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Cost-effectiveness of varicella and zoster vaccination in England&Wales: importance measures for correlated parameters

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Abstract

This study aims to explore irregular relationships between input and outcomes in cost-effectiveness analysis, accounting for interdependencies between many input parameters. We used a dynamic infectious disease transmission model investigating the cost-effectiveness of varicella and zoster vaccination as a case study. Incremental costs and effects were used separately as the outcomes of interest, rather than the ratio between these, and a single R^2 was calculated for groups of interdependent input parameters. Partial R^2 was obtained as measure for the marginal proportion of variance explained. The most important input parameters were related to zoster epidemiology and disease transmission. In case of linear relationships, R^2 is an easy to obtain importance measure, also in the presence of interdependent input parameters.

Keywords: coefficient of determination; correlation; dependency; sensitivity measure; uncertainty; cost-effectiveness

1. Main text

Background: Thorough sensitivity analyses exploring to which degree each input parameter contributes to the dispersion of outcomes are rarely made in health economic evaluations. In such analyses two problems may arise: (1) the relationship between input and outcome (the Incremental Cost Effectiveness Ratio (ICER) = incremental costs/Incremental Quality Adjusted Life Years (QALYs)) is non-linear and non-monotone because the ICER is a ratio, and (2) several groups of input parameters are strongly interdependent.

Aim: We aim to explore the above problems in the context of a cost-effectiveness analysis of childhood varicella vaccination combined with adult zoster vaccination in England&Wales. In this analysis 185 input parameters were modeled to obtain outcomes mainly in terms of incremental costs, incremental QALYs, and the outcome of interest for policy making, the ICER. The uncertainty of each of these parameters was represented by distributions, and propagated into these outcomes using Monte Carlo simulation (van Hoek et al, 2010).

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Methods:

1) Dealing with non-linearity and non-monotonicity - Due to the non-linear and non-monotone relationship between the ICER and the input parameters, obtaining importance measures is not straightforward from a statistical point of view. Also, the interpretation of the ICER depends on the signs of both denominator and numerator separately. To overcome both statistical and interpretation problems, importance measures are obtained for incremental costs and QALY's separately. As measure for importance, the coefficient of determination (R^2) from a regression analysis for each input parameter is used (Briggs et al 2006). R^2 measures how much of the variance in the outcome is explained by a linear relation with that input parameter. Assumptions of linearity and normality of residuals for these regression analyses are checked.

2) Dealing with (many) interdependent input parameters –100 parameters (=10*10) describe the probabilities to transmit the disease from each of 10 different age groups to each of 10 different age groups. These 100 transmission parameters are interdependent because they are estimated using a single model and dataset, and therefore a single R^2 is obtained for this group (Briggs et al 2006). For the same reason, a single R^2 is obtained for 2 parameters describing vaccine efficacy, i.e. "take" and "waning". A single R^2 is also obtained for parameter 'delta' (the rate by which 'boosted' individuals become susceptible to zoster again) and parameter 'chi' (the reduction in zoster reactivation in vaccinees versus non-vaccinees), because the chi parameter is partially based on the delta parameter. Additionally, partial R^2's are obtained for the individual parameters belonging to these interdependent groups. Partial R^2 measures the marginal contribution of a parameter when all other parameters are in the model. It is similar to what Xu & Gertner (2008) call the 'uncorrelated' proportion of variance in the outcome explained.

Results: A linear model with all input parameters (main effects only) approximates well the relationship between input parameters and incremental costs and incremental QALY's (coefficient of determination R^2=0.92 and 0.87 respectively). Residuals are normally distributed (Shapiro-Wilk normality test, W>0.95).

Chi and delta together, and the groups of transmission parameters explain 62% and 28% of the variance in incremental costs, and 47% and 29% of the variance in incremental QALY's, respectively. Zoster vaccine take and waning explain 4% of the variance in incremental costs and 11% of the variance in incremental QALY's. All other parameters explain less than 1% of the variance in incremental costs and QALY's.

Marginal contributions of chi and delta are 38% and 27% to incremental costs, and 19% and 30% to incremental QALY's, respectively. Among the transmission parameters, the marginal contributions to the incremental costs are the highest for the parameters describing transmission between children below 4 years of age (partial R^2's are between 1% and 3%). The marginal contributions of the transmission parameters to incremental QALY's all lie below 0.1%.

Discussion: In case of linear relationships, (partial) R^2 is an easy to obtain importance measure, also in presence of interdependent input. This study shows that a complex health economic model for varicella and zoster vaccination can be approximated by a simple linear regression model (R^2=0.9). Also, assessing the importance of input parameters serves as an internal model check (Saltelli et al 2008). One of the limitations of this study is that only linear relationships and linear associations are taken into account. Assessing importance measures, especially in case of interdependent input, becomes more difficult when relationships become more irregular. Additionally, the importance measures given are conditional on methods, model characteristics, databases and parameter distributions. A future challenge would be to calculate the variance explained by each of the input parameters in an exact way instead of using a statistical approximation to the model. As the model is in fact completely known, this is mathematically possible but needs extensive calculations.

2. References

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