Uncertainty module User Manual

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Contacts for User Support

Further information and advice on using Uncertainty module can be obtained by contacting zlr1220@126.com.

1. Introduction

Cervical cancer is an important cause of new cases and deaths among women worldwide.In the global strategy to eliminate cervical cancer adopted by the World Health Assembly in 2020,it is proposed that 90% of girls should be vaccinated against HPV before the age of 15 by 2030,which means that HPV vaccines in low and middle-income countries need urgent attention in the next decade.Immunization programme activities.Estimates of the possible health and economic impacts of HPV vaccination will provide important evidence to support the introduction of the vaccine into national immunization programme.

Scientists at the London School of Hygiene and Tropical Medicine and Laval University in Quebec,together with the World Health Organization in Geneva,have developed the Microsoft Excel-based Papillomavirus Rapid Interface for Modelling and Economics (PRIME) to assess the full range of vaccinations of adolescent girls before first sexual activity The cost-effectiveness of the HPV vaccine provides non-modeling users with a plan for rapid economic evaluation of the entire HPV vaccination process, which has been widely used around the world. However,PRIME only provides cost-effectiveness results and does not provide an uncertainty analysis module.

We have extended PRIME to include modules that can perform uncertainty analysis of model parameters to reduce bias in economic evaluation results.This guide describes the expanded uncertainty analysis module of the PRIME model and describes how to use it.

1.1 About the Uncertainty module

The uncertainty analysis module is extended on the basis of the PRIME model,and provides users with tools to carry out uncertainty analysis after baseline economic evaluation.This module mainly includes two uncertainty analysis methods:

- Deterministic sensitivity analysis(DSA):Analyze whether the results of the economic evaluation are consistent with the baseline results when changing individual parameters.
- Probabilistic sensitivity analysis(PSA):Evaluate the robustness of economic evaluation results after multiple parameters follow a certain distribution and change simultaneously.

The uncertainty analysis module is designed to help users who need uncertainty analysis after economic evaluation,so as to consider whether the results of economic evaluation have an impact on decision-making in other possible situations.DSA is carried out based on the changes of a single input parameter.PSA evaluates the impact of the changes of multiple parameters to verify the robustness of the evaluation results and provide a basis for decision-making.

2．Usage Guidelines

2.1 Model introduction

Uncertainty module is based on a new module created by Microsoft EXCEL on the PRIME model, including 3 sheets：

- DSA——Select the default variation range of each parameter to obtain the ICER value after each parameter is changed respectively.Users can customize the range of parameters.
- PSA——Select the model parameters to change randomly to ensure that the parameters can change randomly.Using Monte Carlo simulation,select the default number of iterations (1,000 times).In addition,you can also customize the number of input iterations to obtain the probability distribution of ICER values.
- Sensitivity analysis output——The results of the analysis are presented in Tornado charts and Cost-Effectiveness Acceptability Curve(CEAC) format.

These transformations between the sheets s use the sheet navigation tabs in the figure below (see Fig. 2).

Figure 2. Sheet navigation tabs

2.2 Detailed operation

2.2.1 Deterministic sensitivity analysis

- Deterministic sensitivity analysis was operated in the "DSA" sheet.The table is automatically populated with the default variation range,variation value and baseline ICER value for each parameter. Please make sure that the Model Type of the "PSA" sheet is "Deterministic" before performing deterministic sensitivity analysis.

Tabel s10. Explanation of input data fields

Field label	Explanation
Parameter	Parameters of analysis
Value	Parameter baseline values
Decrease in baseline value	Parameter range (decrease)
lower bound	Parameter value after parameter change (low value)
Increase in baseline value	Range ameter range (increase)
upper bound	Dynamic parameter value after parameter change (high value).Among them, the maximum value of the three parameters of Vaccine efficacy vs HPV 16/18、Proportion of cervical cancer cases that are due to HPV 16/18 is 100%.
ICER (lower)	The ICER value after the parameter change (low value)
ICER (upper)	The ICER value after the parameter change (high value)
Absolute Value	Absolute value of the ICER difference after the parameter change

- To use a custom parameter variation range,enter custom values in the "Decrease in baseline value" and "Increase in baseline value" gray fields to override the default values,and click the "RUN DSA" button to generate the result (Fig. 3).

Figure 3. DSA input chart example

Base ICER $1,062

RUN DSA

Parameter	Value	Decrease in baseline value	lower bound	Increase in baseline value	upper bound	ICER(lower)	ICER(upper)	Absolute Value
Vaccine efficacy vs HPV 16/18	100%	0.4	60%	0	100%	1534	899	635
Vaccine price per FIG	$40	0.2	$32	0.2	$49	760	1038	278
Vaccine delivery cost per FIG	$15	0.2	$12	0.2	$18	848	951	103
Cancer treatment cost (per episode, over lifetime)	$552	0.2	$442	0.2	$662	910	889	21
DALYs for cancer diagnosis	0.08	0.1	0.07	0.1	0.09	900	899	1
DALYs for non-terminal cancer sequelae (per year)	0.17	0.1	0.15	0.1	0.19	902	897	6
DALYs for terminal cancer	0.78	0.1	0.70	0.1	0.86	903	896	6
Discount rate	3%	0.02	1%	0.02	5%	404	1732	1328
Proportion of cervical cancer cases that are due to HPV 16/18	74%	0.1	67%	0.1	82%	1005	813	192

- Click the "DSA" button to run DSA and automatically generate a Tornado chart.The results are presented in the "Sensitivity analysis output" sheet.

Figure 4. DSA results run chart example

Parameter	ICER(lower)	ICER(upper)	Absolute Value
Discount rate	1372	6468	5097
Vaccine efficacy vs HPV 16/18	5311	3160	2152
Vaccine price per FIG	2689	3630	942
Proportion of cervical cancer cases that are due to HPV 16/18	3518	2866	652
Vaccine delivery cost per FIG	2985	3334	349
Cancer treatment cost (per episode, over lifetime)	3173	3146	27
DALYs for terminal cancer	3170	3149	21
DALYs for non-terminal cancer sequelae (per year)	3167	3152	15
DALYs for cancer diagnosis	3162	3157	5

2.2.2 Probabilistic sensitivity analysis

- PSA is performed in the "PSA" sheet.In "Model Type" select the option "Stochastic" for random variation of model parameters (Fig. 5).Click "PSA" to run, and the results are displayed in the "Sensitivity analysis output" sheet.

Figure 5. PSA input chart example

PSA

Model Control

model

Model Type: Stochastic

modeltype

Deterministic

Stochastic

Threshold

Parameter	Value Used	Deterministic	Stochastic	Random	Distribution	Param1		Param2
Vaccine efficacy vs HPV 16/18	91.1%	100.0%	91.1%	0.48438	Beta	α	17.33	β
Vaccine price per FIG	$39.27	$40.44	$39.27	0.33859	Gamma	α	225	β
Vaccine delivery cost per FIG	$13.47	$15.00	$13.47	0.05932	Gamma	α	225	β
Cancer treatment cost (per episode, over lifetime)	$701.03	$650.09	$701.03	0.87861	Gamma	α	225	β
DALYs for cancer diagnosis	0.08	0.08	0.08	0.92914	Beta	α	827.92	β
DALYs for non-terminal cancer sequelae (per year)	0.11	0.11	0.11	0.79519	Beta	α	800.89	β
DALYs for terminal cancer	0.78	0.78	0.78	0.48346	Beta	α	197.22	β
Discount rate	3%	3%	3%	0.41898	Beta	α	19.6125	β
'roportion of cervical cancer cases that are due to HPV 16/18	69.6%	68.4%	69.6%	0.69942	Beta	α	283.5358	β

- The default number of iterations for Monte Carlo simulation is 1,000.If other simulation times less than 1,000 are used,enter a custom number of iterations in the "numruns" pink area (Fig. 6).

Figure 6. Example of a Monte Carlo simulation run chart

numruns	1000

txPost-vaccination_cost	txPost-vaccination_DAL\	txPre-vaccination_cost	-vaccination_DALY
$297,319,073	95,540	$9,396,867	0

simulation	txPost-vaccination_cost	txPost-vaccination_DALY	txPre-vaccination_cost	e-vaccination_DALY
1	$313,390,366.84	110796.7613	$8,432,191.49	0
2	$316,177,980.14	102006.4283	$8,336,102.15	0
3	$313,209,108.75	86701.48994	$6,839,433.14	0
4	$301,315,709.36	96497.73041	$9,236,939.10	0
5	$327,296,764.08	76057.6407	$6,994,146.61	0
6	$305,649,118.38	81666.16179	$7,252,591.81	0

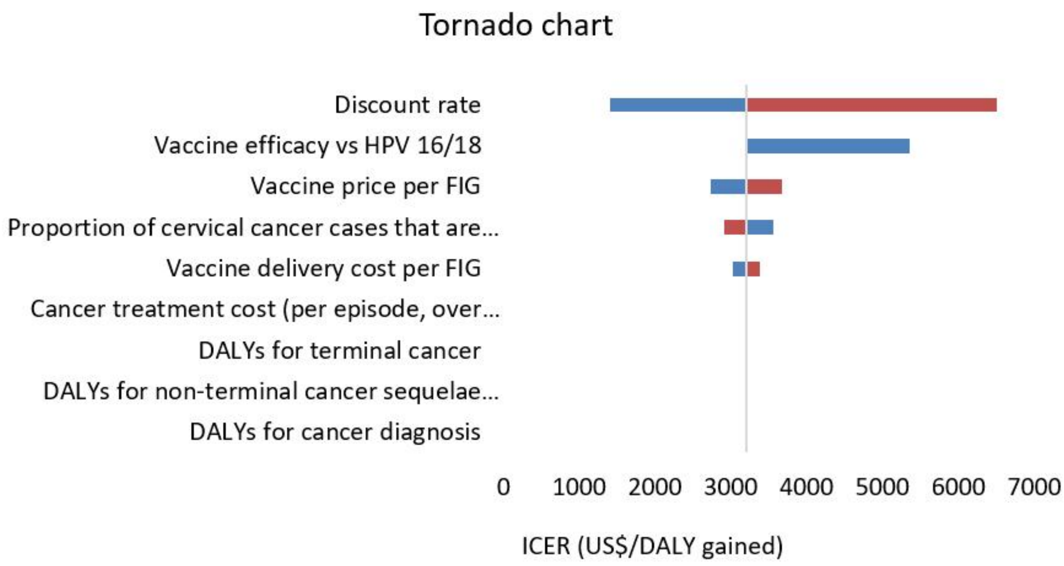
2.2.3 Sensitivity analysis output

The resulting output module includes three graphs.The first graph shows the results of the DSA,and the second and third graphs show the results of the PSA.

2.2.3.1 Results of the DSA

The results of the DSA are output in the form of Tornado charts.The horizontal axis represents the change result of ICER value,the vertical axis represents the analyzed parameter,the middle line represents the baseline result,and the bar length represents the range of parameter change in the analysis.The ends of the bars are the upper and lower bounds of the range for each parameter.Starting from the top of the graph, the bars are arranged in order from longest to shortest,that is,the parameter values are arranged from large to small based on the range of changes in the ICER value.The Tornado chart shows the degree of influence of each parameter on the economic evaluation results and the robustness of the economic evaluation results when each parameter changes (Fig. 7).

Figure 7. Tornado chart



2.2.3.2 Results of the PSA

The PSA produced a incremental effects scatter plot and a CEAC.The points identified by incremental cost and incremental effect in Fig.8 are plotted in the four quadrants represented by the X and Y axes,respectively,and the slope of the line connecting the origin to any cost-effect combination is the ICER result.In the process of generating the incremental effects scatter plot,you can set the axes to adjust the image by entering numerical values in “X” “Y” according to the threshold.

The threshold in the scatter plot provides evidence of the robustness of the cost-effectiveness analysis results,such as at a specific threshold,all scatter points are averaged below the threshold line,indicating that the economic evaluation results are robust.

Figure 8. Incremental effects scatter plot

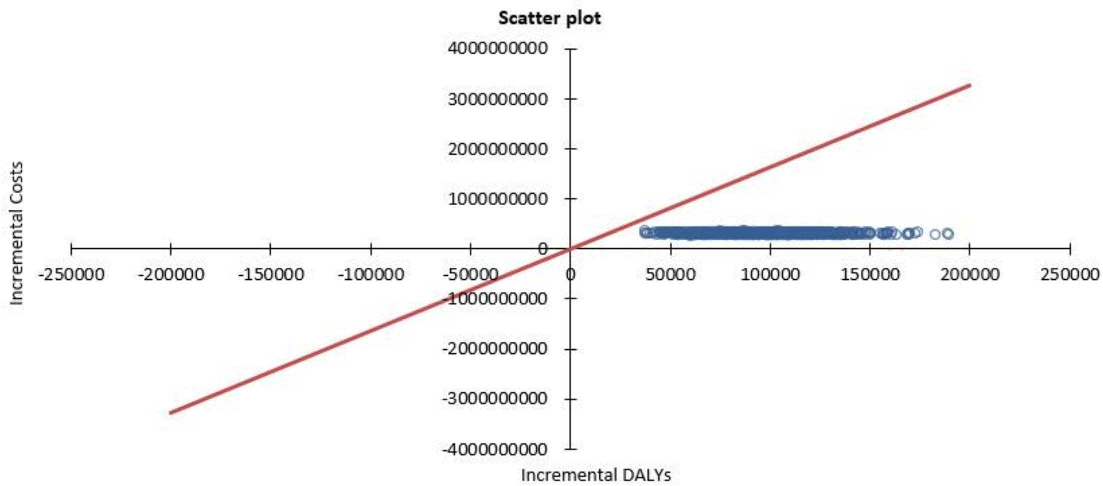
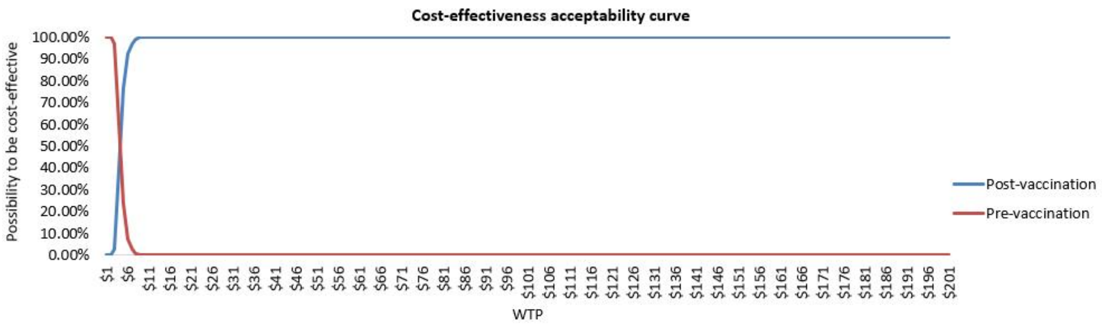


Fig. 9 is the CEAC, in the case of using the net benefit measure, the result of PSA can be displayed as CEAC.The abscissa is the cost-effectiveness threshold,and the ordinate is the probability of cost-effectivenes.The CEAC shows the probability that an intervention is cost-effective at each upper proportion (or WTP threshold), visualizing the results of PSA.

Figure 9. CEAC



3.Further Investigations

Further information about Uncertainty module can be found on the tool's website at https://github.com/PRIME-Uncertainty/PRIME-Tool-Uncertainty-Analysis.