Impact of Model, Methodological, and Parameter Uncertainty in the Economic Analysis of Vaccination Programs

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Guidelines for economic evaluations insist that the sensitivity of model results to alternative parameter values should be thoroughly explored. However, differences in model construction and analytical choices (such as the choice of a cost-effectiveness or cost-benefit framework) also introduce uncertainty in results, though these are rarely subjected to a thorough sensitivity analysis. In this article, the authors quantify the effect of model, methodological, and parameter uncertainty, taking varicella vaccination as an example. They used 3 different models (a static model, a dynamic model that only looks at the effect of vaccination on varicella, and a dynamic model that also assesses the implications of vaccination for zoster epidemiology) and 2 forms of analysis (cost-benefit and cost-utility). They also varied the discount rate and time frame of analysis. Probabilistic sensitivity analyses were performed to estimate the impact of parameter uncertainty. In their example, model and methodological choice had a profound effect on estimated cost-effectiveness, but parameter uncertainty played a relatively minor role. Under cost-utility analysis, the probabilistic sensitivity analysis suggested that there was a near certainty that vaccination dominates no vaccination, or the other way around, depending on model choice and perspective. Under cost-benefit analysis, vaccination always appeared to be attractive. Thus, the authors clearly show that model and methodological assumptions can have greater impact on results than parameter estimates, although sensitivity analyses are rarely performed on these sources of uncertainty. ***Key words:*** *probabilistic sensitivity analysis; uncertainty analysis; model uncertainty; methodological uncertainty; vaccination.* ***(Med Decis Making 2006;26:434–446)***

Most economic evaluations use modeling to predict and compare the potential costs and benefits of alternative health interventions. Models are a simplified description of the underlying processes leading to disease and resource utilization and provide a formal framework to synthesize information from various sources.[1] The process of model development and parameterization requires choices and assumptions to be made regarding 1) the model type and structure, 2) economic methods, and 3) the parameter values that should be used. Each of these choices introduces uncertainty[2-4] that ideally should be described and quantified for policy makers to have the appropriate information on which to make decisions. Here, we concentrate on the choices that lead to decision maker uncertainty (i.e., uncertainty regarding conclusions drawn from results of economic evaluation). Although many guidelines exist and are quite clear on how economic analysis should be conducted[5-8] and how the quality of decision analytic models should be assessed,[1,9,10] they are not exhaustive (particularly in the field of infectious disease prevention[11]) and still many studies do not follow them completely. It is therefore important

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that sources of uncertainty be illustrated, quantified, and discussed to help decision makers and analysts better understand the impact of analytic choices.

In this article, we discuss and illustrate the different sources of uncertainty and their relative impact in the context of model-based economic analyses of mass vaccination. We quantify, to our knowledge for the first time, the effect that these different sources of uncertainty can have.

These sources of uncertainty are expanded on below, with particular reference to vaccination programs (the example used in this study).

Parameter uncertainty arises owing to uncertainty in the choice of parameter values.[2-4] Parameters included in models are biological, demographic, epidemiological, medical, and economic in nature. Examples of parameters are transition rates between disease states, health outcomes (e.g., quality-adjusted life years [QALYs] lost), health care resource utilization, and costs. Sensitivity analyses, usually univariate, and increasingly probabilistic (usually multivariate) sensitivity analyses, are normally performed on parameter values. Indeed, all guidelines for cost-effectiveness analyses require that parameter uncertainty be explored in some way.[2,12-14]

Model uncertainty relates to the type of model and structure (e.g., choice of disease states) that are chosen in an analysis.[2-4] Mass vaccination can produce complex indirect effects that require the modeling of infection and transmission (not just natural history of disease), and thus the type of model used can be critical.[11,15-17] Although there are many types of models that are used to predict the impact of vaccination, they can be broken down into 2 main categories: 1) dynamic and 2) static (usually decision analysis or cohort models). The major difference between these types of models is that dynamic models capture the indirect protection resulting from immunization (herd immunity effects), whereas static models omit them (see Brisson and Edmunds[15] for more details). Currently, most economic evaluations of vaccination programs use static models.[15] Within these broad frameworks of "static" and "dynamic" models, there is further uncertainty about the choice of the appropriate model structure.[2] Although there is great variability and uncertainty surrounding modeling choices, sensitivity analysis is very rarely performed on the model type and structure.

Methodological uncertainty arises from differences in the methodology that can be used in economic evaluation.[3,4] Examples of methodological choices are type of analysis (cost-benefit [CBA], cost-effectiveness [CEA], or cost-utility [CUA]), the perspective (societal or payer), valuation technique (e.g., willingness to pay, standard gamble, multiattribute utility scores), discount rate, and time horizon. Because of its unique characteristics, vaccination may possess its own specific benefits (e.g., altruism, insurance-type benefits), which may influence which intervention outcome, valuation technique, and type of analysis should be performed.[18,19] Although QALYs have been found to be a more sensitive measure to life years gained, there is evidence that they cannot capture all the benefits of vaccination that are important to vaccinees (see Brisson and Edmunds[18] for more details). Such arguments have resulted in an increase in the interest of the willingness-to-pay method and thus CBA.[19] Furthermore, in the economic evaluation of vaccination, the choice of discount rate and time horizon has a greater impact on results than curative interventions against noninfectious disease. First, because vaccination is a preventive intervention, costs of the program are incurred at the moment of vaccination whereas cost offsets and benefits occur in the future. Second, the introduction of mass vaccination can produce long-term nonlinear dynamic effects.[15] Although it is relatively common for analyses to present different analytical perspectives and present results in discounted and undiscounted form, sensitivity analysis is rarely performed on the type of analysis (CBA/CUA/CEA) and time horizon.

The aim of this article is to illustrate the importance of the different sources of uncertainty in the economic evaluation of immunization programs, using routine varicella (chickenpox) vaccination as an example.

Varicella-zoster virus (VZV) produces 2 distinct diseases: varicella (chickenpox) and herpes zoster (shingles).[20] Varicella results from primary infection with VZV. After infection, the virus establishes a latent infection in nerve cells and can reactivate later in life to cause zoster.[20] Two main public health concerns have limited the widespread introduction of the vaccine. First, through herd immunity, 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). Second, mass vaccination could increase the incidence of zoster. It has been suggested that exposure to varicella reduces the risk of reactivation (zoster) by boosting specific immunity to the virus.[20-22] If this is the case, by reducing varicella cases (and thus the opportunity of exposure to VZV), mass vaccination could increase the incidence of zoster in unvaccinated individuals.[21,23-26]

These concerns can clearly have an impact on the economic desirability of varicella vaccination.

Of the 12 economic evaluations of infant varicella vaccination published before 2004,[23,27-37] 5 used dynamic models, which incorporate herd effects including potential age shifts,[23,27-29,30] and only 2 examined the impact of vaccination on zoster.[23,30] Although it is clear from guidelines on good practice for decision analytic modeling that dynamic models should have been used and the impact of zoster should have been examined. A dynamic model should have been used as varicella is infectious and should be modeled as such (i.e., "Structure of models should be consistent with a coherent theory of the health condition"[1]). The impact of vaccination on zoster should have been modeled, even though understanding of the natural history of varicella and zoster is incomplete (i.e., "If evidence regarding structural assumptions is incomplete and there is no universally accepted theory of disease process, then the limitations of the evidence supporting the chosen model structure should be acknowledged-if possible, sensitivity analyses using alternative model structures should be performed"[1]). Additionally, 1 out of 12 economic analyses of infant varicella vaccination, published before 2004, performed a cost-utility analysis[23] and 9 had a base-case time horizon of 30 years or less,[27-30,32-37] which does not capture the long-term impact of vaccination. This illustrates that although guidelines are clear, they are rarely abided by. The differences in parameter values, model construction, and analytic choice resulted in a wide range of results (from cost-savings to incremental losses in overall quality of life), which introduced uncertainty for decision makers. Here, we illustrate the relative impact of the different sources of uncertainty.

METHODS

For our illustrative examples, we assess the health economic desirability of routine varicella vaccination of 1-year-old children compared with the current strategy (no vaccination: current strategy in England and Wales). We only investigate infant vaccination and assume 90% coverage. In previous studies,[23-25] we show that other strategies such as catch-up programs in young children and vaccine coverage of 70% to 95% produce similar results to those presented here.

Simulations were performed for a population with characteristics similar to England and Wales. The population size and average life expectancy were assumed to be 50 million and 75 years, respectively. The overall impact of vaccination was calculated by aggregating the discounted QALYs gained (lost) over no vaccination and the overall additional net present value of the vaccination program as calculated using aggregate willingness to pay estimates (divided by half, was recommended by the American National Oceanic and Atmospheric Administration [NOAA] Panel[38]). See the appendix for a formal description of aggregation methods and parameter values.

Parameter Uncertainty

All base-case parameters describing epidemiological and demographic variables, health outcomes, and costs were taken from Brisson and colleagues.[23,24] 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 triangular probability distributions (see Brisson and Edmunds[23] for data sources and justification of input parameter distributions). 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 the appendix.

Model Uncertainty

To illustrate the impact of model choice on results, 3 different models are used that illustrate the impact of choosing a static or a transmission dynamic model, and also the importance of incorporating other aspects of the epidemiology (in this case, the inclusion of the impact of vaccination against chickenpox on herpes zoster [shingles]).

Static versus dynamic. To illustrate the sensitivity of results to incorporating herd immunity effects (externalities), we compare results from a dynamic model with those of a static model. The dynamic model used here is the realistic age-structured deterministic model presented in Brisson and colleagues[23-25] (see the appendix for a mathematical description of the model). The single difference between the static model and the dynamic model, used here, is that per susceptible rate of infection (sometimes termed the force of infection) in the static model is 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,

$$\lambda = \text{fixed} \quad \text{(static)}$$
$$\lambda(t) = \beta I(t) \quad \text{(dynamic)}$$

where λ is a $(1*k)$ vector representing the force of infection in each of the k age groups, β 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 aging cohort, 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.

Model structure. Mass vaccination could increase the incidence of zoster in unvaccinated individuals,[21,23-26] which can have an impact on the economic desirability of varicella vaccination. To illustrate the sensitivity of results to model structure and the importance of performing sensitivity analysis on all potential effects of the intervention, we compare results from a model that incorporates the natural history of zoster to one that does not (model structures are presented in Brisson and colleagues[25]). All epidemiological model parameter values were taken from Brisson, Edmunds, and Gay[24].

Methodological Uncertainty

Perspective of analysis. The base case perspective is that of the health care provider (National Health Service [NHS]), which includes all direct medical costs including physician contacts, hospitalizations, and prescription medications. We also present results from the societal perspective, which includes all medical and work loss costs as well as household expenditures.

Analytic technique. CUA and CBA are chosen as analytic techniques (the results of CEA are similar to CUA in most—though not all—respects[39] and are omitted for ease of exposition). The summary measures are the cost per QALY gained and cost per benefit (as measured by willingness to pay [WTP][18]). The National Institute for Clinical Excellence (NICE) have stated that their "range of acceptable cost-effectiveness" is between £20,000 and £30,000 per QALY gained,[40] although Devlin and Parkin[41] have analyzed decisions made by NICE and suggest that their cost-effectiveness threshold may be higher. We take the conservative estimate of £30,000 per QALY gained as being the limit below which vaccination is regarded, here, as being cost-effective. The threshold for cost-benefit is 1.

Discount rate. In the base case, future costs and outcomes are discounted at 3%.[2] In the sensitivity analysis, results are also presented with health benefits undiscounted and costs discounted at 3%.

Time horizon. Costs and benefits are presented over an 80-year time horizon (base case). We further present results with a 30-year time horizon.

RESULTS

Unless stated otherwise, results are from the NHS perspective, and vaccine efficacy, vaccine coverage, and duration of immunity to zoster are held at their base-case values. All other parameters are varied simultaneously according to their assigned probability distributions. The time frame of analysis is assumed to be 80 years, and discount rates are 3% per annum for benefits and costs.

Parameter Uncertainty

Figure 1 shows the results of the probabilistic sensitivity analysis of the cost-effectiveness of varicella vaccination from the perspective of the health care provider. The model is static and excludes the possible effect on zoster (most economic analyses of varicella have these features[42]). The solid line shows the cost per QALY threshold value (£30,000 per QALY gained). Each point represents the result of 1 simulation plotted on the cost-effectiveness plane. It is clear from the figure that every simulation resulted in a net cost to the health service but also resulted in a net gain in public health (measured in QALYs). In virtually all of the simulations, the resulting cost per QALY gained was less than the £30,000 threshold (below the line) and would therefore be deemed cost-effective, taking this simple decision rule. Following standard techniques,[3,43] a cost-effectiveness acceptability curve can be derived from the data shown in Figure 1 by assessing the proportion of simulations below the acceptable limit for a variety of threshold values (lines of differing slopes). This is shown in Figure 2, and it suggests that more than 90% of simulations would be deemed cost-effective even at a threshold value of £20,000 per QALY gained. Thus, using the most commonly used model and performing a full probabilistic sensitivity analysis, the results are quite clear: Vaccination is highly likely to be deemed cost-effective at the commonly accepted NICE threshold values.

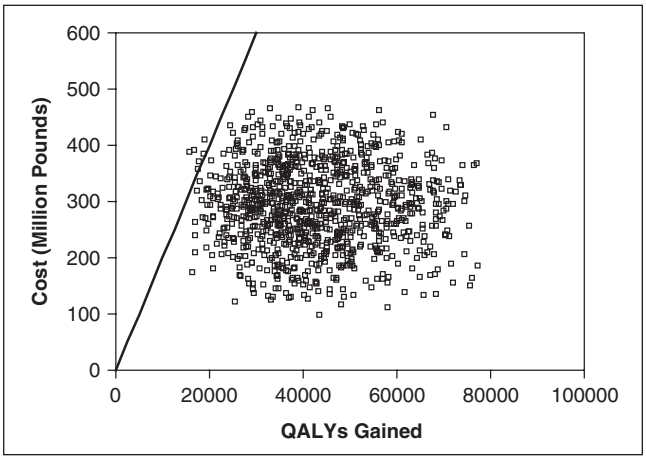

Figure 1 Parameter uncertainty. Results of the multivariate probabilistic sensitivity analysis presented on the cost-effectiveness plane using the National Health Service perspective. Results are from the static model and exclude zoster outcomes. QALY = quality-adjusted life year.

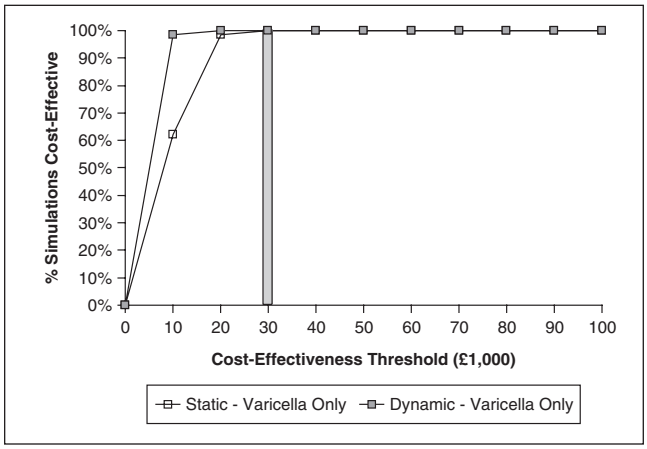

Figure 2 Model uncertainty: dynamic vs. static. Cost-effectiveness acceptability curves for different model types (dynamic and static model) excluding zoster. Results are from the National Health Service perspective.

Model Uncertainty: Dynamic versus Static

Figure 2 also shows a cost-effectiveness acceptability curve using the transmission dynamic model. This demonstrates that if a model is used that can capture the reduction in circulating virus following vaccination and thus the reduced risk of infection in the unimmunized fraction of the population, then vaccination is more likely to be deemed cost-effective (more than 90% of simulations are below £10,000 per QALY gained). The difference between the dynamic and the static model results can be interpreted as the impact of herd immunity on cost-effectiveness. Although herd immunity effects do not seem to have a substantial impact on the illustrative example presented here, it has a significant impact on the estimated cost per life-year gained[39] and on the estimated epidemiological impact of varicella vaccination.[15]

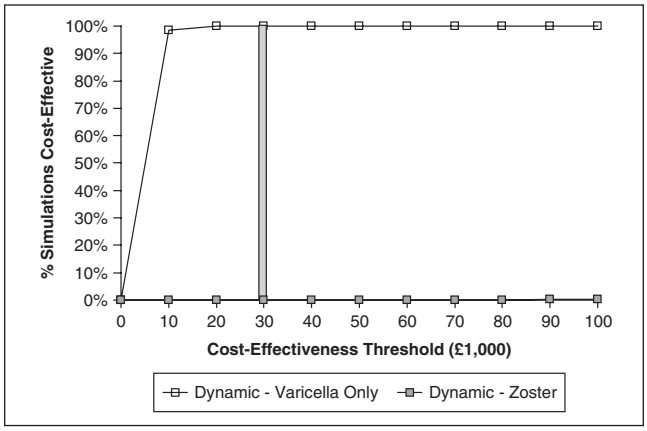

Figure 3 Model uncertainty: inclusion of effect on zoster. Cost-effectiveness acceptability curves for different model structures (excluding and including zoster) using the dynamic model. Results are from the National Health Service perspective.

Model Uncertainty: Inclusion of Effect on Zoster

Figure 3 compares cost-effectiveness acceptability curves for the 2 dynamic models: the one that ignores the possible impact of vaccination on zoster (as in Figure 2 and in Lieu and others[27], Coudeville and others28, and Banz and others[29]) and the model that includes this effect.[23] The results of the model including zoster suggest that there is very little chance of vaccination appearing cost-effective from the perspective of the health care provider, as virtually all simulations resulted in a loss of discounted QALYs (the results of the probabilistic sensitivity analyses for the dynamic models including and excluding the effect on zoster are given in Figure 4, red and blue symbols, respectively). The reduction in circulating virus is expected to result in an increase in zoster. As this is usually more severe than varicella, the vaccination program results in losses in health. Thus, model choice can have a profound effect on the estimated attractiveness of varicella vaccination.

Methodological Uncertainty: Perspective of Analysis

Figure 4 also shows how sensitive results are to the perspective taken. Ignoring the impact on zoster

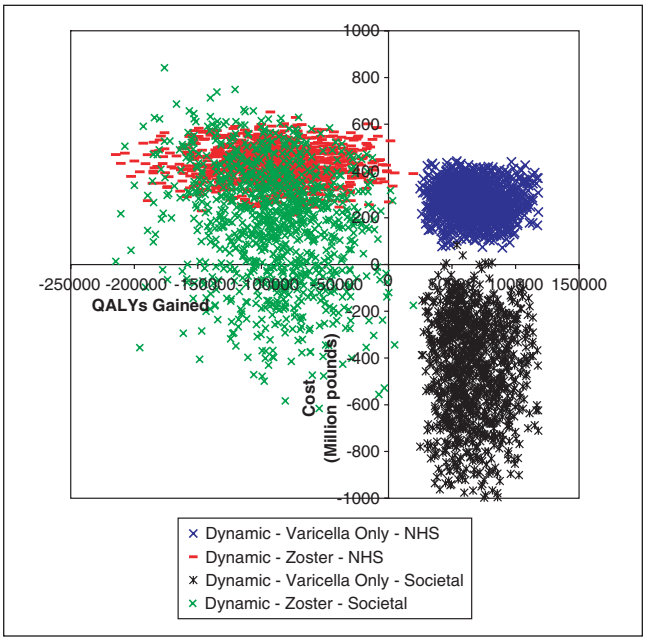

Figure 4 Methodological uncertainty: perspective of analysis. Results of the multivariate probabilistic sensitivity analysis including and excluding zoster from the analysis and using the societal and National Health Service perspectives presented on the cost-effectiveness plane. Results are from the dynamic model. QALY = quality-adjusted life year.

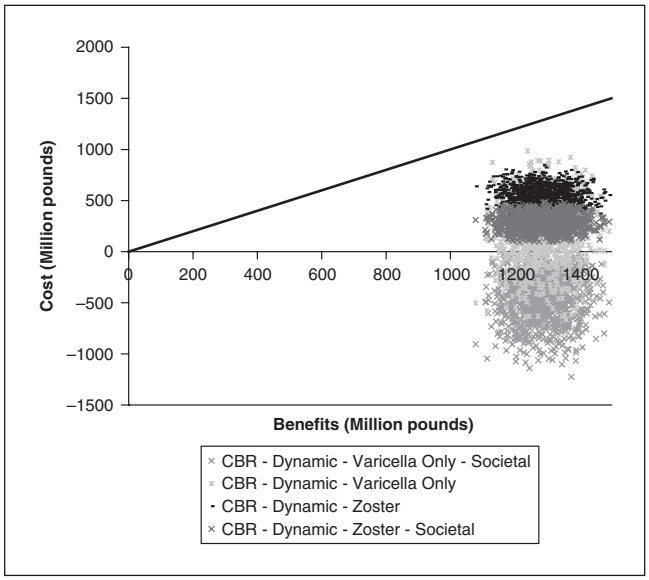

Figure 5 Methodological uncertainty: type of analysis. Results of the multivariate probabilistic sensitivity analysis including and excluding zoster from the analysis and using the societal and National Health Service perspectives presented on cost-benefit plane. Results are from the dynamic model. CBR = cost-benefit ratio.

(as most economic analyses of varicella vaccination have done[42]) and taking a societal perspective, the results of the probabilistic sensitivity analysis suggest that there is close to a 100% chance that vaccination dominates the current strategy, that is, vaccination will result in gains in health and a reduction in costs to society (gray symbols). The same model suggests, however, that there is highly likely to be a net cost to the NHS (blue symbols), though the estimated gains in health are likely to be deemed worth the extra costs (see earlier). The model inclusive of zoster suggests that there will be losses in health (see earlier). Note that a combination of model choice and perspective can result in exactly opposite conclusions (either vaccination is virtually certain to dominate the current strategy, or the other way around) but that the probabilistic sensitivity analysis has very little impact once a model and perspective have been chosen (in 3 of the 4 scenarios, virtually all of the points lie in the same quadrant of the cost-utility plane). That is, dependant on methodological assumptions, varicella vaccination can produce results in all 4 quadrants of the cost-utility plane, but the probabilistic sensitivity analysis has little impact on this.

Methodological Uncertainty: Type of Analysis

Figure 5 shows that the choice of analytic technique can produce conflicting results regarding the desirability of varicella vaccination. The likelihood of varicella vaccination resulting in a positive net present value under CBA is estimated to be 100% independently of whether the effects of vaccination on zoster are included in the analysis or not (all the points are below the line of equality regardless of model choice and perspective), even though the WTP results presented here were halved as recommended by the NOAA panel.[38]

Methodological Uncertainty: Time Frame and Discount Rate

In this example, shortening the time horizon has little impact on results of the CUA (Figure 6). The greatest impact on results occurs when the discount rate is reduced from 3% to 0%, because the increase in zoster following varicella vaccination is estimated to be a temporal phenomenon. Eventually (after 50 years or so[21,23,24]), the incidence of zoster is estimated to fall below the prevaccination level. Hence, when

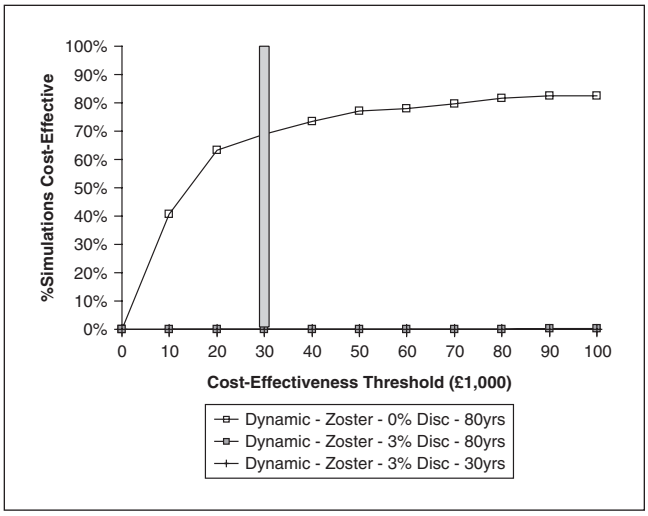

Figure 6 Methodological uncertainty: time frame and discount rate. Cost-effectiveness acceptability curves for different time frame of analysis and discount rates (0% Disc indicates that outcomes are undiscounted while costs are discounted at 3%; 30yrs indicates a time frame of 30 years; 80 yrs, that of 80 years [base-case]). Results are from the dynamic model including zoster outcomes.

the discount rate for benefits is very low (i.e., if time preference is such that short- and long-term benefits are valued equally), infant varicella vaccination is likely to be "cost-effective" (~70% of simulations are below the threshold of £30,000).

DISCUSSION

The aim of this article was to illustrate the importance of the different sources of uncertainty when performing economic analyses of vaccination programs. We clearly show that model and methodological assumptions can have equal or greater impact on results than parameter estimates, although sensitivity analysis is rarely performed on these sources of uncertainty.

The reduction in circulating virus following mass vaccination (herd immunity) can result in improved cost-effectiveness (as seems apparent from Figure 2 and Brisson and Edmunds[15]), but not always (Figure 3). The estimated increase in zoster incidence is a consequence of this herd immunity (reduced exposure to the virus resulting in reduced boosting of immunity to zoster). Most economic evaluations of vaccination programs ignore these herd immunity effects, often arguing that they are beneficial, so by ignoring them the analysis is conservative, or biased against immunization. This is not always the case. As we have demonstrated here and elsewhere,[15] they can result in unwelcome public health consequences that can have a profound effect on the economic attractiveness of vaccination programs (and perhaps other control programs aimed at infectious diseases). Even when analysts include these effects, the full range of their consequences should be explored. In our example, it is not sufficient to just look at their effect on varicella, which is generally beneficial (Figure 2), but also to look at the effects on zoster, which may be harmful to public health (at least in the short and medium term). In a review of economic evaluations of varicella vaccination published by 2002,[42] 10 studies were identified, 7 of which used a static model. Of the 3 that used a transmission dynamic model, only 1 included the effect that vaccination might have on zoster. There are many other types of positive and negative indirect effects that can be produced by vaccination.[15] For instance, a number of vaccines (e.g., pneumococcal conjugate vaccines and human papillomavirus virus [HPV] vaccine) are targeted at a limited number of circulating strains, hence vaccination might increase the occurrence of related strains that are currently being out-competed. It is therefore important that indirect effects be identified, and if not incorporated into the model or assessed in the sensitivity analysis, that their likely impact be discussed. Finally, when indirect effects are included in economic models, the level of uncertainty, due to lack of scientific evidence, must be qualified and/or quantified when presenting results and conclusions. Careful consideration of all of these effects should be taken into account, to avoid a distorted picture of the attractiveness of the program being produced.

Our analysis predicts that although the economic desirability of varicella vaccination is uncertain using CUA and may produce an increase in morbidity using discounted QALYs, it is deemed highly beneficial using WTP and CBA. Hence, basing policy decisions on CBA or CUA can lead to very different resource allocation decisions. If we assume QALYs adequately measure disease severity, our results suggest that using WTP as the outcome measure may bias resource allocation toward less severe diseases, which may lead to reduction in population health. Here, the differences can be explained by the fact that the average WTP per QALY gained was higher for varicella (a usually mild disease of children) than zoster (a more severe disease of adults, particularly the elderly). The fact that WTP is capped by ability to pay could explain results[44] showing that WTP increases as QALYs increase but at a decreasing rate. Such results

have produced concerns among health economists about using WTP as a basis for the allocation of health care resources.[45] Further empirical research is needed to better understand the effects of the choice of outcome measure and elicitation technique. Indeed, in epidemiology it is well known what biases are inherent in certain study designs. This is not, however, the case in economic evaluation, and this study attempts to illustrate (among other things) what biases in decision recommendations may result from analysts' choice of method.

Vaccination is a preventive intervention; thus, costs of the program are incurred at the time 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 our results: Varicella vaccination is "cost-effective" when discounting is very low and a long time frame is adopted because the long-term decline in zoster (after 50 years or so) then becomes significant. Another example where discounting will have an impact is with the HPV vaccine. The vaccine will probably be given to 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. Decision makers must be made aware of the impact of discounting and its impact on the results of economic evaluation of health interventions that produce long-term benefits.

Uncertainties introduced by methodological choice led the US Panel on Cost-Effectiveness to recommend using a reference set of methods to improve comparability, with the impact of methodological choices being addressed through sensitivity analysis. However, as seen above, different sources of uncertainty are likely to have varying effects depending on the treatment type and disease being modeled. Thus, the use of a reference case, for comparability, may prejudice against certain medical interventions. More work should be focused on understanding the impact of methodological choice so that decision makers and analysts have a better idea of the biases inherent in using a reference case.

For illustrative purposes and ease of exposition, we did not present the full sensitivity analysis conducted in our previous economic evaluation of varicella vaccination.[23] Hence, we did not present the sensitivity to mixing matrix assumptions, vaccine efficacy parameters, or vaccine coverage. Furthermore, the variability within the multivariate sensitivity analysis is controlled in our examples as additional sources of uncertainty can be included. For example, the uncertainty surrounding the impact of vaccination on zoster could have further been explored by varying the many parameters needed to model the natural history of varicella and zoster. Although the scope of the probabilistic sensitivity analysis has been reduced, it does not impact the conclusions of this article.

In this article, we did not examine an additional, potentially critical source of uncertainty, namely, the selection of strategies that are modeled. Similar to model uncertainty, the exclusion of relevant strategies (such as vaccination of high-risk populations) can have an important impact on conclusions particularly if an incremental analysis is performed. For example, adolescent vaccination has consistently been shown to be cost-effective[42] and is robust to model and methodological assumptions.[23] Hence, stating that varicella vaccination is or is not cost-effective, without examining alternative strategies, would be misleading.

The results of this article reinforce the importance of not only clearly stating methodological and model assumptions but also justifying the choices made and discussing their impact. Complexity or lack of information/data should not be an acceptable justification for the choice of methodology or modeling technique, if this can have a major impact on results. Further research is needed to better understand the effect the choice of model and methodological technique can have on results and resource allocation decisions. In the meantime, although this may be resource intensive, sensitivity analysis should be performed on key model and methodological assumptions. It is the role of peer review to ensure that this is indeed being done.

Finally, probabilistic sensitivity analyses are essential; however, conclusions based on these analyses (such as viewing results from cost-effectiveness acceptability curves as cost-effectiveness probabilities) must be done with care, as they are conditional on the validity of the model and methodological technique used. If model and methodological assumptions are not appropriate, then the results of a probabilistic sensitivity analysis can be misleading in that they may give a false sense of security in the results and may lead to inappropriate research priorities being set or policy decisions being made.

APPENDIX
MATHEMATICAL STRUCTURE WITHOUT ZOSTER

The equations represent the transmission dynamics of varicella. The model possesses 66 age cohorts, i (0, 1, 2, . . . , 64, and 65+). Children enter continuously throughout the year into the 1st 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.[46] 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 model are as follows:

$$dS_i(t)/dt = B_i - [\lambda_i(t) + (c_i\ (1\text{-}P) + \mu_i]\ S_i(t) \quad (1)$$

$$dE_i(t)/dt = \lambda_i(t)\ S_i(t) - (\sigma + \mu_i)\ E_i(t) \quad (2)$$

$$dI_i(t)/dt = \sigma\ E_i(t) - (\alpha + \mu_i)\ I_i(t) \quad (3)$$

$$dR_i(t)/dt = \alpha\ I_i(t) - \mu_i\ R_i(t) \quad (4)$$

$$dVP_i(t)/dt = c_i\ T\ S_i(t) - (W + K\ \lambda_i(t + \mu_i)\ VP_i(t) \quad (5)$$

$$dVS_i(t)/dt = c_i\ [1\text{-}T\text{-}P]\ S_i(t) + W\ VP_i(t) - (b\ \lambda_i(t) + \mu_i)VS_i(t) \quad (6)$$

$$dVE_i(t)/dt = b\ \lambda_i(t)\ VS_i(t) - (\sigma + \mu_i)\ VE_i(t) \quad (7)$$

$$dVI_i(t)/dt = \sigma\ VE_i(t) - (\alpha + \mu_i)\ VI_i(t) \quad (8)$$

$$dVR_i(t)/dt = K\ \lambda_i(t)\ VP_i(t) + \alpha\ VI_i(t) - \mu_i\ VR_i(t) \quad (9)$$

The number of individuals of age i 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 $S_i(t)$, $E_i(t)$, $I_i(t)$, $R_i(t)$, $VP_i(t)$, $VS_i(t)$, $VE_i(t)$, $VI_i(t)$, and $VR_i(t)$, respectively. The different parameters determining the rates of flow between disease states for natural varicella are B_i, rate of entry into the 1st age cohort; μ_i, mortality rate; c_i, vaccine coverage in age group i; σ and α, rates of flow from latent to infectious and infectious to immune; $\lambda_i(t)$, force of varicella infection by age group is given by

$$\lambda_i(t) = \sum_j \beta_{ij} I_j(t)\,, \quad (10)$$

where β_{ij} is a mixing matrix describing the rate of effective contact between individuals of age group i and j (see methods and Brisson and colleagues[24,25] for details). The initial conditions for the set of equations are taken to be the prevaccination 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.[47]

The flow between vaccinated disease states are c_iT, the percent of vaccinees who become temporarily protected after vaccination; c_iP, the percent of vaccinees for which vaccine fails completely after vaccination; W, waning rate; b $\lambda_i(t)$, rate of infection among vaccine susceptible vaccinees; k $\lambda_i(t)$, rate of boosting.

MATHEMATICAL STRUCTURE INCLUDING ZOSTER

The model below represents the transmission dynamics of both varicella and zoster. Differential equations 1, 2, 3, 5, 6, 7, 8, and 9 are identical for the models that include and exclude zoster. The remaining differential equations for the model that includes zoster are as follows:

$$dR_i(t)/dt = \alpha I_i + z\ \lambda_i(t)\ ZS_i(t) - (\delta + \mu_i)\ R_i(t) \quad (11)$$

$$dZS_i(t)/dt = \delta R_i - (\rho_i + z\lambda_i(t) + \mu_i)\ ZS_i(t) \quad (12)$$

$$dZI_i(t)/dt = \rho_i\ ZS_i(t) - (\alpha_z + \mu_i)\ ZI_i(t) \quad (13)$$

$$dZR_i(t)/dt = \alpha_z\ ZI_i(t) - \mu_i\ ZR_i(t) \quad (14)$$

The zoster disease states are lifelong immunity to varicella and temporary immunity to zoster ($R_i(t)$), susceptible to zoster ($ZS_i(t)$), reactivation episode ($ZI_i(t)$), and permanently immune to zoster ($ZR_i(t)$). The rates are determined by δ, rate of loss of immunity to zoster; $z\lambda_i(t)$, rate of boosting against zoster; and ρ_i, the age-dependent rate of reactivation of varicella-zoster virus in those who are susceptible to zoster. See Brisson and colleagues[21,24] for details on the estimation of these rates.

AGGREGATION OF WTP AND QUALITY-ADJUSTED LIFE YEARS

WTP. The total benefit of varicella vaccination was calculated as the sum of the present value of the benefit of preventing chickenpox in vaccinees and nonvaccinees as well as its negative effect on zoster. The present value of the benefit of varicella vaccination over l years in vaccinees (B^{vac}), in nonvaccinated individuals (B^{nvac}), and impact of vaccination on zoster (B^z) were calculated as follows:

$$B^{vac} = WTP^{vac} \sum_{t=0}^{l} r^t N_t^{vac}$$

$$B^{nvac} = \sum_{t=0}^{l}\sum_{a} r^t C_{0at}^{nvac} WTP_a^{chick} - \sum_{t=0}^{l}\sum_{a} r^t C_{1at}^{nvac} WTP_a^{chick} = \sum_{t=0}^{l}\sum_{a} r^t WTP_a^{chick}\left(C_{0at}^{nvac} - C_{1at}^{nvac}\right)$$

$$B^z = \sum_{t=0}^{l}\sum_{a} r^t WTP_a^z\left(C_{0at}^z - C_{1at}^z\right)$$

where $r^t = 1/(1 + \text{discount rate})^t$; N_t^{vac} is the number of individuals vaccinated at time t; WTP^{vac} is the average willingness to pay for varicella vaccination; C_{iat}^{nvac} is the number of predicted chickenpox cases among nonvaccinees of age a, at time t, in state of the world with (i = 1) and without (i = 0) vaccination; WTP^{chick} is the average willingness to pay to prevent chickenpox once infected; C_{iat}^{z} is the number of zoster cases in individuals of age a, at time t, and in state of the world with (i = 1) and without (i = 0) vaccination; WTP^{z} is the average willingness to pay to prevent zoster assuming one has zoster. See Table A1 for *WTP* values and sources.

Quality-adjusted life years. We consider total quality-adjusted life years (QALYs) gained from varicella vaccination as the sum of the QALYs gained from the prevention of chickenpox in vaccinees and nonvaccinees, and its indirect effect on zoster. QALYs gained attributed to varicella in vaccinees ($QALY_{gained}^{vac}$) and nonvaccinees ($QALY_{gained}^{nvac}$), and zoster ($QALY_{gained}^{z}$) were calculated as follows:

$$QALY_{gained}^{vac} = \sum_{t=0}^{l}\sum_{a} r^t C_{0at}^{vac}\left(Q_a^{var} + p_a^{var} LYL_a\right) - \sum_{t=0}^{l}\sum_{a} r^t C_{1at}^{vac}\left(Q_a^{var} + p_a^{var} LYL_a\right)$$

$$QALY_{gained}^{nvac} = \sum_{t=0}^{l}\sum_{a} r^t C_{0at}^{nvac}\left(Q_a^{var} + p_a^{var} LYL_a\right) - \sum_{t=0}^{l}\sum_{a} r^t C_{1at}^{nvac}\left(Q_a^{var} + p_a^{var} LYL_a\right)$$

$$QALY_{gained}^{z} = \sum_{t=0}^{l}\sum_{a} r^t C_{0at}^{z}\left(Q_a^{z} + p_a^{z} LYL_a\right) - \sum_{t=0}^{l}\sum_{a} r^t C_{1at}^{z}\left(Q_a^{z} + p_a^{z} LYL_a\right)$$

where Q_a^{var} are the age-specific QALY lost associated with a case of varicella; Q_a^{z} is the age-specific QALY lost due to a case of zoster; p_a^{var} is the age-specific varicella case-fatality ratio, p_a^{z} is the age-specific zoster case-fatality ratio, and LYL_a is the present value of the expected life years lost of an individual who dies at age a. See Table A1 for values and sources.

Table A1 Health Outcome Estimates

Parameters	0–4	5–14	15–44	45–64	65+	Source
Case fatality						
Varicella	0.001%	0.001%	0.009%	0.073%	0.689%	23, ONS
Zoster	0.000%	0.001%	0.002%	0.002%	0.061%	23, ONS
QALY lost per case						
Varicella	0.004	0.004	0.005	0.005	0.005	18,39
Zoster	0.01	0.01	0.02	0.06	0.14	23,48
Value (£) of a case or vaccination						
Vaccination	60					18,39
Varicella	47	47	101	101	101	18,39
Zoster	118	118	135	191	312	18,39

Note: QALY = quality-adjusted life year.

MULTIVARIATE ANALYSIS

Table A2 Input Values for the Multivariate Analysis

Parameter	Mode (source)		Minimum (source)		Maximum (source)	
% cases consult GP[A]						
Varicella: 0–4	45%	RCGP	36%	RCGP	48%	RCGP
5–14	45%	RCGP	26%	RCGP	45%	RCGP
15–44	72%	RCGP	30%	RCGP	72%	RCGP
45–64	82%	RCGP	48%	RCGP	100%	RCGP
65+	100%	RCGP	57%	RCGP	100%	RCGP
Hospitalization per case						
Varicella[B]: 0–4	0.4%	HES	0.4%	HES	0.5%	HES
5–14	0.1%	HES	0.1%	HES	0.2%	HES
15–44	0.6%	HES	0.6%	HES	0.8%	HES
45–64	1.4%	HES	1.4%	HES	1.9%	HES
65+	3.1%	HES	3.1%	HES	5.8%	HES
Zoster[B]: 0–4	1.1%	HES	1.1%	HES	1.4%	HES
5–14	0.7%	HES	0.7%	HES	1.0%	HES
15–44	0.5%	HES	0.5%	HES	0.8%	HES
45–64	0.6%	HES	0.6%	HES	1.2%	HES
65+	2.3%	HES	2.3%	HES	5.0%	HES
Length of stay						
Varicella[B]: 0–4	2.2	HES	2.2	HES	2.7	HES
5–14	3.0	HES	3.0	HES	3.6	HES
15–44	4.0	HES	4.0	HES	4.8	HES
45–64	5.8	HES	5.8	HES	7.9	HES
65+	10.6	HES	10.6	HES	15.8	HES
Zoster[B]: 0–4	3.5	HES	3.5	HES	5.3	HES
5–14	3.4	HES	3.4	HES	3.4	HES
15–44	4.6	HES	4.6	HES	6.1	HES
45–64	5.2	HES	5.2	HES	8.7	HES
65+	13.5	HES	13.5	HES	17.4	HES
Case fatality						
Varicella[C]: 0–4	0.001%	ONS	0.0006%	ONS	0.0017%	ONS
5–14	0.001%	ONS	0.0004%	ONS	0.0006%	ONS
15–44	0.009%	ONS	0.0063%	ONS	0.0167%	ONS
45–64	0.073%	ONS	0.0733%	ONS	0.1011%	ONS
65+	0.689%	ONS	0.3880%	ONS	0.8536%	ONS
Zoster[C]: 0–4	0.0000%	ONS	0.0000%	ONS	0.0000%	ONS
5–14	0.001%	ONS	0.0000%	ONS	0.0068%	ONS
15–44	0.002%	ONS	0.0000%	ONS	0.0086%	ONS
45–64	0.002%	ONS	0.0012%	ONS	0.0035%	ONS
65+	0.061%	ONS	0.0403%	ONS	0.0831%	ONS
Postherpetic neuralgia (PHN) per zoster case						
0–4	0%	48	0.0%	48	0.0%	48
5–14	1%	48	0.0%	48	1.7%	48
15–44	4%	48	2.6%	48	4.9%	48
45–64	11%	48	10.0%	48	11.9%	48
65+	31%	48	28.7%	48	33.4%	48
Duration of PHN	551	48	339	48	781	48
Value (£) of a case or vaccination[%]						
Vaccination	60	18[D]	52	18[D]	69	18[D]
Varicella: 0–14	47	18[E]	45	18[E]	60	18[E]
15+	101	18[F]	52	18[F]	176	39[F]

(continued)

Table A2 (continued)

Parameter	Mode (source)		Minimum (source)		Maximum (source)	
Zoster	118	39[G]	76	39[G]	176	39[G]
PHN	685	39[H]	523	39[H]	847	39[H]
QALY lost per case						
Varicella: 0–14	0.4%	18[I]	0.01%	18[I]	0.64%	18[I]
15+	0.5%	18[J]	0.32%	18[J]	1.02%	18[L]
Zoster	1.0%	48[K]	0.85%	48[K]	1.67%	48[L]
Cost estimates		23	–25%Base		+25% Base	

Note: A) Minimum is minimum number of varicella consultations observed in the Royal College of General Practitioners data in a year between 1991 and 2000 (www.rcgp.org.uk). Maximum is maximum number of varicella consultations in a year between 1991 and 2000. B) Minimum is varicella or zoster in the 1st diagnostic field (Hospital Episode Statistics [HES], www.dh.gov.uk). Maximum is varicella or zoster in any of the diagnostic fields. C) Minimum is minimum case-fatality in a year between 1991 and 2000 (observed in the Office for National Statistics mortality statistics). Maximum is maximum case-fatality in a year between 1991 and 2000. D) 95% confidence interval (CI) of willingness to pay for vaccination. E) 95% CI of WTP for treatment. 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 quality-adjusted life year (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 **the** Communicable Disease Surveillance Centre using the HUI2 generic health status index. K) QALY value for mild zoster. L) QALY value for severe zoster. % WTP values elicited in Brisson and colleagues[18] were reduced by 50% as recommended by the National Oceanic and Atmospheric Administration[38] to take into account the worry that WTP from Conjoint Valuation overestimates actual WTP.

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