Papillomavirus Rapid Interface for Modelling and Economics Tool

User Manual

List of abbreviations

DALYs disability adjusted life years

GDP gross domestic product

HPV human papillomavirus

IARC International Agency for Research on Cancer

IVIR-AC Immunization and Vaccines related Implementation Research Advisory Committee

PRIME papillomavirus rapid interface for modelling and economics

UNPD United Nations Population Division

WHO World Health Organisation

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Acknowledgements

This manual was developed by Morag Hickman in collaboration with Mark Jit and Raymond Hutubessy.

PRIME was developed by Mark Jit, Marc Brisson, Allison Portnoy and Raymond Hutubessy.

We thank Hoang van Minh, Patricia Rasoamihanta and Anais Colombini for providing feedback on the pilot version of PRIME.

We thank the Bill and Melinda Gates Foundation for their financial support.

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Contacts for User Support

Further information and advice on using PRIME can be obtained by contacting vaccineresearch@who.int

1 Introduction

HPV is a necessary condition for cervical cancer, which is the fourth most common cancer in women, with an estimated 266,000 deaths and 528,000 new cases worldwide in 2012. A large majority (around 85%) of the global burden occurs in the less developed regions, where it accounts for almost 12% of all female cancers.

HPV is the most common viral infection of the reproductive tract. Although most HPV infections cause no symptoms, persistent genital HPV infection can cause cervical cancer in women. HPV can also cause other types of anogenital cancers, head and neck cancers, and genital warts in both men and women. HPV infections are transmitted through sexual contact. More information on HPV can be found on the WHO website.

Several vaccines that prevent HPV infection are now available in many countries throughout the world. These include a bivalent, a quadrivalent and a nonavalent vaccine. All three vaccines are highly efficacious in preventing infection with virus types 16 and 18, which are together responsible for approximately 70% of cervical cancer cases globally. The nonavalent vaccine also prevents types 31, 33, 45, 52 and 58 which also cause some cases of cervical cancer. The vaccines are also highly efficacious in preventing precancerous cervical lesions caused by these virus types. The quadrivalent and nonvalent vaccines are also highly efficacious in preventing anogenital warts, a common genital disease which is usually caused by infection with HPV types 6 and 11. Data from clinical trials and initial post-marketing surveillance conducted in several continents show all three vaccines to be safe.

The WHO recommends giving two doses of the bivalent vaccine, or two to three doses of the quadrivalent vaccine, to girls aged 9 to 13 years old. More information can be found in the WHO position paper[1]. Consideration of cost-effectiveness is also recommended. For countries without the capacity to develop their own cost-effectiveness models, PRIME is offered as a simple economic model which can support evidence-based decision-making.

1.1 About the PRIME Tool

PRIME is a spreadsheet-based tool, designed to give users an idea of:

- The magnitude of the burden of cervical cancer
- The impact of introducing HPV vaccination for girls prior to sexual debut
- Healthcare costs incurred as a result of cervical cancer treatment
- Costs associated with vaccination
- Long-term savings which may result from a vaccination program

The tool is intended for use by non-modeller users such as country program managers and planners and decision makers in low- and middle income countries. It was created by scientists at the London School of Hygiene and Tropical Medicine in London, Université Laval in Quebec, Johns Hopkins Bloomberg School of Public Health in Baltimore in conjunction with the World Health Organization in Geneva.[2] It has been appraised by WHO's expert committee on modelling, IVIR-AC. It gives reliable, validated estimates for impact and cost-effectiveness of HPV vaccination of adolescent girls prior to sexual debut.

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1 http://www.who.int/wer/2014/wer8943.pdf

2 Further details can be found in the scientific publication describing PRIME (Jit M, Brisson M, Portnoy A, Hutubessy R. Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study. Lancet Global Health 2014; 2(7):e406) which is available at http://www.thelancet.com/journals/langlo/article/PIIS2214-109X%2814%2970237-2/abstract.

Please note that the PRIME Tool is not suitable for more complex scenarios such as:

- Assessing herd immunity (indirect protection for non-vaccinees as a result of reduced circulation of the virus)
- The effect of catch-up campaigns to vaccinate older girls/women
- Male vaccination
- Comparison between vaccines with different valencies
- Assessing vaccine impact on cervical screening programmes

This guide introduces the tool and explains how to use it, but assumes some familiarity with spreadsheet software.

Further information and advice on using PRIME can be obtained by contacting vaccineresearch@who.int

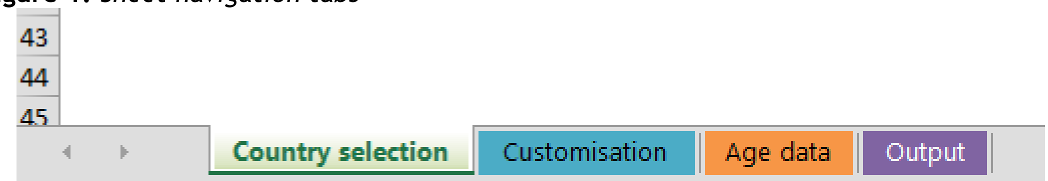
2 Usage Guidelines

PRIME is a spreadsheet-based tool created in Microsoft Excel, comprising four sheets:

- Country Selection - select a country of interest and load default input values
- Customisation - an opportunity to override the default input values
- Age Data - an opportunity to override default age-related input values
- Output - displays the results of the tool's analysis as a chart and graph

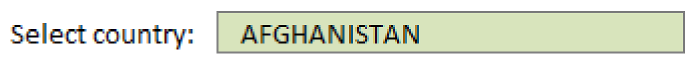
Navigation between these sheets is via buttons within each sheet, or using the sheet tabs in the bottom left corner (see fig. 1).

Figure 1: *Sheet navigation tabs*

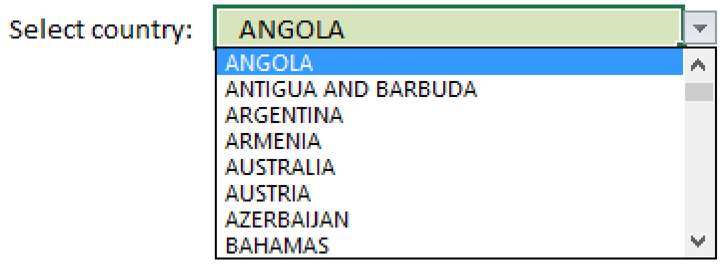


2.1 Localising Data

On the first sheet titled 'Localization', use the drop-down menu:



To select your country of interest:



The fields below will be automatically populated with default information which has been collected from global databases, position papers and publications compiled by WHO and its academic collaborators. However, default data is not available for all countries and hence will sometimes need to be entered manually. For example, population information from the United Nations Population Division's World Population Prospects is not available for some smaller countries.

Further information can be found in the scientific publication describing PRIME[3].

Table 1: *Explanation of input data fields*

Field label	Explanation
Cohort size at birth (female)	The number of female newborns in the country in the base year
Cohort size at vaccination age (female)	The number of females in the country at the age at which routine vaccination is given (based on the age in "Target age group")
Full-dose coverage	The expected proportion of girls in the relevant age group who will receive the full course of the vaccine (either 2 or 3 doses)
Vaccine efficacy vs HPV 16/18	The proportionate reduction in risk of cervical cancers due to HPV 16/18 in vaccinees. This should normally be 100%.
Target age group	The age at which HPV vaccines are normally given. Note that PRIME is only suitable to be used to look at HPV vaccines delivered to girls in the WHO recommended ages of 9-13 years old.
Vaccine price procurement cost per fully vaccinated girl	The procurement cost to purchase enough vaccines (either 2 or 3 doses) to fully vaccinate one girl
Vaccine delivery cost per fully vaccinated girl	The cost of delivering and administering enough vaccines (either 2 or 3 doses) to fully vaccinate one girl
Total vaccine cost per fully vaccinated girl	The total cost to purchase enough vaccines (either 2 or 3 doses) to fully vaccinate on girl. This is automatically calculated as the sum of the procurement and delivery cost

3 Jit M, Brisson M, Portnoy A, Hutubessy R. Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study. Lancet Global Health 2014; 2(7):e406) which is available at http://www.thelancet.com/journals/langlo/article/PIIS2214-109X%2814%2970237-2/abstract

4 Tan-Torres Edejer T et al. Making Choices in Health: WHO guide to cost-effectiveness analysis. Geneva, WHO, 2003 for more information

Field label	Explanation
Cancer treatment cost (per episode, over lifetime)	The cost on average to treat a woman with cervical cancer, from diagnosis to death
DALYs for cancer diagnosis	DALYS incurred for a year of life in which cervical cancer is diagnosed. Advice from a health economist is recommended before altering this parameter
DALYs for non-terminal cancer sequelae (per year)	DALYS incurred for a year of life following the year in which cervical cancer is diagnosed, assuming the cancer is non-terminal. This may vary depending on the country. Advice from a health economist is recommended before altering this parameter.
DALYs for terminal cancer	DALYS incurred for a year of life immediately prior to dying from terminal cervical cancer. Advice from a health economist is recommended before altering this parameter.
Discount rate (%)	The rate representing society's preference for consumption and health gains in the present rather than in the future. WHO recommends a rate of 3% per annum[3].
Proportion of cervical cancer cases due to 16/18	The proportion of cervical cancer cases diagnosed in the base year that are caused by HPV 16 or 18 infection.
GDP per capita	The value of all the goods and services produced in the country divided by the total population.

The output of the tool can be viewed directly by going to the 'output' sheet using the navigation tab (see Fig. 1), or the 'output' button embedded in the sheet:

After you choose the country, the fields in the table in the Country Selection worksheet are automatically populated with data from global databases. These databases may not necessarily contain the most appropriate data from the country you are looking at. If you have access to additional data sources and/or are able to plan further data collection activities, then customization is strongly recommended. To edit the input values, go to the 'customization' sheet, accessible by tab or using the 'customize' button:

2.2 Customise Data

To use different input values, enter them into the 'override value' cells on the 'customize' sheet:

Figure 2: *Overriding default values*

Override these default values:

Parameter	Default Value	Override Value
Country	ANGOLA	
Birth cohort size (female)	468,910	
Cohort size at vaccination age (female)	326,352	
Coverage (all doses)	80%	
Vaccine efficacy vs HPV 16/18	100%	
Target age group	12	
Vaccine price per FIG	$14	
Vaccine delivery cost per FIG	$15	
Total vaccine cost per FIG	$29	$29
Cancer treatment cost (per episode, over lifetime)	$538	
DALYs incurred per non-fatal cancer episode	0.71	
DALYs incurred per fatal cancer episode (excluding life years lost)	0.84	
Discount rate	3.0%	
Proportion of cervical cancer cases that are due to HPV 16/18	74.3%	
GDP per capita	$5,318	

We recommend that customizing the parameter inputs and any activities to collect suitable data to inform such an exercise is done in discussion with a team of epidemiologists, health economists, clinicians, policy makers and other experts familiar with cervical cancer data sources in the country.

When entering data, please ensure that you are consistent in the use of units (eg. currency), as well as in the population and year that the data represent.

Changes made to these values will be reflected automatically in the output on the final sheet, accessible as before using the output button:

View output using current values

Further improvements to accuracy can be made by editing the age-related profile of the cohort represented by the model, which can be carried out on the 'age data' sheet, accessible by the tabs or via the 'customize age data' button:

Further customise - edit age data

2.3 *Age Data*

The 'Age Data' sheet offers another opportunity to customize the PRIME tool's inputs.

Default values

Age	Cervical cancer incidence	Cervical cancer mortality	All-cause mortality
0	0	0	0.06684146
1	0	0	0.01063439
2	0	0	0.01063439
3	0	0	0.01063439
4	0	0	0.01063439
5	0	0	0.00225707
6	0	0	0.00225707
7	0	0	0.00225707
94	0.001225	0.001176	0.29157146
95	0.001225	0.001176	0.41195366
96	0.001225	0.001176	0.41195366
97	0.001225	0.001176	0.41195366
98	0.001225	0.001176	0.41195366
99	0.001225	0.001176	0.41195366
100	0.001225	0.001176	1

Override values

Age	Cervical cancer incidence	Cervical cancer mortality	All-cause mortality
0			
1			
2			
3			
4			
5			
6			
7			
94			
95			
96			
97			
98			
99			
100			

For each year of life, from age 0 to 100 years old, the model accepts three parameters, outlined in Table 2.

Table 2: *Age related parameters*

Field label	Explanation
Cervical Cancer Incidence	The probability that a case of cervical cancer is diagnosed in any given woman in the corresponding age group in the base year.
Cervical Cancer Mortality	The probability that any given woman dies of cervical cancer in the corresponding age group in the base year.
All-cause Mortality	The probability that any given woman dies of any cause in the corresponding age group in the base year.

The default values are based on information in global databases compiled by WHO, IARC , UNPD and other sources. Further information can be found in the scientific publication describing PRIME[4].

Any override values entered in the 'override values' cells on this sheet will be reflected automatically in the output on the final sheet

4 Jit M, Brisson M, Portnoy A, Hutubessy R. Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study. Lancet Global Health 2014; 2(7):e406 which is available at http://www.thelancet.com/journals/langlo/article/PIIS2214-109X%2814%2970237-2/abstract.

2.4 Understanding the Output

The ‘Output’ sheet contains a table of values and a chart.

2.4.a Understanding the Chart

The chart includes two output columns, as seen in Figure 3.

Undiscounted values are those which do not have a discount rate applied, i.e. they represent no preference between consumption and health gains occurring today or in the future.

Discounted values are values which incorporate the discount rate from the list of input values, i.e. they represent values after taking into account a preference for consumption and health gains occurring today against similar gains in the future.

Figure 3: *Example output chart*

Outcomes for country: ANGOLA

Outcomes in cohort	Undiscounted	Discounted
Cohort size at birth (female)	468,910	468,910
Cohort size at vaccination age (female)	326,352	326,352
Cost of vaccination	$7,440,835	$7,440,835
Treatment costs saved	$4,439,461	$1,340,469
Net cost	$3,001,374	$6,100,366
Cervical cancers prevented	5,739	1,733
Deaths prevented	3,663	970
Life years saved	61,874	18,897
Nonfatal DALYs prevented	4,545	1,355
Incremental cost per...		
... cervical cancer prevented	$523	$3,520
... life saved	$819	$6,292
... life year saved	$49	$323
... DALY prevented	$45	$301
GDP per capita	$5,318	$5,318

Here is more information to aid understanding of the model’s outputs:

Table 3: *Output values explained*

Field label	Explanation
Cohort size at birth (female)	The number of female newborns in the country in the base year.

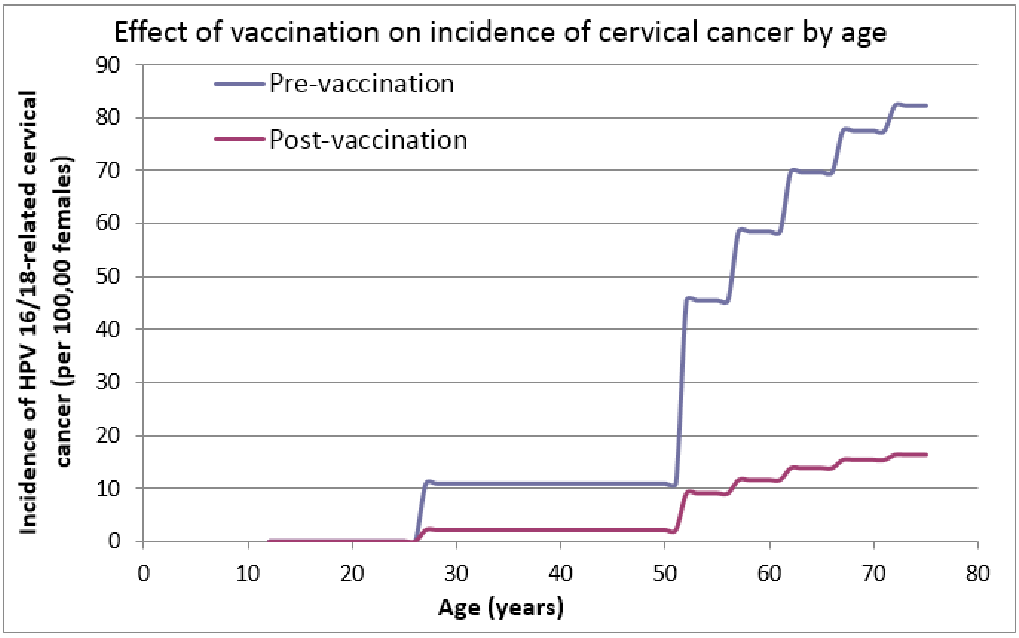
Field label	Explanation
Cohort size at vaccination age (female)	The number of females in the country at the age at which routine vaccination is given (based on the age in "Target age group").
Cost of Vaccination including delivery costs	The total cost of vaccinating a single age cohort in the base year.
Treatment Costs Saved	The treatment costs eventually averted due to cervical cancer cases prevented by vaccinating a single age cohort in the base year.
Net cost	The net (incremental) cost of vaccinating a single age cohort in the base year. This is equal to the cost of vaccination minus the treatment costs saved.
Cervical cancers prevented	The number of cervical cancers eventually averted by vaccinating a single age cohort in the base year.
Deaths prevented	The number of deaths eventually averted due to cervical cancer cases prevented by vaccinating a single age cohort in the base year.
Life years saved	The number of life year losses eventually averted due to cervical cancer cases prevented by vaccinating a single age cohort in the base year.
Nonfatal DALYs averted	The number of DALY losses eventually averted due to cervical cancer cases prevented by vaccinating a single age cohort in the base year.
Incremental cost per...	
... cervical cancer prevented	The net (incremental) cost of vaccination divided by the number of cervical cancers eventually averted by vaccinating a single age cohort in the base year.
... life saved	The net (incremental) cost of vaccination divided by the number of deaths eventually averted due to cervical cancer cases prevented by vaccinating a single age cohort in the base year.
... life years saved	The net (incremental) cost of vaccination divided by the number of deaths eventually averted due to cervical cancer cases prevented by vaccinating a single age cohort in the base year.
... DALY prevented	The net (incremental) cost of vaccination divided by the number of deaths eventually averted due to cervical cancer cases prevented by vaccinating a single age cohort in the base year.

2.4.b Understanding the chart:

The chart shows the reduction of HPV incidence in the vaccinated population with age.

The incidence of cervical cancer that would be expected over the lifetime of an age cohort with and without vaccination is shown.

Figure 4: *Example chart*



3 *Further Investigations*

The model underlying PRIME is described in Jit M, Brisson M, Portnoy A, Hutubessy R. Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study. Lancet Global Health 2014; 2(7):e406) which is available at http://www.thelancet.com/journals/langlo/article/PIIS2214-109X%2814%2970237-2/abstract.

Modellers interested in the exact calculations involved can find these by right-clicking on a sheet's tab, and selecting 'unhide…' to reveal additional sheets. We recommend that this is only done by expert modellers, and are unable to provide any support for modifying the underlying model equations outside of a formal research collaboration that has been agreed to in advance.

Further information can be found on the tool's website at http://primetool.org