. London, HMSO, 1999.

224. Office for National Statistics. Twentieth Century Mortality. CDROM. London: HMSO, 2000.

225. Olsen JA, Smith RD. Theory versus practice: A review of 'Willingness-to-pay' in health and health care. Health Econ 2001; 10:39-52.

226. Olsen JA. Aiding priority setting in health care: is there a role for the contingent valuation method? Health Econ 1997; 6:603-12.

227. Onwujekwe O, Chima R, Shu E, Nwagbo D, Akpala C, Okonkwo P. Altruistic willingness to pay in community-based sales of insecticide-treated nets exists in Nigeria. Soc Sci Med 2002; 54:519-27.

228. Oxman MN. Immunization to reduce the frequency and severity of herpes zoster and its complications. Neurology 1995; 45(Suppl 8):S41-6.

229. Palmer SR, Caul EO, Donald DE, Kwantes W, Tillet H. An outbreak of shingles? Lancet 1985; 2:1108-11.

230. Panagiotopoulos T, Antoniadou I, Valassi-Adam E. Increase in congenital rubella occurrence after immunisation in Greece: retrospective survey and systematic review. BMJ 1999; 319:1462-7.

231. Paparatti UL, Arpinelli F, Visona G. Herpes zoster and its complications in Italy: an observational survey. J Infect 1999; 38: 116-20.

232. Patrick DL, Starks HE, Cain KC, Uhlmann RF, Pearlman RA. Measuring preferences for health states worse than death. Med Decis Making 1994; 14:9-18.

233. Petrou S. Methodological issues raised by preference-based approaches to measuring the health status of children. Health Econ 2003; 12: 697-702.

234. Pliskin JS, Sheppard DS, Weinstein MC. Utility function for life-years and health status. Operations Research 1980; 28: 206-224.

235. Plotkin, S. Vaccines for varicella-zoster virus and cytomegalovirus: recent progress. Science 1994; 265: 1383-1385.

236. Preblud SR. Age-specific risks of varicella complications. Pediatrics 1981; 68:14-17.

237. Preblud SR. Varicella: Complications and Costs. Pediatrics 1986; 78(Suppl): 728-735.

238. Rabin R, Rosser RM, Butler C. Impact of diagnosis on utilities assigned to states of illness. J R Soc Med 1993; 86:444-8.

239. Ragozzino MW, Melton LJ, Kurland LT, CHU CP, Perry HO. Population-based study of herpes zoster and its sequelae. Medicine 1982; 61: 310-6.

240. Rawson H, Crampin A, Noah N. Deaths from chickenpox in England and Wales 1995-7: analysis of routine mortality data. BMJ 2001;323:1091-3.

241. Read JL, Quinn RJ, Berwick DM, Fineberg HV, Weinstein MC. Preferences for health outcomes. Comparison of assessment methods. Med Decis Making 1984; 4:315-29.

242. Reardon G, Pathak DS. Segmenting the antihistamine market: an investigation of consumer preferences. J Health Care Mark 1990; 10:23-33.

243. Richardson J. Cost-utility analysis: What should be measured? Soc Sci Med 1994; 39: 7-21.

244. Rooney C, Devis T. Mortality trends by cause of death in England and Wales 1980-94: the impact of introducing automated cause coding and related changes in 1993. Popul Trends 1996; 86:29-35.

245. Ross AH. Modification of Chickenpox in family contacts by administration of gamma globulin. N Engl J Med 1962; 267:369-376.

246. Ross AM, Fleming DM. Chickenpox increasingly affects preschool children. Commun Dis Public Health 2000; 3:213-5.

247. Rothberg M, Bennish ML, Kao JS, Wong JB. Do the benefits of varicella vaccination outweigh the long-term risks? A decision-analytic model for policymakers and pediatricians. Clin Infect Dis 2002; 34:885-94.

248. Rowe RD, d'Arge RC, Brookshire DS. An experiment on the economic value of visibility. Journal of Environmental Economics and Management 1980; 7:1-19.

249. Rutten-van Molken MP, Bakker CH, van Doorslaer EK, van der Linden S. Methodological issues of patient utility measurement. Experience from two clinical trials. Med Care 1995; 33: 922-37.

250. Rutten-van Molken MP, Bakker CH, van Doorslaer EK, van der Linden S. Methodological issues of patient utility measurement. Experience from two clinical trials. Med Care 1995; 33:922-37.

251. Saddier P, Floret D, Guess HA et al. Cost of varicella in France: a study in day care centers. J Infect Dis 1998; 178:S58-S63.CDC-Prop BV/NV see a Medic.

252. Salaffi F, Stancati A, Carotti M. Responsiveness of health status measures and utility-based methods in patients with rheumatoid arthritis. Clin Rheumatol 2002; 21:478-87.

253. Samuelson PA. Foundations of economic analysis. Cambridge (MA): Harvard University Press, 1947.

254. Sansom SL, Barker L, Corso PS, Brown C, Deuson R. Rotavirus vaccine and intussusception: how much risk will parents in the United States accept to obtain vaccine benefits? Am J Epidemiol 2001;154:1077-85.

255. Schenzle D. An Age-Structured Model of Pre-and Post-Vaccination Measles Transmission. IMA J Math Appl Ned Biol 1984; 1:169-191.

256. Schlottmann A. Children's probability intuitions: understanding the expected value of complex gambles. Child Dev 2001;72:103-22.

257. Schoenbaum SC, Hyde JN Jr Bartoshesky L, Crampton K. Benefit-cost analysis of rubella vaccination policy. N Engl J Med 1976; 294:306-10.

258. Schuette MC, Hethcote HW. Modeling the effects of varicella vaccination programs on the incidence of chickenpox and shingles. Bulletin of Mathematical Biology 1999; 61:1031-1064.

259. Scuffham P, Devlin N, Eberhart-Phillips J, Wilson-Salt R. The cost-effectiveness of introducing a varicella vaccine to the New Zealand immunisation schedule. Soc Sci Med 1999; 49:763-779.

260. Scuffham PA, Lowin AV, Burgess MA. The cost-effectiveness of varicella vaccine programs for Australia. Vaccine 1999; 18:407-415.

261. Seip K, Strand J. Willingness to pay for environmental goods in Norway: A contingent valuation study with real payment. Environmental and Resource Economics 1992; 2:91-106.

262. Seward JF, Watson BM, Peterson CL, Mascola L, Pelosi JW, Zhang JX, Maupin TJ, Goldman GS, Tabony LJ, Brodovicz KG, Jumaan AO, Wharton M. Varicella disease after introduction of varicella vaccine in the United States, 1995-2000. JAMA 2002; 287:606-11.

263. Seward JF, Jumaan AO, Galil K, Wharton M. Varicella Vaccine and Shingles. JAMA 2002b;287:2211-2212

264. Slovic P. Perception of risk. Science 1987 17; 236:280-5.

265. Smith RD. The relative sensitivity of willingness-to-pay and time-trade-off to changes in health status: an empirical investigation. Health Econ 2001; 10:487-97.

266. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Med Decis Making. 1993; 13:322-38.

267. Sperber SJ, Smith BV, Hayden FG. Serologic response and reactogenicity to booster immunization of healthy seropositive adults with live or inactivated varicella vaccine. Antiviral Res 1992; 17: 213-22.

268. Stalhammar NO. An empirical note on willingness to pay and starting point bias. Med Decis Mak 1996; 16:242-7.

269. Stalmeier PF, Bezembinder TG, Unic IJ. Proportional heuristics in time tradeoff and conjoint measurement. Med Decis Making 1996; 16:36-44.

270. Stalmeier PF, Bezembinder TG, Unic IJ. Proportional heuristics in time tradeoff and conjoint measurement. Med Decis Making 1996; 16:36-44.

271. StataCorp. Stata Statistical Software. Release 7.0. College Station, TX: Stata Corporation; 2002.

272. Stavem K. Association of willingness to pay with severity of chronic obstructive pulmonary disease, health status and other preference measures. Int J Tuberc Lung Dis 2002; 6:542-9.

273. Stavem K. Reliability, validity and responsiveness of two multiattribute utility measures in patients with chronic obstructive pulmonary disease. Qual Life Res. 1999; 8:45-54.

274. Stevens A, Colin-Jones D, Gabbay J. 'Quick and clean': authoritative health technology assessment for local health care contracting. Health Trends 1995; 27:37-42.

275. Stiggelbout AM, Kiebert GM, Kievit J, Leer JW, Habbema JD, De Haes JC. The "utility" of the Time Trade-Off method in cancer patients: feasibility and proportional Trade-Off. J Clin Epidemiol 1995; 48:1207-14.

276. Streefland PH. Public doubts about vaccination safety and resistance against vaccination. Health Policy 2001;55:159-72.

277. Streiner DL, Norman GRHealth Measurment Scales: Apractical guide to their development and use. New York, Oxford University Press; 1989.

278. Sulivan-Bolyai JZ, Yin EK, Cox P, et al. Impact of chickenpox on households of healthy children. Pediatr Infect Dis J 1987; 6: 33-35.

279. Takahashi M, Okuno Y, Otsuka T, Osame J, Takamizawa A. Development of a live attenuated varicella vaccine. Biken J 1975; 18:25-33.

280. Terada K, Hiraga Y, Kawano S, Kataoka N. Incidence of herpes zoster in pediatricians and history of reexposure to varicella-zoster virus in patients with herpes zoster. Kansenshogaku Zasshi 1995; 69:908-12.

281. Theunissen NC, Vogels T, Koopman HM, Verrips GH, Zwinderman K, Verloove-Vanhorick SP et al. The proxy problem: child report versus parent report in health related quality of life-research. Qual Life Res 1998; 7:387-97.

282. Thomas SL, Wheeler JG, Hall AJ. Contacts with varicella or with children and protection against herpes zoster in adults: a case-control study. Lancet 2002; 360(9334):678-82.

283. Thomas SL, Wheeler JG, Hall AJ. Risk factors for herpes zoster in immunocompetent adults. J Epid Comm Health 2001; 55(Suppl): A29 (Abstract 108).

284. Torrance GW, Blaker D, Detsky A, Kennedy W, Schubert F, Menon D, Tugwell P, Konchak R, Hubbard E, Firestone T. Canadian guidelines for economic evaluation of pharmaceuticals. Canadian Collaborative Workshop for Pharmacoeconomics. Pharmacoeconomics 1996a; 9:535-59.

285. Torrance GW, Feeny DH, Furlong WJ, Barr RD, Zhang Y, Wang Q. Multiattribute utility function for a comprehensive health status classification system. Health Utilities Index Mark 2. Med Care 1996b; 34:702-22.

286. Torrance GW, Thomas WH, Sackett DL. A utility maximization model for the evaluatiopn of health care programs. Health Serv Res 1972; 7:118-33.

287. Torrance GW. Measurements of health state utilities for economic appraisal: a review. J Health Econ 1986;5:1-30.

288. Torrance GW. Utility approach to measuring health-related quality of life. J Chronic Dis 1987; 40:593-603

289. Tsevat J, Goldman L, Soukup JR, Lamas GA, Connors KF, Chapin CC, Lee TH. Stability of time-tradeoff utilities in survivors of myocardial infarction. Med Decis Making 1993; 13:161-5.

290. Tsuchiya A, Williams A. Welfare economics and economic evaluation. In: Drummond MF, McGuire A. Economic evaluation in health care: Merging theory with practice. Oxford, Oxford University Press; 2001

291. Valis T, Vesikari T. Efficacy of High-Titer Live Attenuated Varicella Vaccine in Healthy Young Children. J Infect Dis 1996; 174(Suppl 3): S330-4.

292. Vazquez M, LaRussa PS, Gershon AA, Steinberg SP, Freudigman K, Shapiro ED. The effectiveness of the varicella vaccine in clinical practice. N Engl J Med 2001; 344:955-60.

293. Viscusi WK, Magat A, Forrest A. Altruistic and private willingness to pay for antihypertensive therapy - further results. Journal of Policy Analysis and Management 1988; 7:227-45.

294. Viscusi WK. Labor market valuations of life and limb: empirical estimates and policy implications. Public Policy 1978; 26: 259-89.

295. Vogels T, Verrips GH, Verloove-Vanhorick SP, Fekkes M, Kamphuis RP, Koopman HM, Theunissen NC, Wit JM. Measuring health-related quality of life in children: the development of the TACQOL parent form. Qual Life Res 1998; 7:457-65.

296. von Neumann J, Morgenstern O. Theory of games and economic behaviour. Princetown, New Jersey: Princetown University Press; 1944.

297. Wagner TH, Hu T, Duenas GV, Kaplan CP, Nguyen BH, Pasick RJ. Does willingness to pay vary by race/ethnicity? An analysis using mammography among low-income women. Health Policy 2001; 58:275-88.

298. Wagstaff A. Inequality aversion, health inequalities and health achievement. J Health Econ 2002; 21:627-41.

299. Wagstaff A. QALYs and the equity-efficiency trade-off. J Health Econ. 1991; 10:21-41.

300. Watson BM, Piercy SA, Plotkin SA, Star SE. Modified Chickenpox in Children Immunized With the Oka/Merck Varicella Vaccine. Pediatrics 1993; 91:17-22.

301. Weibel RE, Kuter BJ, Neff BJ *et al.* Live Oka/Merck varicella vaccine in healthy children. Further clinical and laboratory assessment. JAMA 1985; 254:2435-9.

302. Weibel RE, Neff BJ, Kuter BJ *et al.* Live attenuated varicella virus vaccine. Efficacy trial in healthy children. N Engl J Med 1984; 310:1409-15.

303. Weinstein MC, Manning WG Jr. Theoretical issues in cost-effectiveness analysis. J Health Econ 1997; 16:121-8.

304. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-Effectiveness in Health and Medicine. JAMA 1996; 276: 1253-7.

305. Weller TH. Varicella: Historical Perspective and Clinical Overview. JID 1996; 174 (Suppl 3): S306-S309.

306. Wharton M, Fehrs LJ, Cochi SL, et al. Health impact of varicella in the 1980s (abstract). In:Program and abstracts of the 30th Interscience Conference on Amtimicromial Agents and Chemotherapy, Atlanta, Georgia, Octobre 21-24 1990.

307. Wharton M. The Epidemiology of Varicella-Zoster Virus Infetions. Infectious Disease Clinics of North America 1996; 10:571-581.

308. White CJ, Kuter BJ, Hildebrand CS *et al.* Varicella vaccine (VARIVAX) in healthy children and adolescents: results from clinical trials, 1987 to 1989. Pediatrics 1991; 87(5):604-10.

309. Wise RP, Salive ME, Braun MM, et al. Postlicensure safety surveillance for varicella vaccine. JAMA 2000; 284: 1271-1279.

310. Wood MJ, Kay R, Dworkin RH, Soong SJ, Whitley RJ. Oral acyclovir therapy accelerates pain resolution in patients with herpes zoster: A meta-analysis of placebo-controlled trials. Clin Infec Dis 1996; 22: 341-7.

311. Wood MJ, Kay R, Dworkin RH, Soong SJ, Whitley RJ. Oral acyclovir therapy accelerates pain resolution in patients with herpes zoster: A meta-analysis of placebo-controlled trials. Clin Infec Dis 1996; 22: 341-7.

312. Wood MJ, Shukla S, Fiddian AP, Crooks RJ. Treatment of Acute Herpes Zoster: Effect of Early (<48 h) versus Late (48-72 h) Therapy with Acyclovir and Valaciclovir on Prolonged Pain. J Infect Dis 1998; 178(Suppl 1): S81-84.

313. Wood MJ, Shukla S, Fiddian AP, Crooks RJ. Treatment of Acute Herpes Zoster: Effect of Early (<48 h) versus Late (48-72 h) Therapy with Acyclovir and Valaciclovir on Prolonged Pain. J Infect Dis 1998; 178(Suppl 1): S81-84.

314. Woodward RS, Schnitzler MA, Kvols LK. Reduced uncertainty as a diagnostic benefit: an initial assessment of somatostatic receptor scintigraphy's value in detecting distant metastases of carcinoid liver tumours. Health Econ 1998; 7:149-60.

315. World Bank. World Development report 1993: investing in health. New York: Oxford University Press, 1993.

316. World Health Organisation. Preamble to the Constitution of the World Health Organization. International Health Conference, New York, 19-22 June, 1946.

317. Wreghitt TG, Whipp J, Redpath C, Hollingworth W. An analysis of infection control of varicella-zoster virus infection in Addenbrooke's Hospital Cambridge over a 5-year period, 1987-92. Epidemiol Infect 1996; 117:165-71.

318. Yawn BP, Yawn RA, Lydick E. Community impact of childhood varicella infections. J Pediatr 1997; 130:759-765

319. Zillich AJ, Blumenschein K, Johannesson M, Freeman P. Assessment of the relationship between measures of disease severity, quality of life, and willingness to pay in asthma. Pharmacoeconomics 2002; 20: 257-65.

320. Zivin JG. Cost-effectiveness analysis with risk aversion. Health Econ 2001; 10:499-508.

APPENDIX

APPENDIX 1 - VACCINE EFFICACY MODEL

MATHEMATICAL STRUCTURE

The model represents natural history of varicella in a cohort of vaccine responders stratified according to time since vaccination. The population is divided into 3 mutually excusive vaccinated groups (see Chapter 3, Figure 3.1 for flow diagram): the proportion completely protected, denoted VP(t); the proportion vaccinated but susceptible to varicella, VS(t); and immune to varicella VR(t). The rates at which individuals flow between the vaccine states are described by the following set of differential equations:

$$dVP(t)/dt = T(t) - (W + K\lambda)\, VP(t) \qquad (1)$$

$$dVS(t)/dt = [1-T(t)] + W\, VP(t) - b\lambda VS(t) \qquad (2)$$

$$dVR(t)/dt = b\lambda\, VS(t) + K\lambda VP(t) \qquad (3)$$

Where, λ is the force of varicella infection ($\lambda = 0.2$ per year). The flow between vaccinee states are: T(a), the percent of vaccine responders who become temporarily protected after vaccination; W, waning rate; $b\lambda$, rate of infection among vaccine susceptible vaccinees; $k\lambda$, rate of boosting.

APPENDIX 2 - MODEL 1

MATHEMATICAL STRUCTURE

Model 1 represents the transmission dynamics of varicella. The model possesses 66 age cohorts (0, 1, 2,..., 64 and 65+). Children enter continuously throughout the year into the first age cohort (at 6 months of age). Thereafter, individuals change age cohorts at the beginning of each school year thus taking into account the importance of school transmission on the dynamics of varicella (Schenzle, 1984). Vaccination is performed at the end of the year as individuals move up an age class. Within each cohort, the differential equations for this deterministic RAS model are as follows:

$$dS(a,t)/dt = B(a) - [\lambda(a,t) + (c(a)\,(1-P) + \mu(a)]\,S(a,t) \quad (1)$$

$$dE(a,t)/dt = \lambda(a,t)\,S(a,t) - (\sigma + \mu(a))\,E(a,t) \quad (2)$$

$$dI(a,t)/dt = \sigma\,E(a,t) - (\alpha + \mu(a))\,I(a,t) \quad (3)$$

$$dR(a,t)/dt = \alpha\,I(a,t) - \mu(a)\,R(a,t) \quad (4)$$

$$dVP(a,t)/dt = c(a)\,T\,S(a,t) - (W + K\,\lambda(a,t) + \mu(a))\,VP(a,t) \quad (5)$$

$$dVS(a,t)/dt = c(a)\,[1-T-P]\,S(a,t) + W\,VP(a,t) - (b\,\lambda(a,t) + \mu(a))VS(a,t) \quad (6)$$

$$dVE(a,t)/dt = b\,\lambda(a,t)\,VS(a,t) - (\sigma + \mu(a))\,VE(a,t) \quad (7)$$

$$dVI(a,t)/dt = \sigma\,VE(a,t) - (\alpha + \mu(a))\,VI(a,t) \quad (8)$$

$$dVR(a,t)/dt = K\,\lambda(a,t)\,VP(a,t) + \alpha\,VI(a,t) - \mu(a)\,VR(a,t) \quad (9)$$

The number of individuals of age a at time t who are varicella susceptible, naturally infected but not infectious, infectious, immune, temporary protected, modified susceptible, vaccinated infected but not infectious, vaccinated infectious, vaccinated immune are defined by the state variables S(a,t), E(a,t), I(a,t), R(a,t), VP(a,t), VS(a,t), VE(a,t), VI (a,t) and VR(a,t) respectively. The different parameters determining the rates of flow between disease states for natural varicella are: B(a), rate of entry into the first age cohort; $\mu(a)$ mortality

rate; c(a), vaccine coverage; $\lambda(a,t)$, force of varicella infection by age group; σ and α, rates of flow from latent to infectious and infectious to immune.

The flow between vaccinee disease states are: c(a) T, the percent of vaccinees who become temporarily protected after vaccination; c(a)P, the percent of vaccinees for which vaccine fails completely after vaccination; W, waning rate; b $\lambda(a,t)$, rate of infection among vaccine susceptible vaccinees; k $\lambda(a,t)$, rate of boosting.

FORCE OF VARICELLA INFECTION

The pre-vaccination force of varicella infection was estimated using the methodology described in section 2.3.

In Model 1, the age and time dependant force of varicella infection is defined as:

$$\lambda(a,t) = \lambda_v(a,t) + \lambda_z$$

$$= \Sigma_{a'=0}^{L} \beta(a',a)(I(a',t) + m\, VI(a',t)) + \lambda_z \qquad (10)$$

Where, $\lambda_v(a,t)$ is the force of infection due to varicella, λ_z is the force of infection due to zoster, $\beta(a',a)$ is the rate at which an infective of age a' will infect a susceptible of age a, L is life expectancy and m is the rate of varicella infectiousness of vaccines compared to non-vaccinees.

APPENDIX 3 - MODEL 2

MATHEMATICAL STRUCTURE

Model 2 represents the transmission dynamics of both varicella and zoster. Differential equations 1, 2, 3, 6, 7, 8 and 9 are identical for Model 1 and 2. The remaining differential equations for Model 2 are as follows:

$$dR(a,t)/dt = \alpha\, I(a) + z\,\lambda(a,t)\, ZS(a,t) - (\delta + \mu(a))\, R(a,t) \quad (11)$$

$$dZS(a,t)/dt = \delta\, R(a) - (\rho(a) + z\lambda(a,t) + \mu(a))\, ZS(a,t) \quad (12)$$

$$dZI(a,t)/dt = \rho(a)\, ZS(a) - (\alpha_z + \mu(a))\, ZI(a,t) \quad (13)$$

$$dZR(a,t)/dt = \alpha_z\, ZI(a,t) - \mu(a)\, ZR(a,t) \quad (14)$$

The zoster disease states are: lifelong immunity to varicella and temporary immunity to zoster (R(a,t)), susceptible to zoster (ZS(a,t)), reactivation episode (ZI(a,t)) and permanently immune to zoster. The rates are determined by: δ, rate of loss of immunity to zoster; $z\lambda(a,t)$, rate of boosting against zoster; and $\rho(a)$, the age-dependent rate of reactivation of VZV in those who are susceptible to zoster.

FORCE OF VARICELLA INFECTION

The age- and time-specific force of varicella infection is defined as:

$$\lambda(a,t) = \lambda_v(a,t) + \lambda_z(t)$$

$$= \Sigma_{a'=0}^{L} \beta(a',a)\, (I(a',t) + m\, VI(a',t)) + \omega\, \Sigma_{a'=0} ZI(a',t) \quad (15)$$

Where, $\omega = 5.4^{e-7}$.

RATE OF REACTIVATION

The age-specific rate of reactivation, $\rho(a)$, and duration of boosting ($1/\delta$) were estimated in section 2.4.

COMPUTER DETAILS

Numerical results were generated by a Model *Maker* version 3.0 program. The system was solved using Runge-Kutta (Burden and Faires (1993)) integration of ordinary differential equations with adaptable time steps. Simulations were performed on a PC.

APPENDIX 4 - WAIFW MATRIX ESTIMATION AND STRUCTURE

The standard technique developed by Anderson and May was used to describe the age-dependant mixing patterns of the population (Who-Acquired-Infection-From-Whom (WAIFW) matrix) (Anderson and May, 1991). The elements of the WAIFW matrix, $\beta(a',a)$, were estimated from the pre-vaccination force of infection, $\lambda(a,0)$, using equation 10. Here, we present the estimation the base matrix values as an example.

The base case matrix structure is:

	0-1	2-4	5-11	12-18	19-24	25-44	45-64	65+
0-1	β_1	β_1	β_1	β_1	β_6	β_6	β_7	β_8
2-4	β_1	β_2	β_5	β_5	β_6	β_6	β_7	β_8
5-11	β_1	β_5	β_3	β_5	β_6	β_6	β_7	β_8
12-18	β_1	β_5	β_5	β_4	β_6	β_6	β_7	β_8
19-24	β_6	β_6	β_6	β_6	$1.5*\beta_4$	β_7	β_7	β_8
25-44	β_6	β_6	β_6	β_6	β_7	β_7	β_7	β_8
45-64	β_7	β_7	β_7	β_7	β_7	β_7	β_7	β_8
65+	β_8	β_8	β_8	β_8	β_8	β_8	β_8	β_8

The value of the WAIFW matrix (β_i's) are estimated by solving the following set of linear equations (based on equation 10):

$$\lambda_v(1,0)= \beta_1(I(1,0)+ I(2,0)+ I(3,0)+ I(4,0))+ \beta_6(I(5,0)+ I(6,0))+ \beta_7 I(7,0)+ \beta_8 I(8,0)$$
$$\lambda_v(2,0)=\beta_1 I(1,0)+ \beta_2 I(2,0)+\beta_5(I(3,0)+I(4,0))+\beta_6(I(5,0)+ I(6,0))+ \beta_7 I(7,0)+ \beta_8 I(8,0)$$
$$\lambda_v(3,0)=\beta_1 I(1,0)+ \beta_3 I(3,0)+\beta_5(I(2,0)+I(4,0))+\beta_6(I(5,0)+ I(6,0))+ \beta_7 I(7,0)+ \beta_8 I(8,0) \quad (16)$$
$$\lambda_v(4,0)=\beta_1 I(1,0)+\beta_5(I(2,0)+I(3,0))+\beta_4 I(3,0)+\beta_6(I(5,0)+ I(6,0))+ \beta_7 I(7,0)+ \beta_8 I(8,0)$$
$$\lambda_v(5,0)=\beta_6(I(1,0)+I(2,0)+I(3,0)+I(4,0))+ 1.5*\beta_4 I(5,0) + \beta_7(I(6,0)+I(7,0))+ \beta_8 I(8,0)$$
$$\lambda_v(6,0)= \beta_6(I(1,0)+I(2,0)+ I(3,0)+ I(4,0))+\beta_7(I(5,0)+I(6,0)+I(7,0)) + \beta_8 I(8,0)$$
$$\lambda_v(6,0)= \beta_7(I(1,0)+I(2,0)+ I(3,0)+ I(4,0)+I(5,0)+I(6,0)+I(7,0))+ \beta_8 I(8,0)$$
$$\lambda_v(8,0)= \beta_8(I(1,0)+I(2,0)+ I(3,0)+ I(4,0)+I(5,0)+I(6,0)+I(7,0)+I(8,0))$$

where, $\beta_i=\beta(a,i)$, $\lambda_v(a,0)$ is the force of infection of varicella calculated in section 2.3 and I(i,0) is the annual number of infectives in age group i calculated by applying the pre-vaccination force of infection (calculated in section 2.3) to an imaginary cohort of susceptibles. The WAIFW matrix does not change during the simulation, only the number of infectives.

Five different Matrix structures were used, yielding the following values for the WAIFW matrices:

Base Matrix (β units are effective contact per 100 day):

	0-1	2-4	5-11	12-18	19-24	25-44	45-64	65+
0-1	1.6	1.6	1.6	1.6	1.2	1.2	1.0	1.0
2-4	1.6	5.2	1.1	1.1	1.2	1.2	1.0	1.0
5-11	1.6	1.1	3.4	1.1	1.2	1.2	1.0	1.0
12-18	1.6	1.1	1.1	3.2	1.2	1.2	1.0	1.0
19-24	1.2	1.2	1.2	1.2	4.8	1.0	1.0	1.0
25-44	1.2	1.2	1.2	1.2	1.0	1.0	1.0	1.0
45-64	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
65+	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

Matrix 1:

	0-1	2-4	5-11	12-18	19-24	25-44	45-64	65+
0-1	1.60	1.60	1.60	1.60	1.19	1.17	1.02	1.02
2-4	1.60	5.19	1.07	1.07	1.19	1.17	1.02	1.02
5-11	1.60	1.07	3.45	1.07	1.19	1.17	1.02	1.02
12-18	1.60	1.07	1.07	3.45	1.19	1.17	1.02	1.02
19-24	1.19	1.19	1.19	1.19	5.17	0.82	0.82	0.82
25-44	1.17	1.17	1.17	1.17	0.82	0.82	0.82	0.82
45-64	1.02	1.02	1.02	1.02	0.82	0.82	0.82	0.82
65+	1.02	1.02	1.02	1.02	0.82	0.82	0.82	0.82

Matrix 2:

	0-1	2-4	5-11	12-18	19-24	25-44	45-64	65+
0-1	1.60	1.60	1.60	1.60	1.25	1.15	1.00	1.00
2-4	1.60	5.10	1.14	1.14	1.25	1.15	1.00	1.00
5-11	1.60	1.14	3.38	1.14	1.25	1.15	1.00	1.00
12-18	1.60	1.14	1.14	2.74	1.25	1.15	1.00	1.00
19-24	1.25	1.25	1.25	1.25	2.74	1.15	1.00	1.00
25-44	1.15	1.15	1.15	1.15	1.15	1.15	1.00	1.00
45-64	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
65+	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Assortative:

	0-1	2-4	5-11	12-18	19-24	25-44	45-64	65+
0-1	8.91	1.00	1.00	1.00	1.00	1.00	1.00	1.00
2-4	1.00	5.45	1.00	1.00	1.00	1.00	1.00	1.00
5-11	1.00	1.00	3.64	1.00	1.00	1.00	1.00	1.00
12-18	1.00	1.00	1.00	5.01	1.00	1.00	1.00	1.00
19-24	1.00	1.00	1.00	1.00	10.74	1.00	1.00	1.00
25-44	1.00	1.00	1.00	1.00	1.00	5.37	1.00	1.00
45-64	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
65+	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Proportional:

	0-1	2-4	5-11	12-18	19-24	25-44	45-64	65+
0-1	0.43	1.88	1.85	0.62	0.49	0.45	0.30	0.28
2-4	1.88	3.13	2.63	1.48	1.38	1.24	1.04	1.04
5-11	1.85	2.63	2.04	1.40	1.53	1.34	1.26	1.28
12-18	0.62	1.48	1.40	0.87	0.80	0.71	0.51	0.49
19-24	0.49	1.38	1.53	0.80	0.73	0.65	0.43	0.32
25-44	0.45	1.24	1.34	0.71	0.65	0.58	0.39	0.33
45-64	0.30	1.04	1.26	0.51	0.43	0.39	0.23	0.19
65+	0.28	1.04	1.28	0.49	0.32	0.33	0.19	0.14

APPENDIX 5 - SIMPLIFIED DYNAMIC MODEL USED FOR COMPARISON WITH STATIC MODELS

The model possesses 66 age cohorts (0, 1, ..65+). Following Schenzle (1984) children enter continuously throughout the year into the first age cohort at 6 months of age. Thereafter, individuals change age cohorts at the beginning of each school year (boundary conditions). Vaccination is performed at the end of the year as individuals move up an age class. Within each age cohort *i*, the differential equations for this deterministic model are as follows:

$$dS_i(t)/dt = B_i - [\lambda_i(t) + v_i + \mu_i]\, S_i(t) \qquad (17)$$

$$dE_i(t)/dt = \lambda_i(t)\, S_i(t) - (\sigma + \mu_i)\, E_i(t) \qquad (18)$$

$$dI_i(t)/dt = \sigma\, E_i(t) - (\alpha + \mu_i)\, I_i(t) \qquad (19)$$

$$dR_i(t)/dt = \alpha\, I_i(t) - \mu_i\, R_i(t) + v_i S_i(t) \qquad (20)$$

where the number of individuals in age cohort *i* at time *t* who are varicella susceptible, naturally infected but not infectious, infectious, and immune are given by the state variables $S_i(t)$, $E_i(t)$, $I_i(t)$ and $R_i(t)$ respectively, B_i is the birth rate, μ_i the mortality rate, v_i vaccine coverage (by age), σ and α, rates of flow from latent to infectious and infectious to immune groups, and $\lambda_i(t)$ the force of infection by age group (see Section 2.3 for values). The initial conditions for the set of equations are taken to be the pre-vaccination equilibrium number of individuals in each epidemiological class by age, which are determined by treating $\lambda_i(0)$ as a fixed parameter (i.e. by using the static cohort model). The equations are solved numerically using a Fourth -Order Runge-Kutta algorithm (Burden and Faires (1993)).

Note that the model (above) differs from that used in section 3.2 only in that vaccination is assumed to result in lifelong immunity, hence it is no longer

necessary to include vaccinated classes (with varying degrees of immunity and infectiousness), as all those who are vaccinated pass directly into the immune class ($R_i(t)$).

APPENDIX 6 - INFORMATION LEAFLET

INFORMATION LEAFLET

THE SURVEY: Valuing the benefit of treatment and vaccination

We are currently recruiting parents and caregivers for a survey, which is being carried out by the Public Health Laboratory Service (PHLS) and City University. The recruitment will take place in Health Centers at the moment of the 9 and 18-month check-up of your child. This leaflet tells you more about the survey and why it is being done.

What is it about?

I am a member of a research team, which is trying to find out what parents value in the treatment and prevention of disease in their children. The aim is to help health policy decision-making taking into account parents' preferences.

What will you be required to do?

If you agree to participate in the study we will ask you to fill in a short face-to-face questionnaire, which will last about **10 minutes**.

Remember, this questionnaire is not a test. There are no right or wrong answers. If at any time you feel uncomfortable about a specific question simply do not answer it.

Is the survey confidential?

Yes. Your answers will remain confidential and your name will not be written on the form.

Is the survey compulsory?

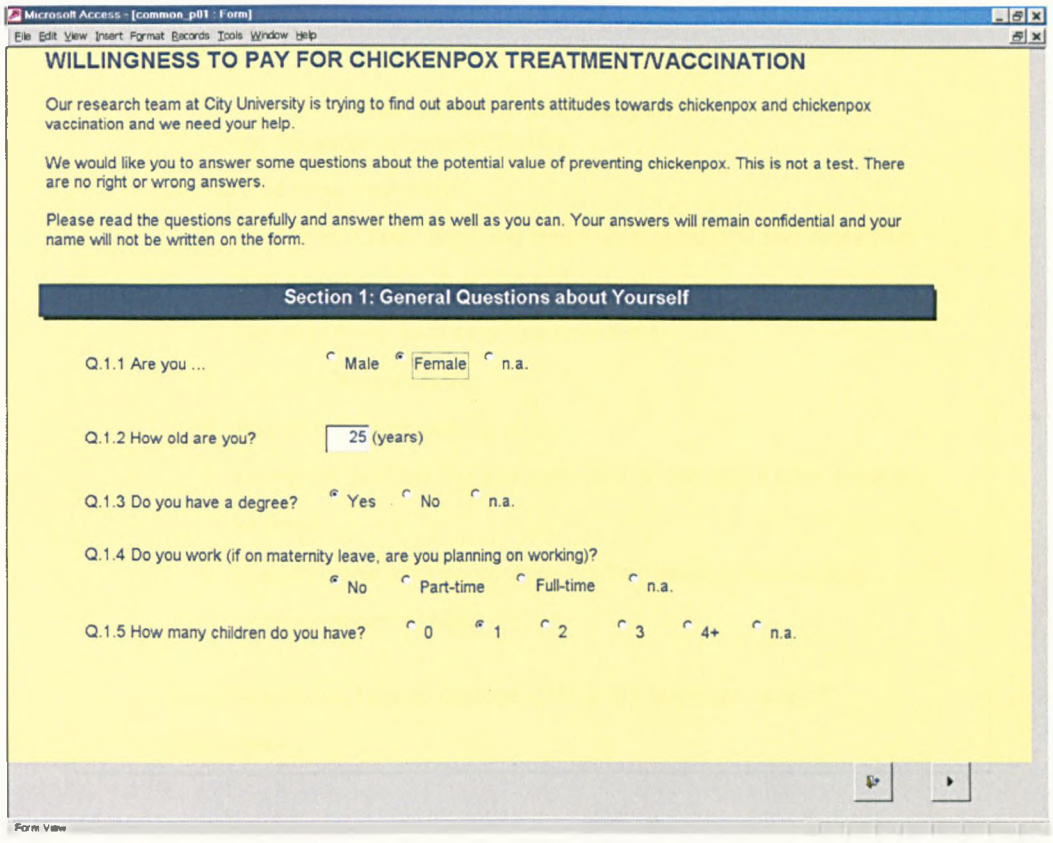
No. Our survey relies on voluntary co-operation. The success of the survey depends on the goodwill and co-operation of those who take part. Future care will not be affected if the questionnaire is not completed.

Parents should feel free to discuss the questionnaire with health visitors, medical professionals and/or GPs.

We hope that this leaflet answers some of the questions you might have. Your co-operation is very much appreciated.

If you have any queries please contact Marc Brisson at the following address.

APPENDIX 7 - SOCIO-ECONOMIC QUESTIONNAIRE



Microsoft Access - [common_p01 : Form]

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WILLINGNESS TO PAY FOR CHICKENPOX TREATMENT/VACCINATION

Our research team at City University is trying to find out about parents attitudes towards chickenpox and chickenpox vaccination and we need your help.

We would like you to answer some questions about the potential value of preventing chickenpox. This is not a test. There are no right or wrong answers.

Please read the questions carefully and answer them as well as you can. Your answers will remain confidential and your name will not be written on the form.

Section 1: General Questions about Yourself

Q.1.1 Are you ... ○ Male ◉ Female ○ n.a.

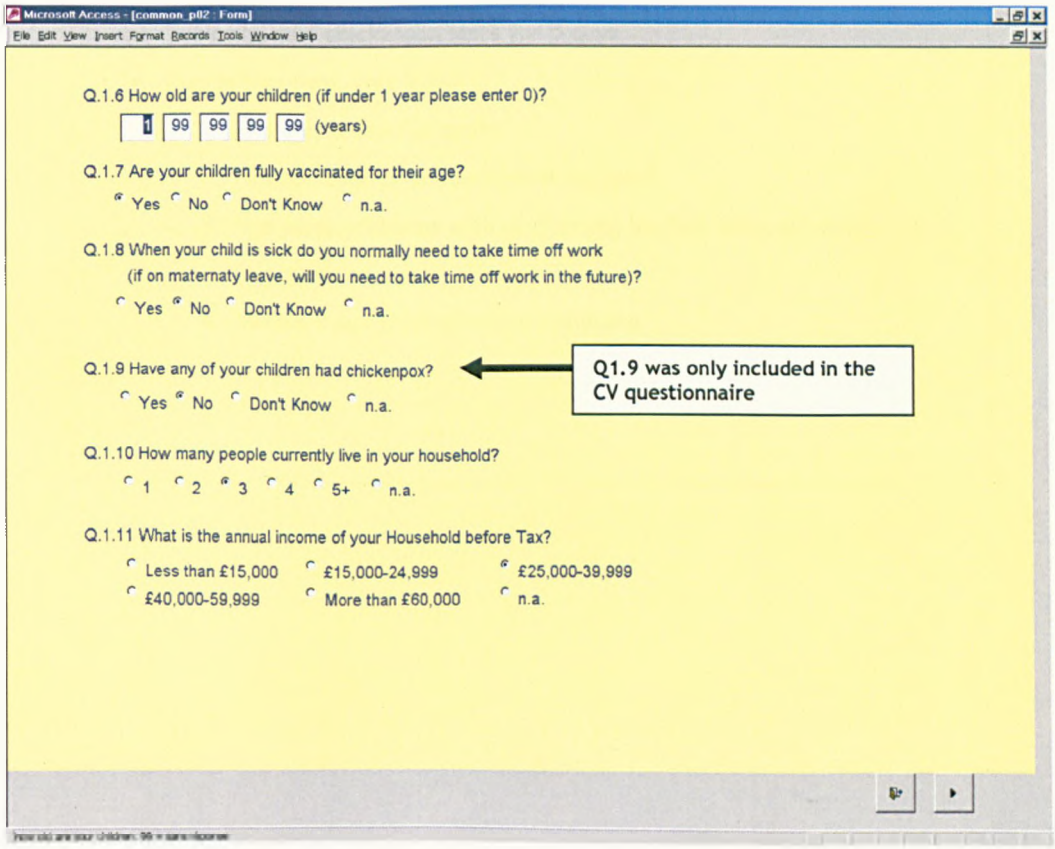
Q.1.2 How old are you? 25 (years)

Q.1.3 Do you have a degree? ◉ Yes ○ No ○ n.a.

Q.1.4 Do you work (if on maternity leave, are you planning on working)?
◉ No ○ Part-time ○ Full-time ○ n.a.

Q.1.5 How many children do you have? ○ 0 ◉ 1 ○ 2 ○ 3 ○ 4+ ○ n.a.

Form View



Microsoft Access - [common_p02 : Form]

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Q.1.6 How old are your children (if under 1 year please enter 0)?
1 99 99 99 99 (years)

Q.1.7 Are your children fully vaccinated for their age?
◉ Yes ○ No ○ Don't Know ○ n.a.

Q.1.8 When your child is sick do you normally need to take time off work
(if on maternaty leave, will you need to take time off work in the future)?
○ Yes ◉ No ○ Don't Know ○ n.a.

Q.1.9 Have any of your children had chickenpox?
○ Yes ◉ No ○ Don't Know ○ n.a.

Q1.9 was only included in the CV questionnaire

Q.1.10 How many people currently live in your household?
○ 1 ○ 2 ◉ 3 ○ 4 ○ 5+ ○ n.a.

Q.1.11 What is the annual income of your Household before Tax?
○ Less than £15,000 ○ £15,000-24,999 ◉ £25,000-39,999
○ £40,000-59,999 ○ More than £60,000 ○ n.a.

APPENDIX 8 - CONTINGENT VALUATION QUESTIONNAIRE
PART 1 - DISEASE DESCRIPTION CARDS

Description of Chickenpox

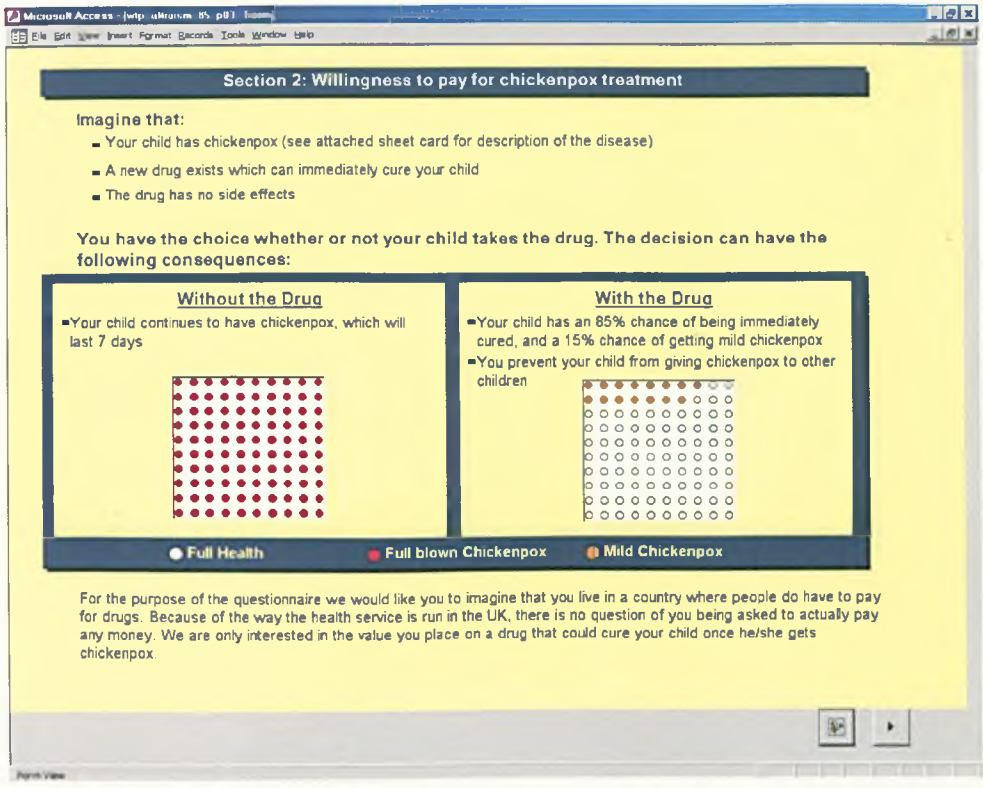
- Typically, chickenpox lasts for 7 days
- During this time, your child:
    1. Is covered (face, body and arms) with up to 500 red spots that itch intensely, which is highly frustrating
    2. Has mild fever with cold-like symptoms
    3. Has problems sleeping
    4. Has no problems walking about
    5. Cannot go to school or day care until all the spots have dried or crusted.
    6. Has problems with performing his/her usual activities (e.g. hobbies, sport, playing)
- Working parents take an average 2 days off work per case of chickenpox

Description of Mild Chickenpox

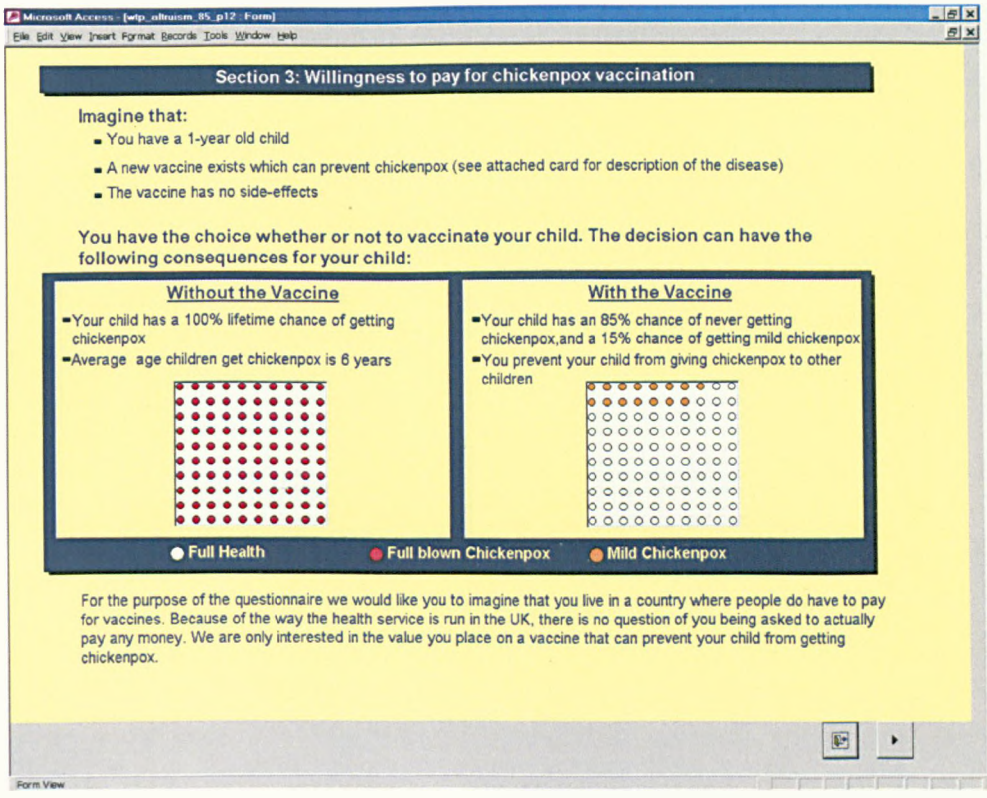
- Typically, mild chickenpox lasts for 5 days
- During this time, your child:
    1. Has only a few red spots
    2. Has no fever or problems walking about
    3. Has some problems with performing his/her usual activities (e.g. hobbies, sport, playing)
    4. Misses 1 day from school or childcare.

PART 2 - 85% VACCINE EFFICACY AND ALTRUISM

WTP FOR TREATMENT

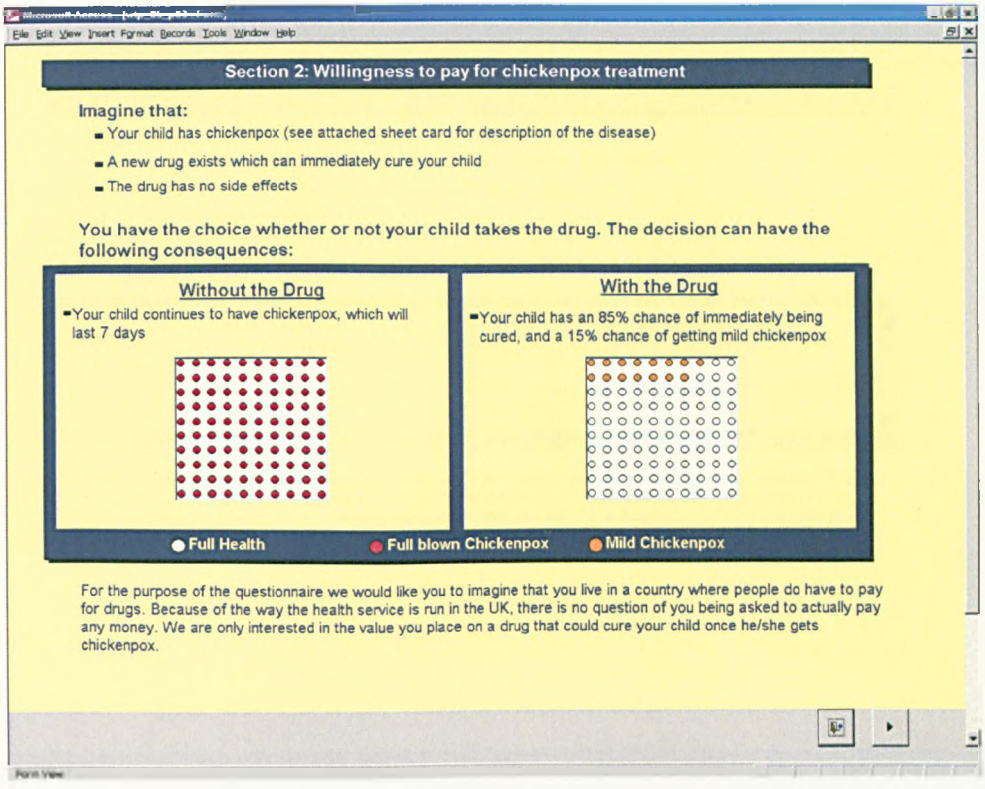


WTP FOR VACCINATION

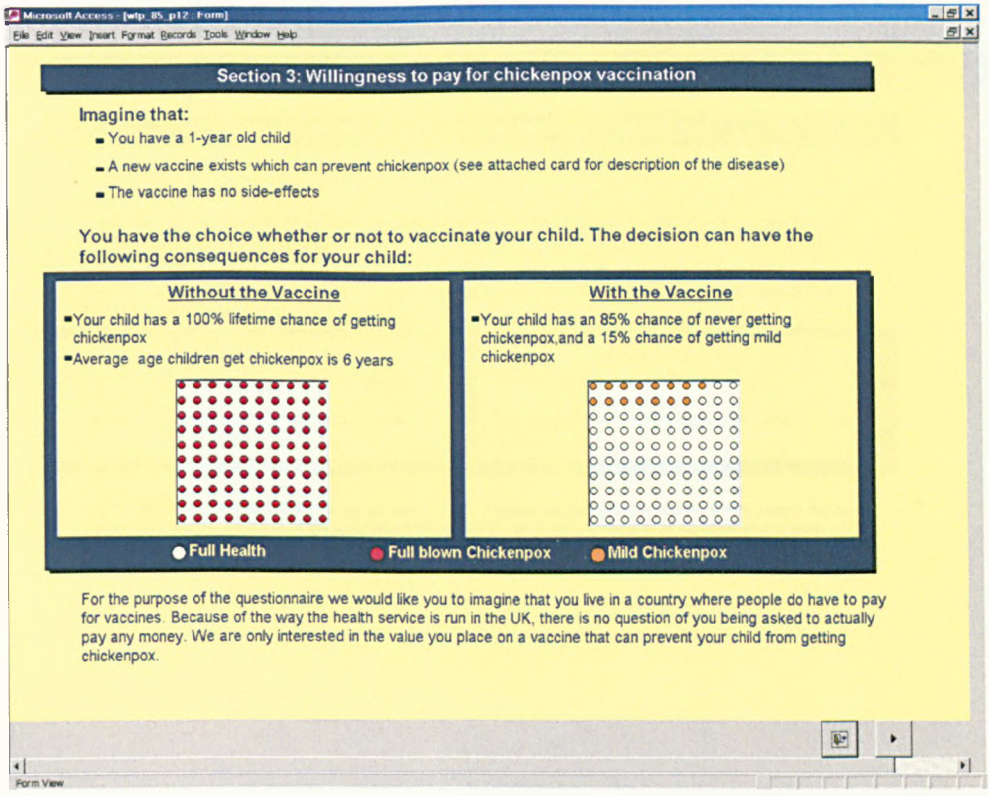


PART 3 - 85% VACCINE EFFICACY

WTP FOR TREATMENT

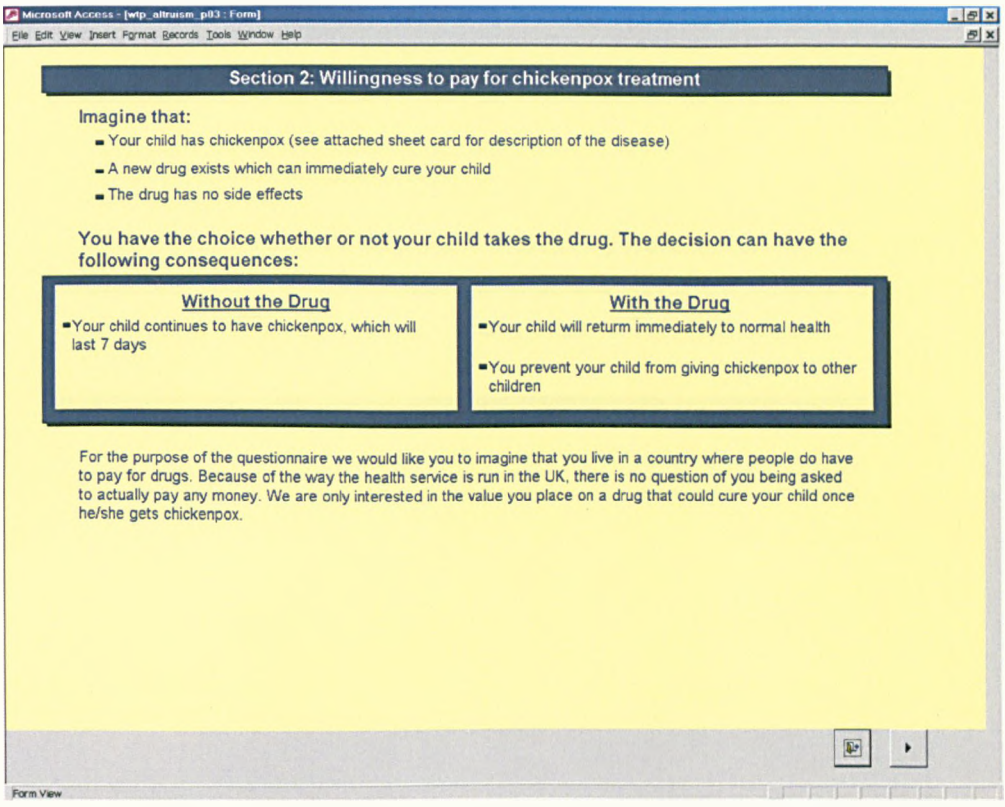


WTP FOR VACCINATION

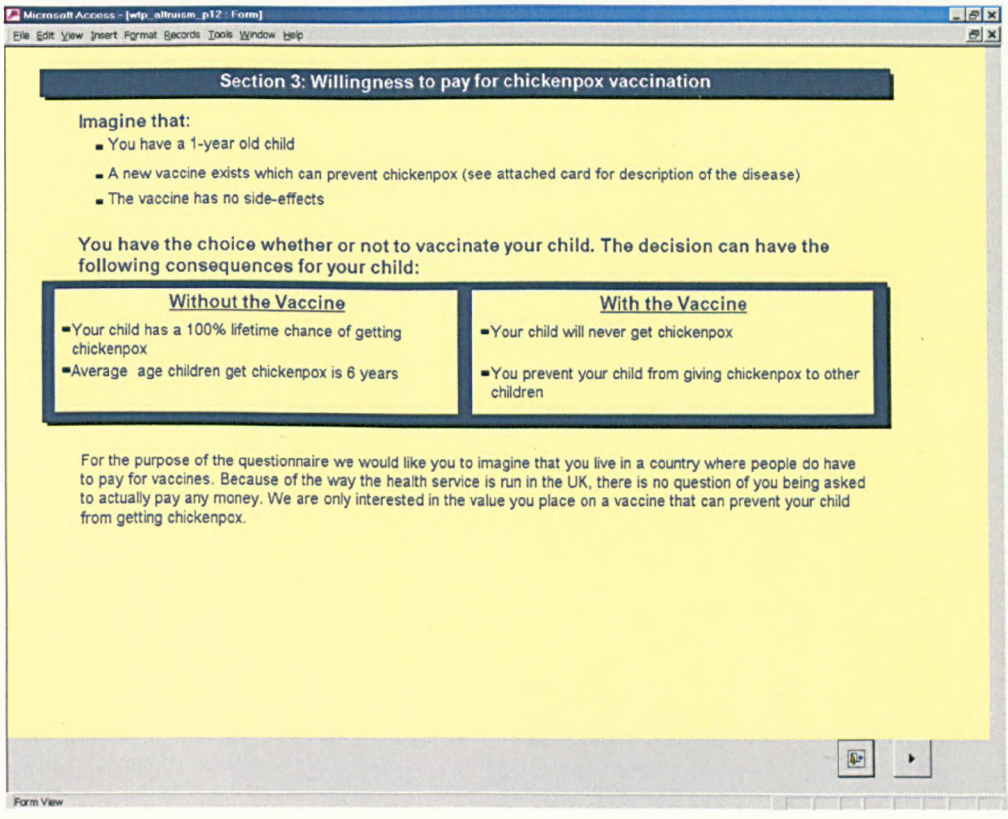


PART 4 - 100% VACCINE EFFICACY AND ALTRUISM

WTP FOR TREATMENT

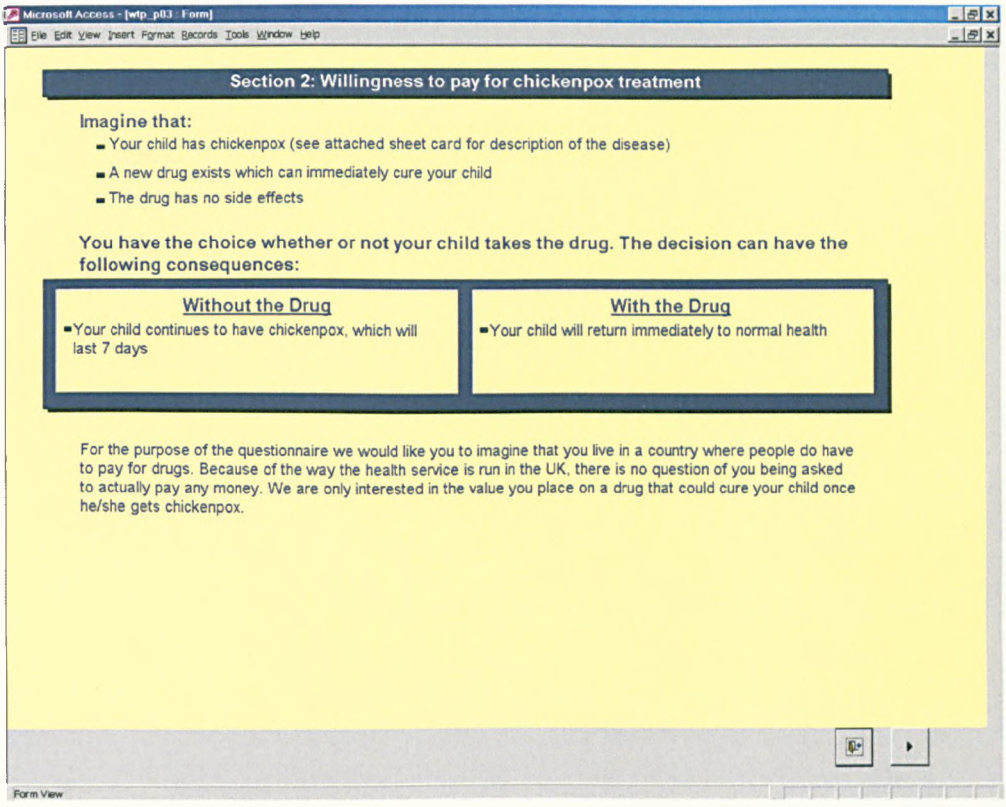


WTP FOR VACCINATION

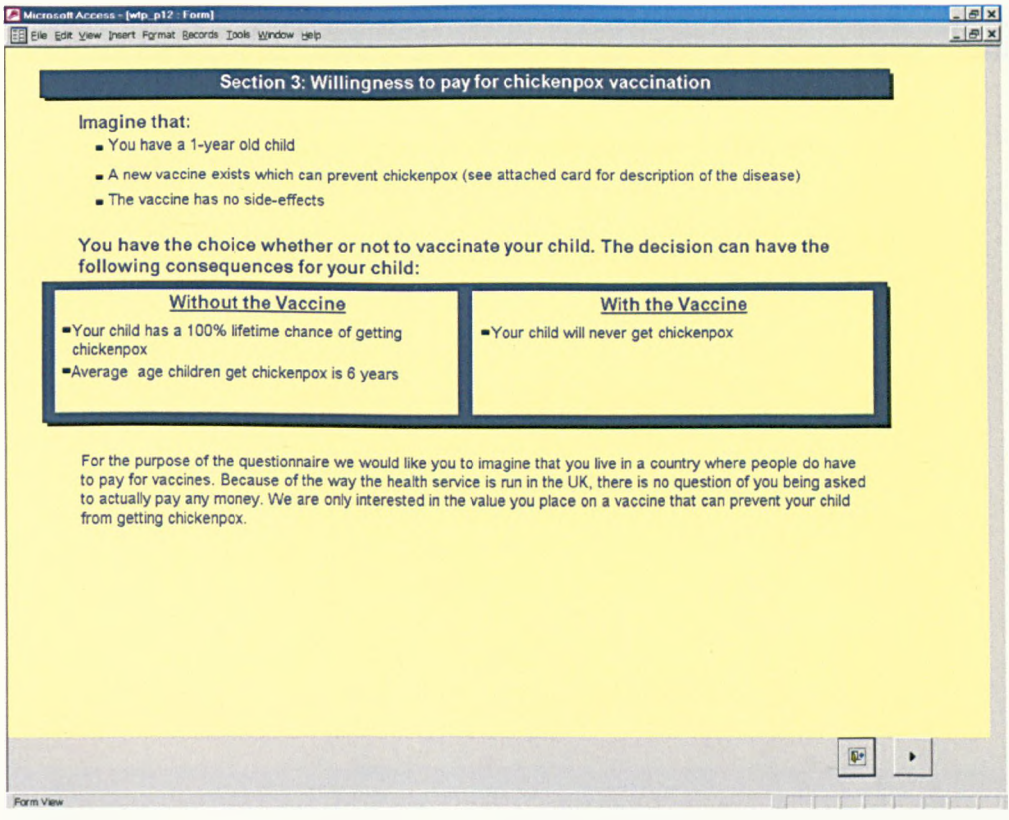


PART 5 - 100% VACCINE EFFICACY

WTP FOR TREATMENT

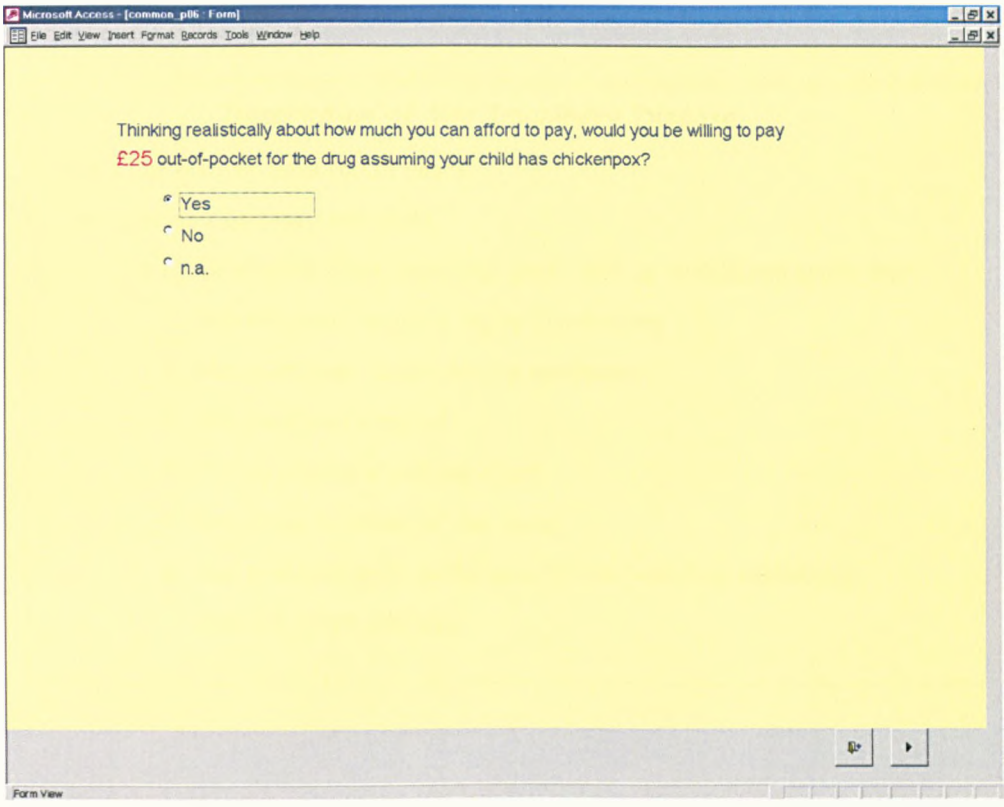


WTP FOR VACCINATION

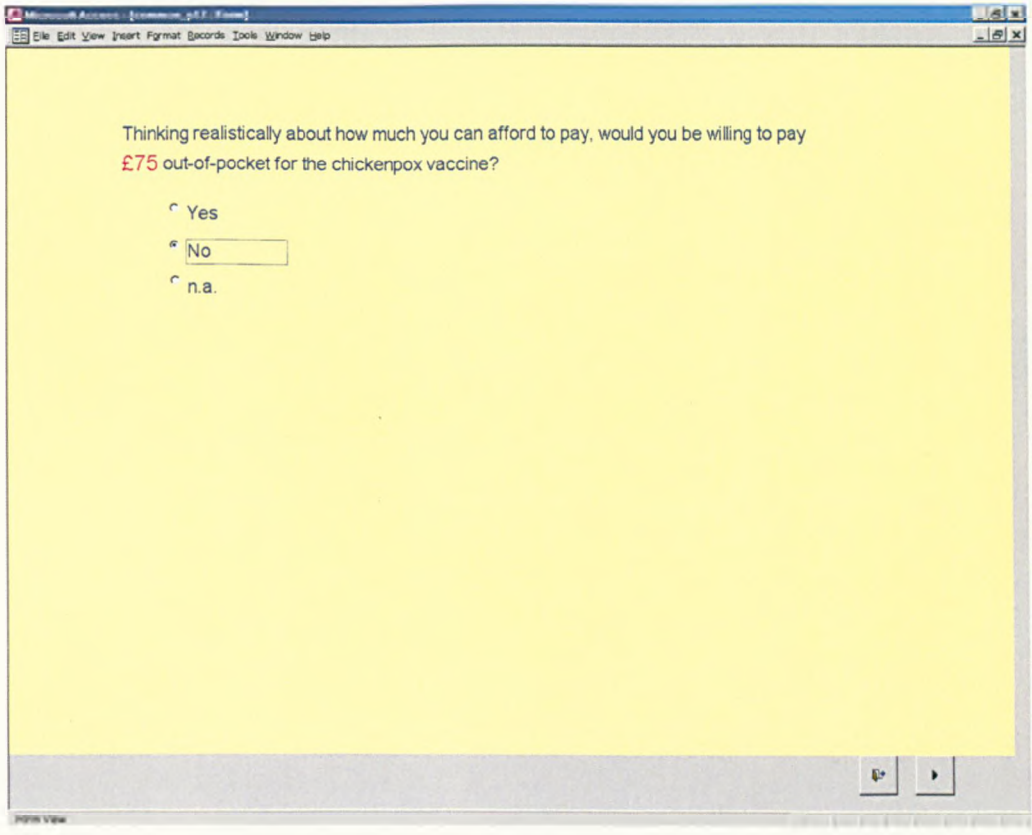


PART 6 - WILLINGNESS-TO-PAY QUESTION

WTP FOR TREATMENT



WTP FOR VACCINATION



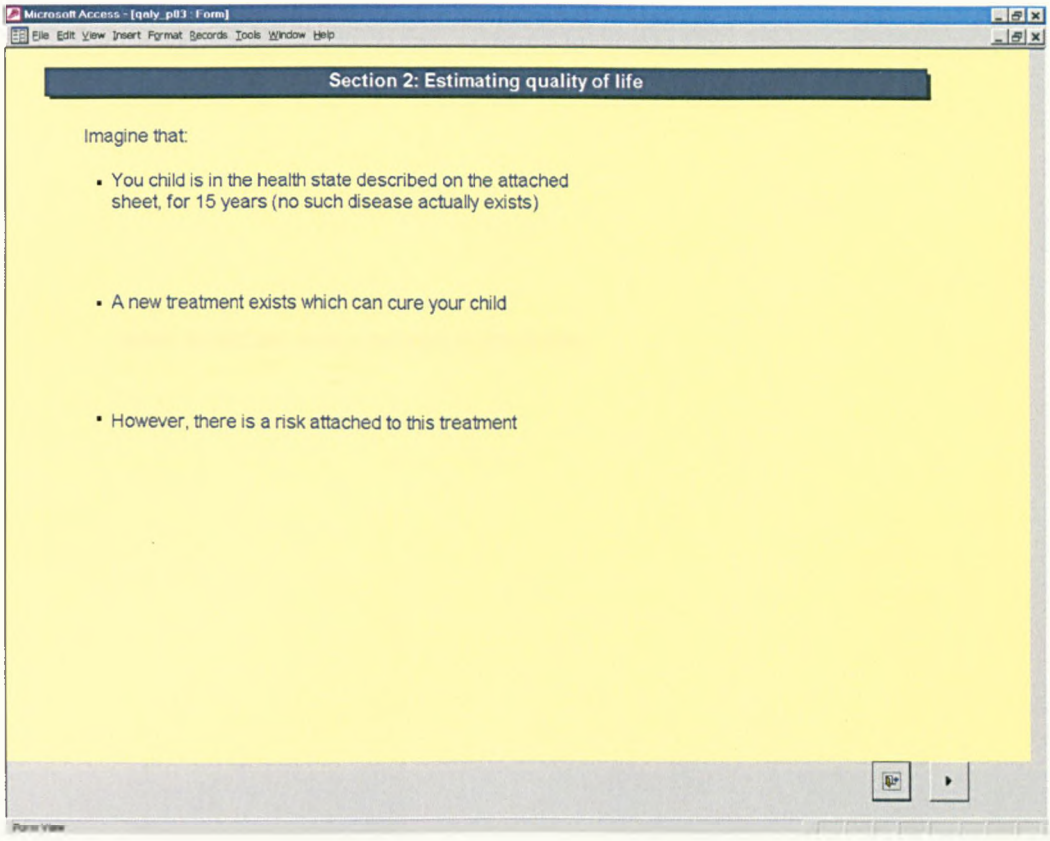
APPENDIX 9 - STANDARD GAMBLE QUESTIONNAIRE

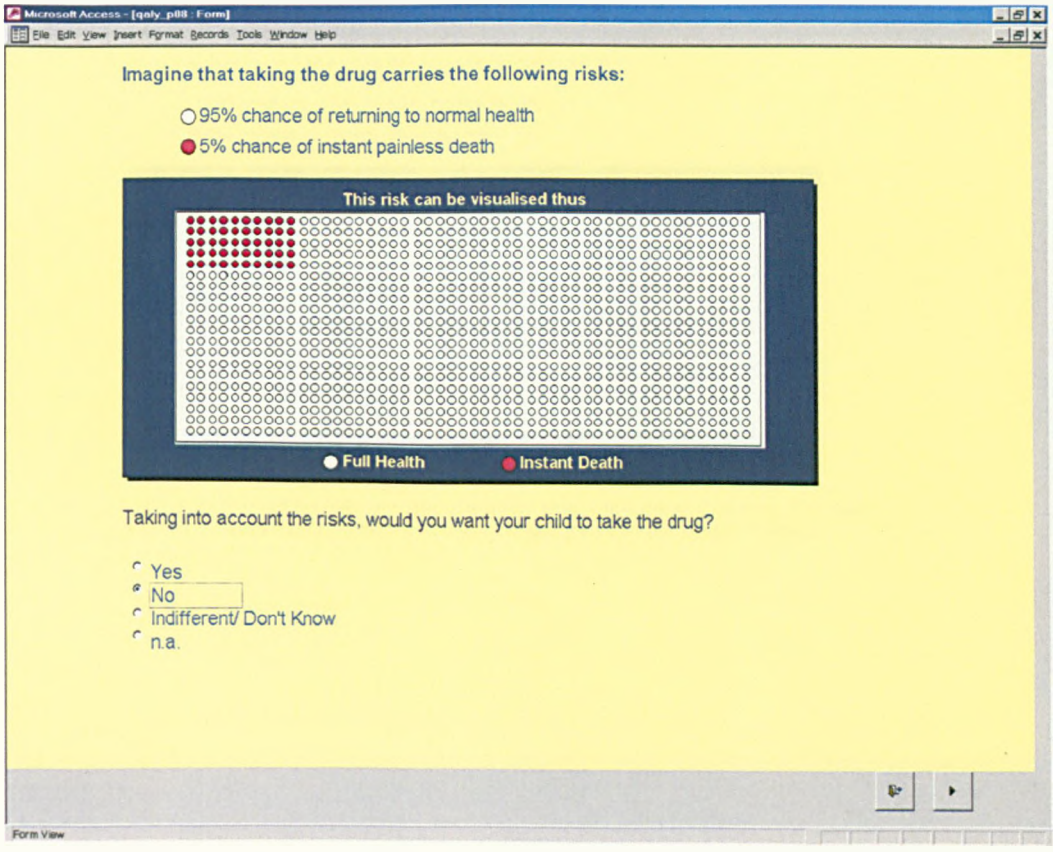
PART 1 - DISEASE DESCRIPTION CARD

Description of the Imaginary Disease

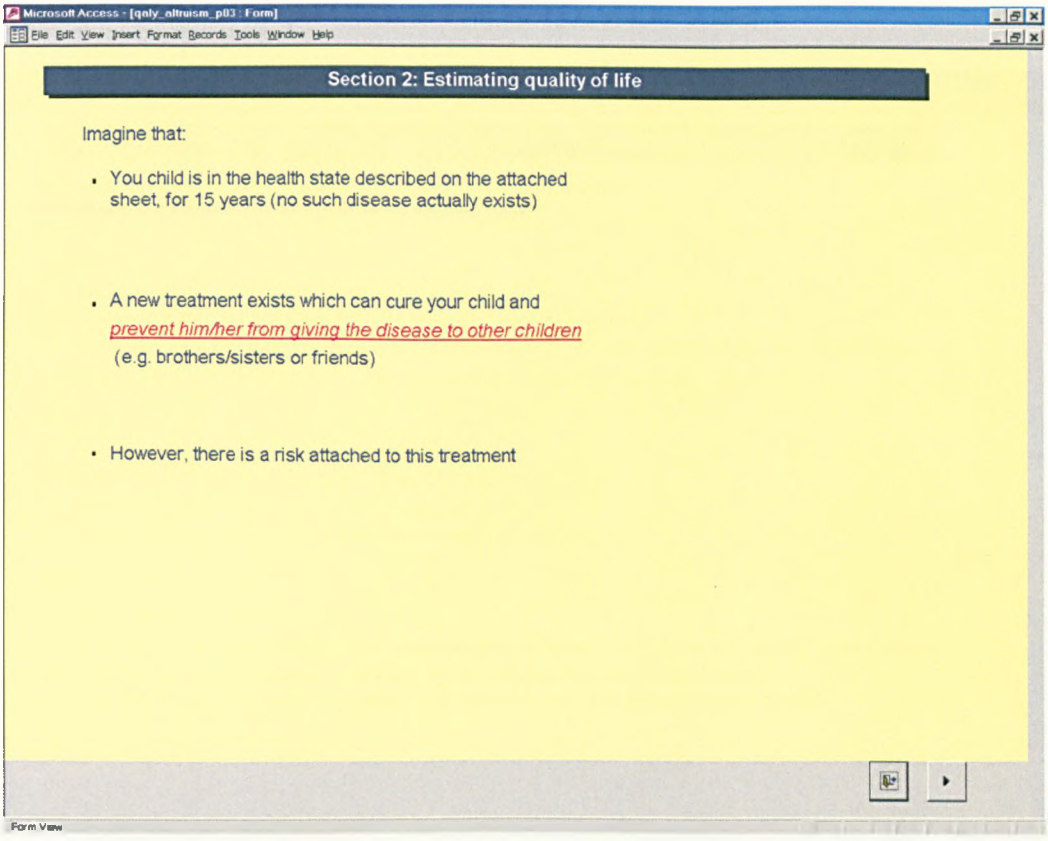
- The disease lasts for 15 years
- During this time, your child:
    1. Is covered (face, body and arms) with up to 500 red spots that itch intensely, which is highly frustrating
    2. Has mild fever with cold-like symptoms
    3. Has problems sleeping
    4. Has no problems walking about
    5. Cannot go to school or day care
    6. Has problems with performing his/her usual activities (e.g. hobbies, sport, playing)

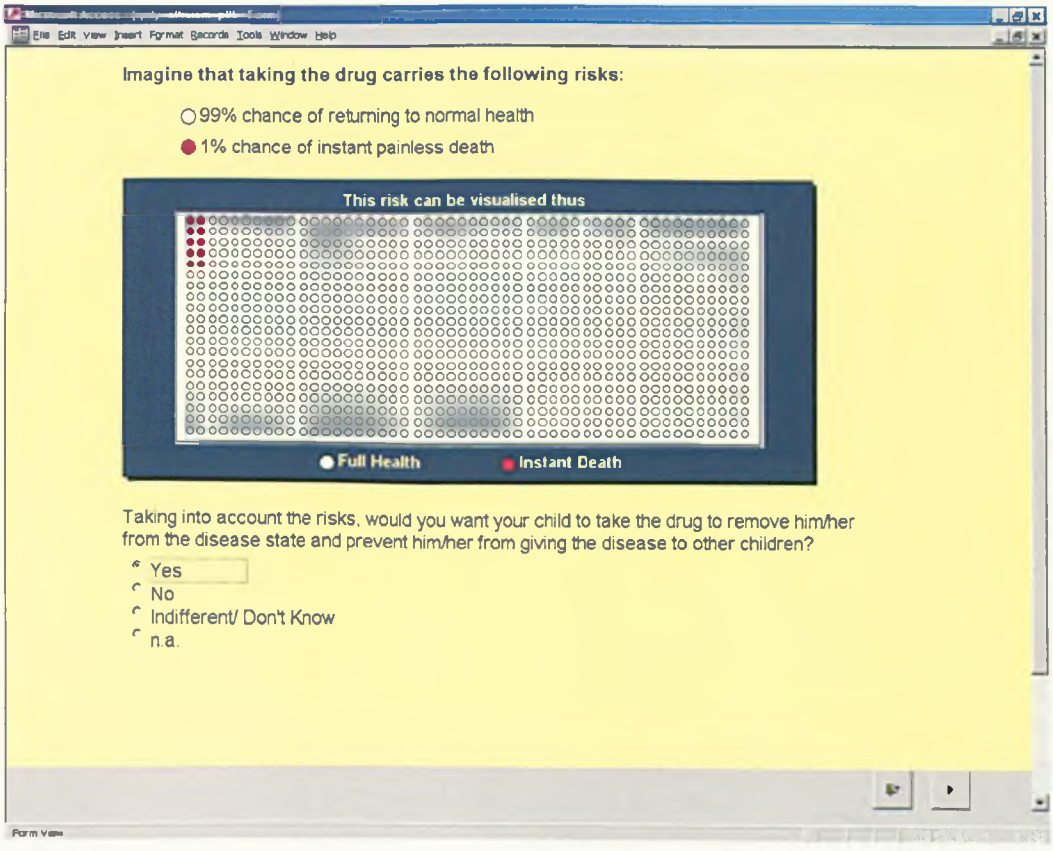
PART 2- STANDARD GAMBLE QUESTION - NO ALTRUISM



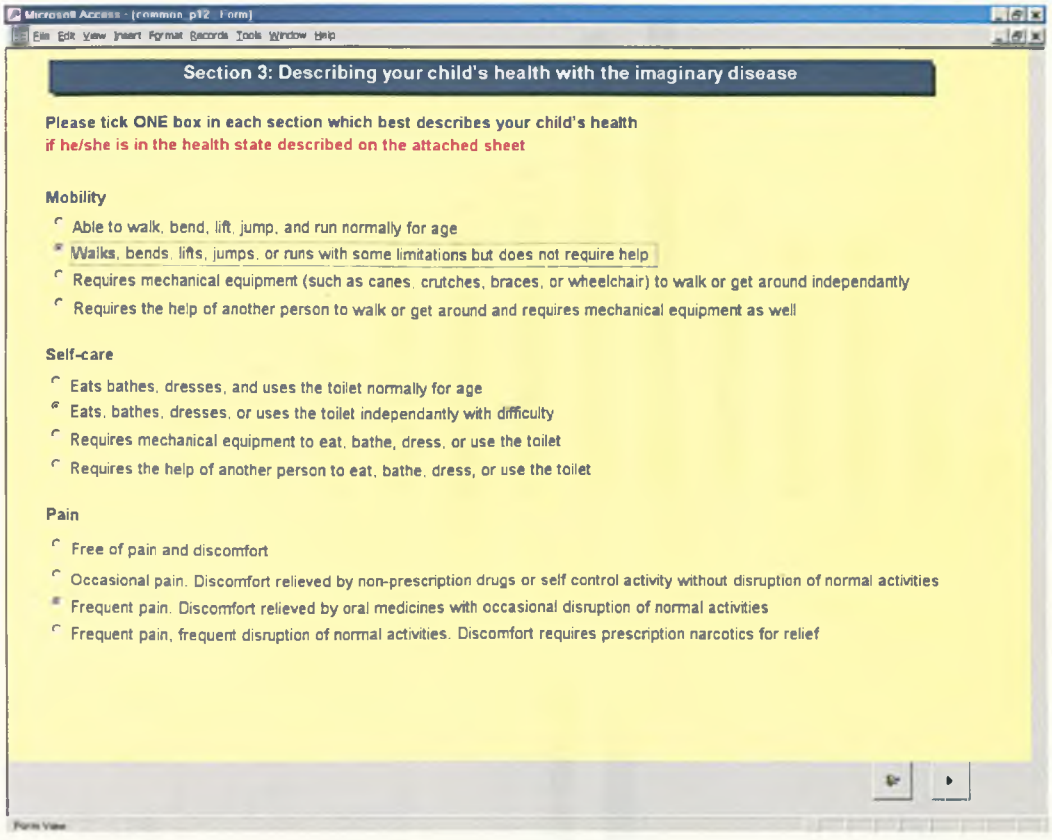


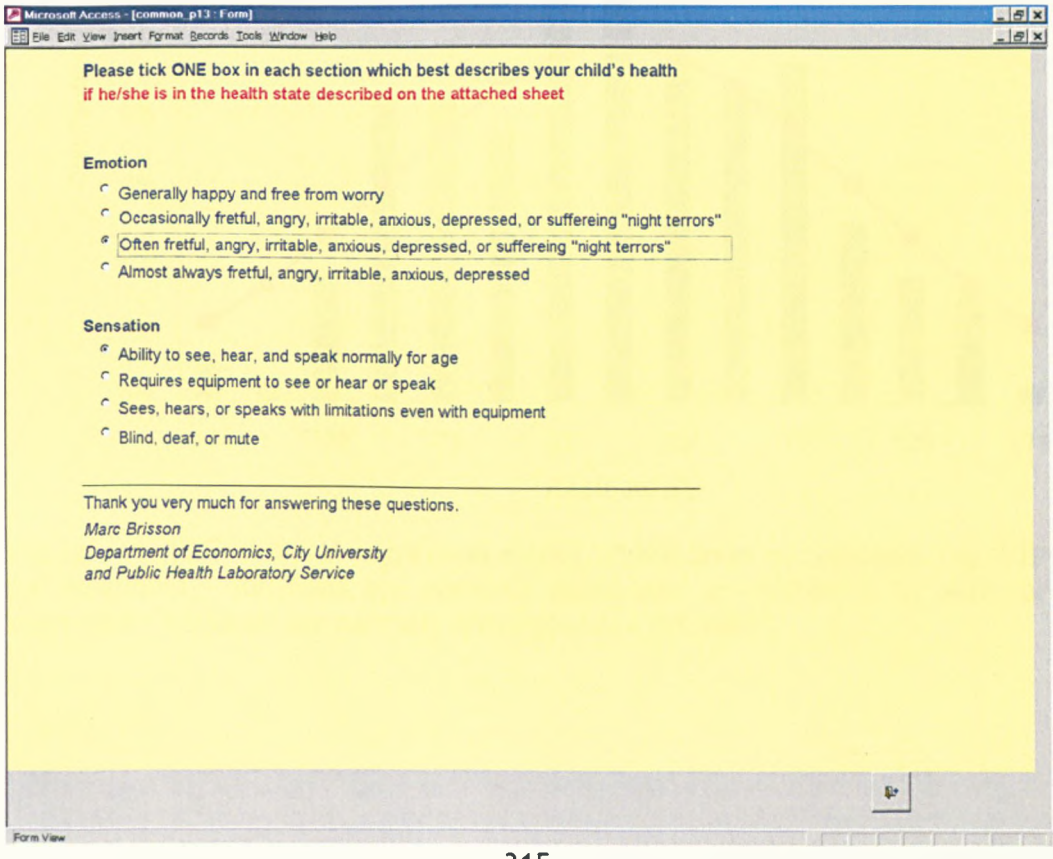
PART 3- STANDARD GAMBLE QUESTION - ALTRUISM





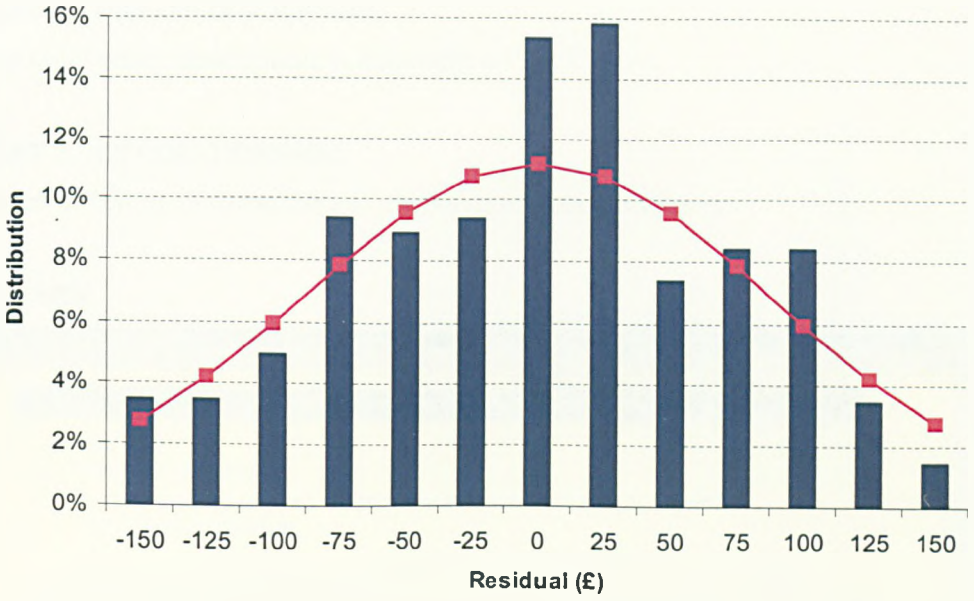
APPENDIX 10 - HEALTH UTILITIES INDEX MARK 2 (HUI2) QUESTIONNAIRE (AS USED IN THE SG QUESTIONNAIRE)





APPENDIX 11 - RESIDUAL DISTRIBUTION

a)



b)

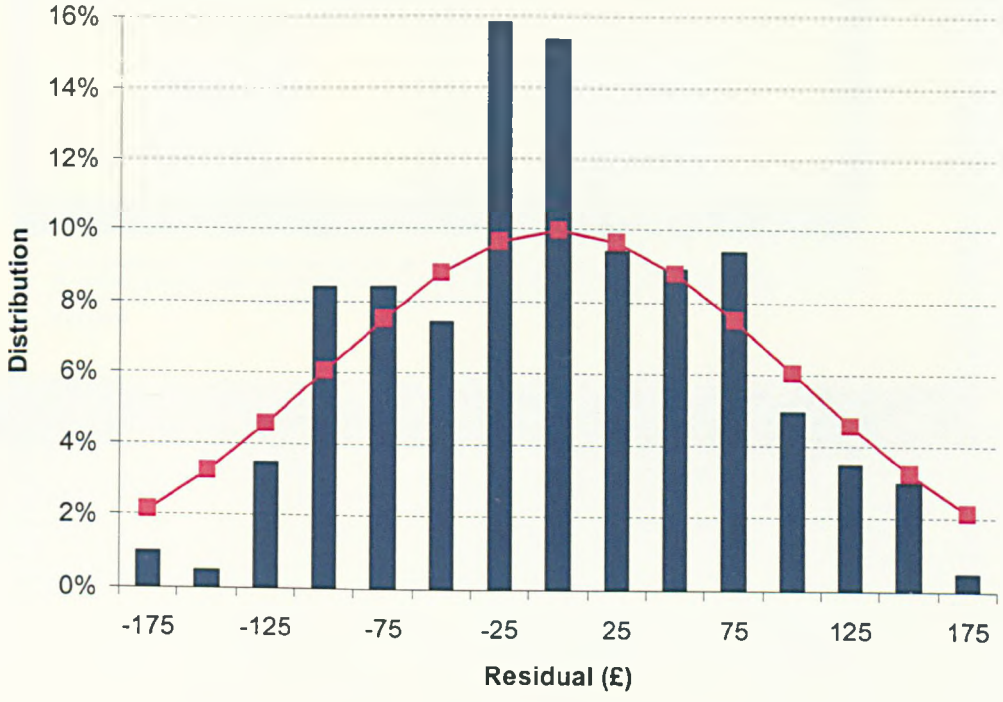


Figure A.1. WTP interval regression model, distribution of residuals. a) WTP for treatment - Residuals are normally distributed ($\varepsilon \sim N(0,89^2)$), b) WTP for treatment - Residuals are normally distributed ($\varepsilon \sim N(0,109^2)$).

APPENDIX 12 - CONTINGENT VALUATION QUESTIONNAIRE TO ASSESS RELATIONSHIP BETWEEN RISK OF DISEASE AND WTP

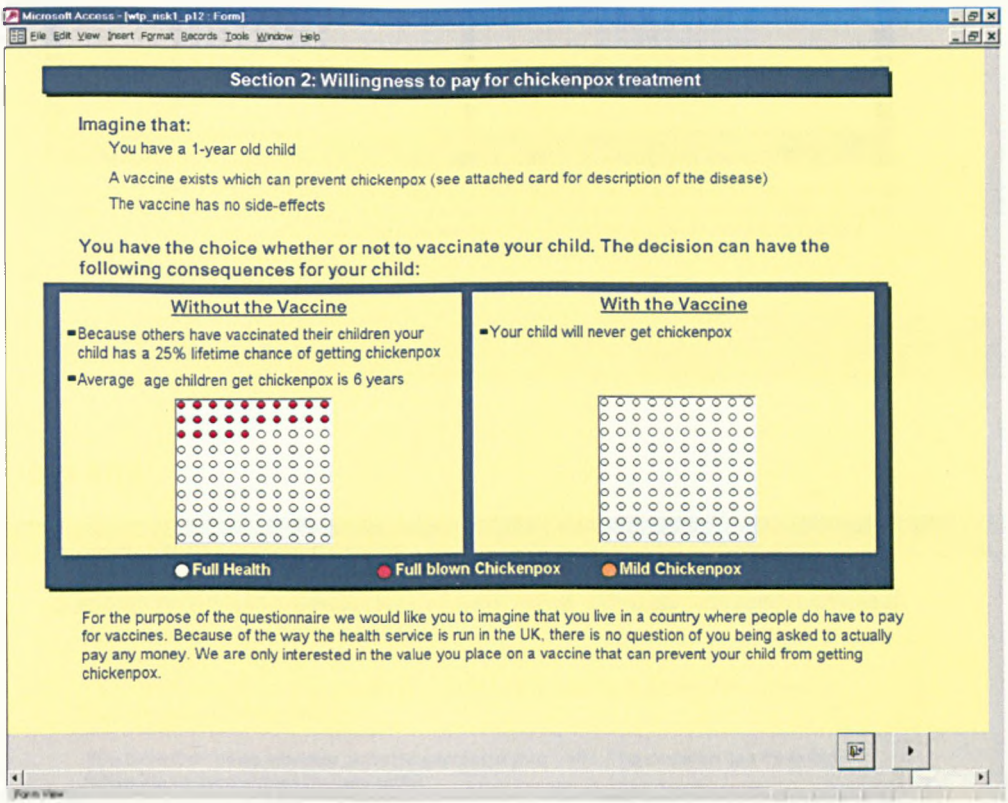
PART 1 - DISEASE DESCRIPTION.

See Chickenpox description in Appendix 8 - Part 1.

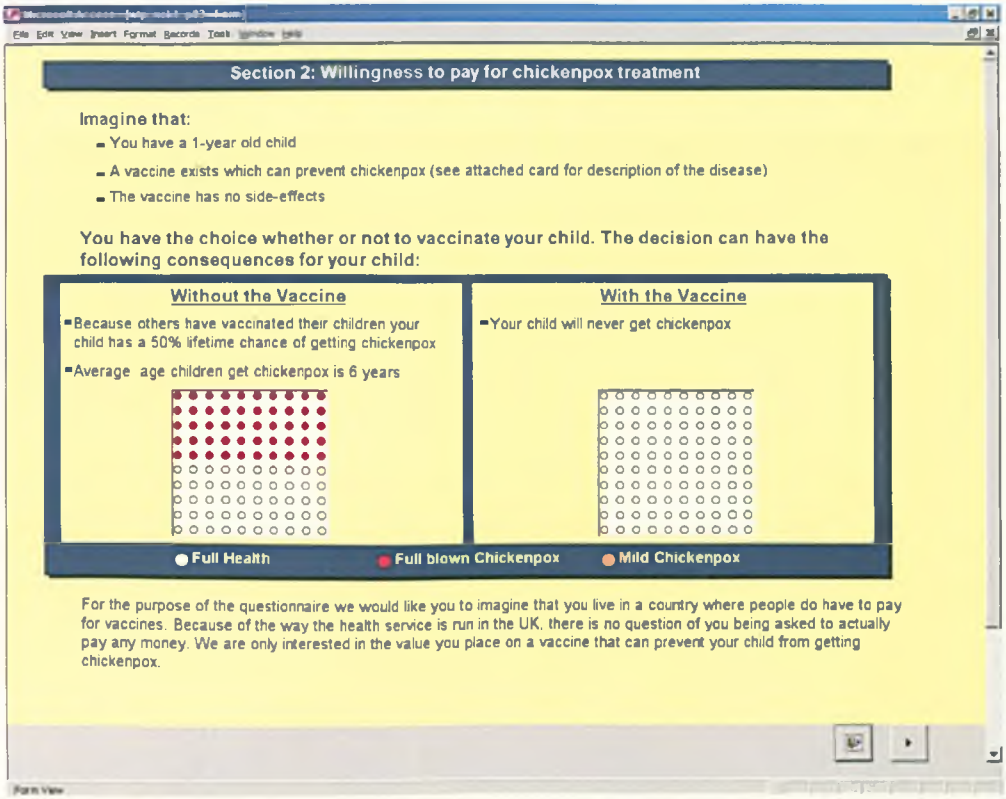
PART 2 - CV QUESTIONNAIRE

Three different lifetime risks of chickenpox were presented.

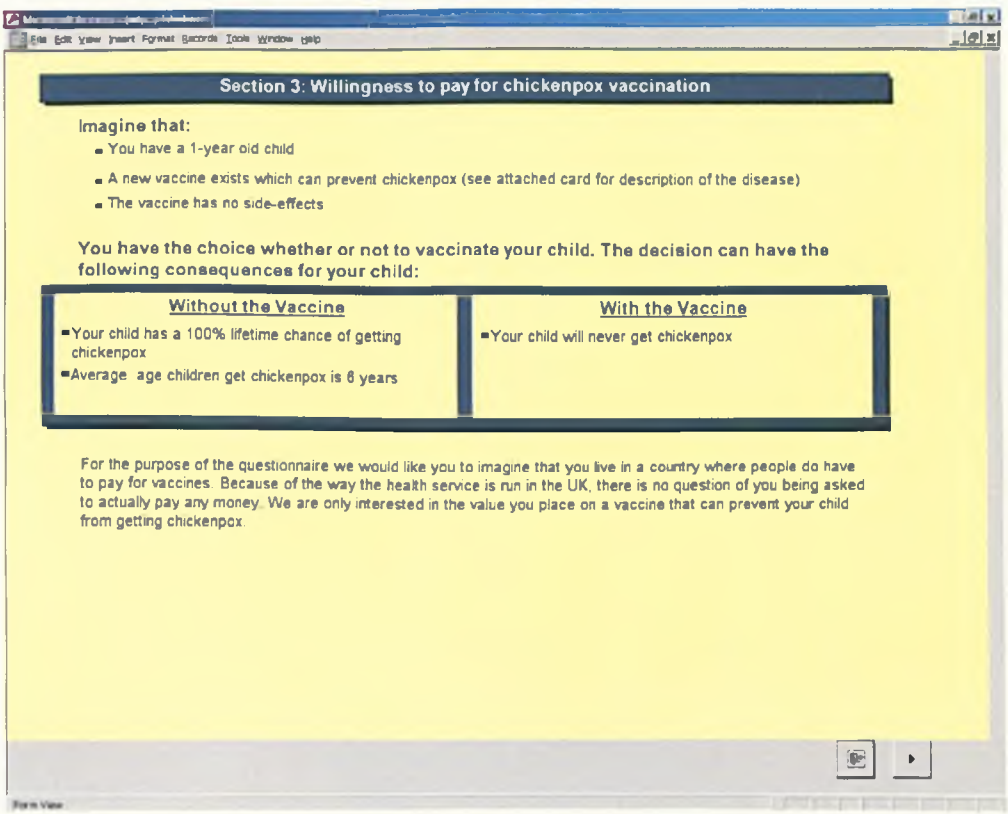
25% RISK



50% RISK

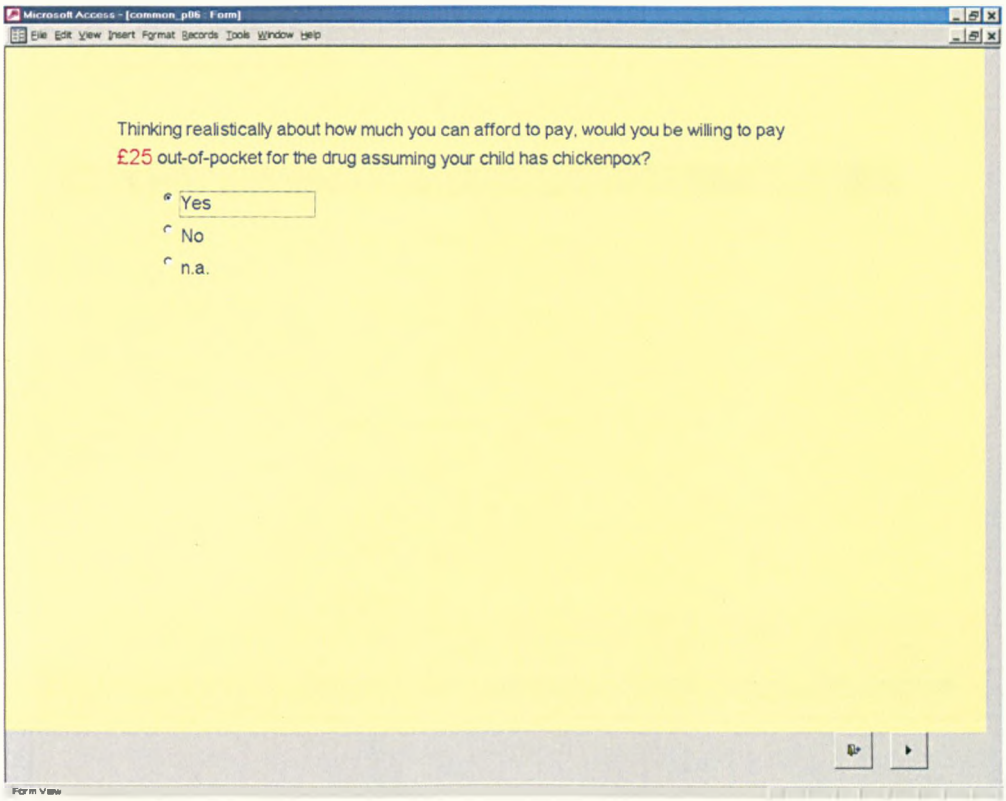


100% RISK

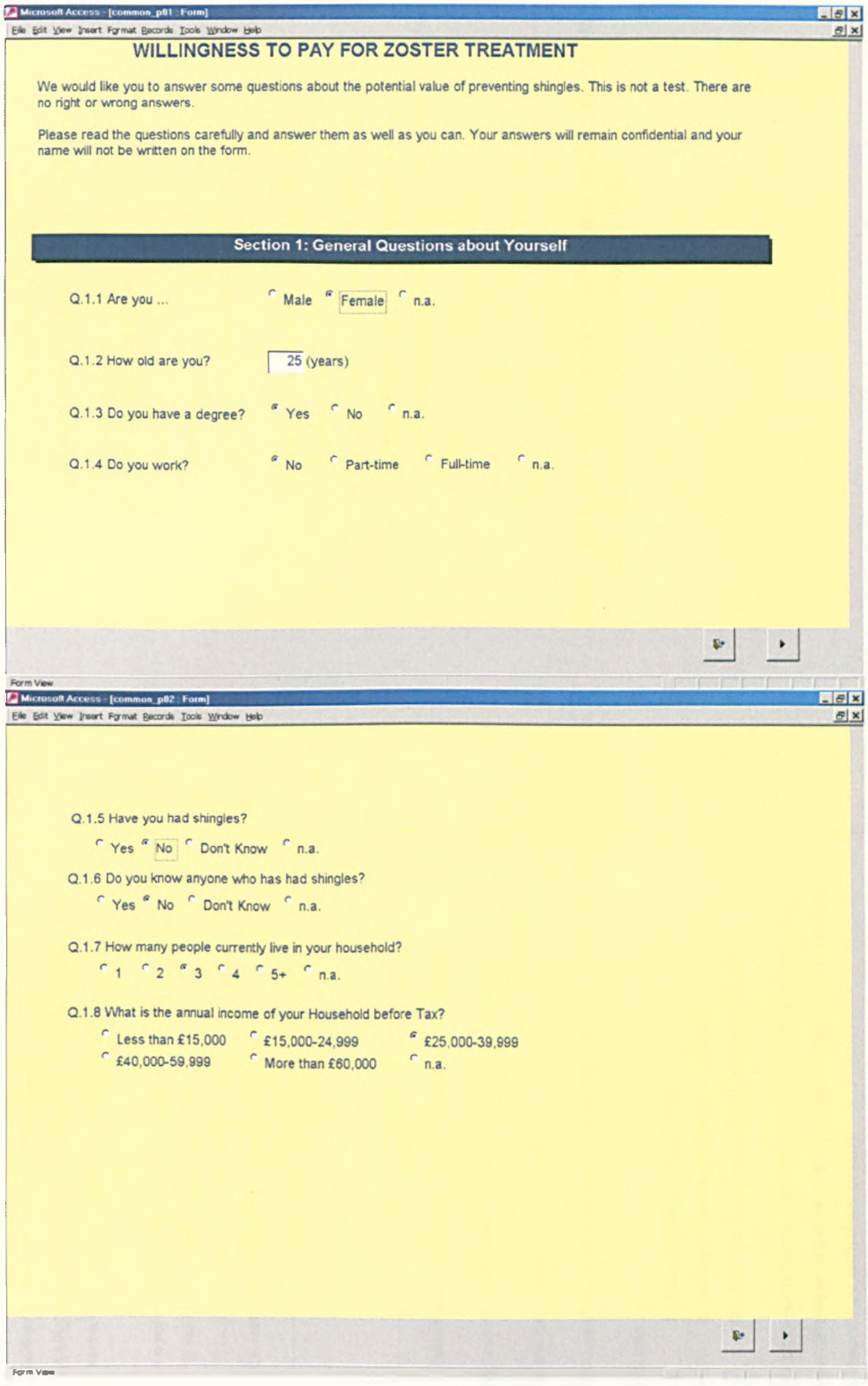


PART 3 - WILLINGNESS-TO-PAY QUESTION

The bidding scale used is identical to the one presented in Chapter 4 - Table 4.4.



APPENDIX 13 - CONTINGENT VALUATION QUESTIONNAIRE FOR ZOSTER AND PHN



Microsoft Access - [common_p01 : Form]

File Edit View Insert Format Records Tools Window Help

WILLINGNESS TO PAY FOR ZOSTER TREATMENT

We would like you to answer some questions about the potential value of preventing shingles. This is not a test. There are no right or wrong answers.

Please read the questions carefully and answer them as well as you can. Your answers will remain confidential and your name will not be written on the form.

Section 1: General Questions about Yourself

Q.1.1 Are you ... ○ Male ◉ Female ○ n.a.

Q.1.2 How old are you? 25 (years)

Q.1.3 Do you have a degree? ◉ Yes ○ No ○ n.a.

Q.1.4 Do you work? ◉ No ○ Part-time ○ Full-time ○ n.a.

Form View

Microsoft Access - [common_p02 : Form]

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Q.1.5 Have you had shingles?

○ Yes ◉ No ○ Don't Know ○ n.a.

Q.1.6 Do you know anyone who has had shingles?

○ Yes ◉ No ○ Don't Know ○ n.a.

Q.1.7 How many people currently live in your household?

○ 1 ○ 2 ◉ 3 ○ 4 ○ 5+ ○ n.a.

Q.1.8 What is the annual income of your Household before Tax?

○ Less than £15,000 ○ £15,000-24,999 ◉ £25,000-39,999
○ £40,000-59,999 ○ More than £60,000 ○ n.a.

Form View

PART 1 - SOCIO-ECONOMIC QUESTIONNAIRE.

A)

Description of mild Shingles

- Typically, shingles lasts for 2 weeks
- During this time you have:
  - Clusters of blister-like lesions in a strip-like pattern on your body (either on the back, chest, head or face)
  - A tingling, burning, pin-prick sensation in the affected area. Any contact with the affected area is uncomfortable.
- Some patients who have had mild shingles pain said:
  - "It feels like surges of pain from inside"
  - "It itches terribly, it drives me up the wall"
  - "It feels like someone has stuck a pin in me"

B)

Description of severe Shingles

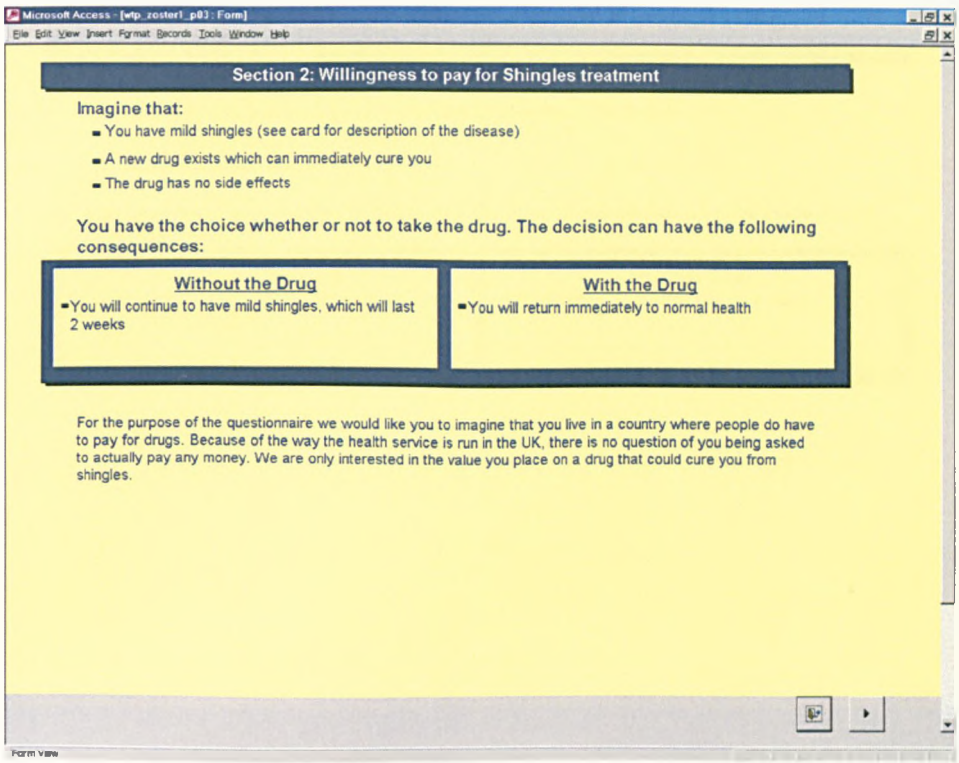
- Typically, shingles lasts for 2 weeks
- During this time you have:
  - Clusters of blister-like lesions in a strip-like pattern on your body (either on the back, chest, head or face)
  - A constant, excruciating pain, like electrical shock.
- Shingles patients often cannot:
  - sleep
  - concentrate
  - perform common household tasks.
- Some patients who have had **severe** shingles pain said:
  - "I've never had so much pain in my life"
  - "It hurts so much I can't keep still, all I can do is pace."
  - "I've passed kidney stones and this is comparable."
  - "I don't enjoy life as much anymore – it interferes with my life style."

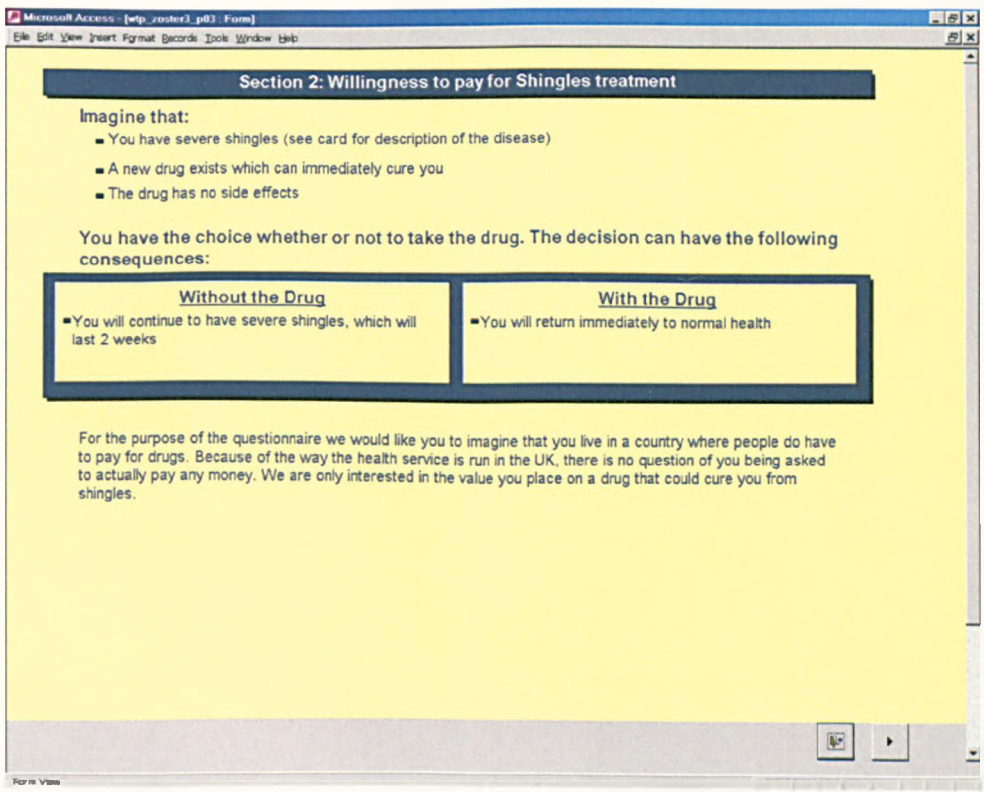
C)

Description of Post-Herpetic Neuralgia (PHN)

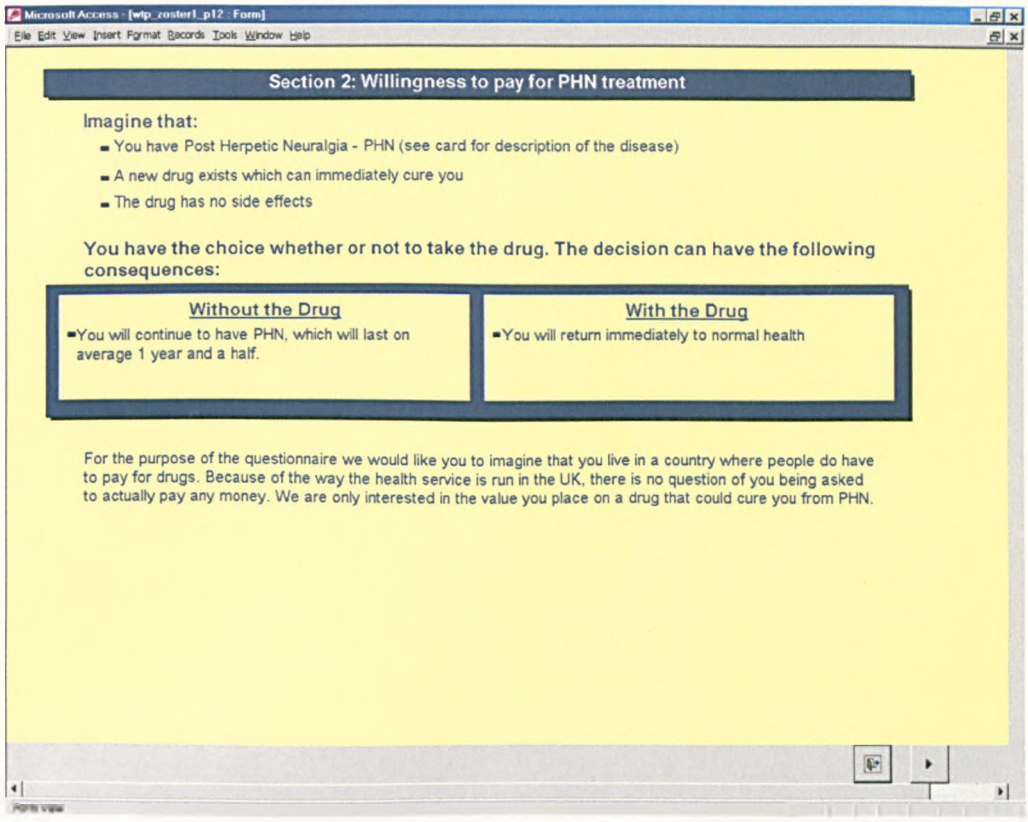
- PHN occurs in individuals who's shingles rash has healed.
- On average, PHN lasts for 1.5 year.
- PHN causes pain where shingles initially appeared.
- PHN pain can:
  1. be continuous or intermittent
  2. be sharp, burning, throbbing or stabbing.
  3. interfere with daily routines and quality of life.
- The skin may be unusually sensitive to even the lightest touch (as from clothing or bed sheets), to the smallest breeze, and to changes in temperature (either hot or cold).

PART 2A,B,C - DISEASE DESCRIPTION CARDS FOR A) MILD ZOSTER, B) SEVERE ZOSTER AND C) PHN





PART 2D -CV QUESTIONNAIRE FOR MILD AND SEVERE ZOSTER.



PART 3 - CV QUESTIONNAIRE FOR PHN.