

Prevention Model Tool User Guide

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Introduction

This tool is designed to perform analysis of compartmentalized population models on infectious diseases. The tool will allow you to: (1) Include the necessary data files to fully parameterize the model, (2) create and solve the differential equations that define the model, and (3) visualize and download the results.

Objective

This manual aims to help and guide the user when using the cost effectiveness tool, in order to do so it requires:

1. Disclose the necessary characteristics of the tool
2. Provide the user with the necessary information to use the tool

Manual Organization

This manual is organized into 4 main panels: (1) Installation (about R), (2) quick view, (3) input parameters, and finally (4) results.

Installation (about R)

The tool is created on R environment. For its correct installation it is necessary that the user downloads R and RStudio. For more information of R (including how to download it), visit cran.r-project.org. Once downloaded and installed R and RStudio, save the attached folder "Cost-effectiveness Tool" into a location you remember.

The folder contains: (1) a folder named "www" that loads some images to the tool and (2) the files "server.R" and "ui.R" which create the tool. The next step to correctly install the tool is to open the files "server.R" and "ui.R". When opening the files you should see:

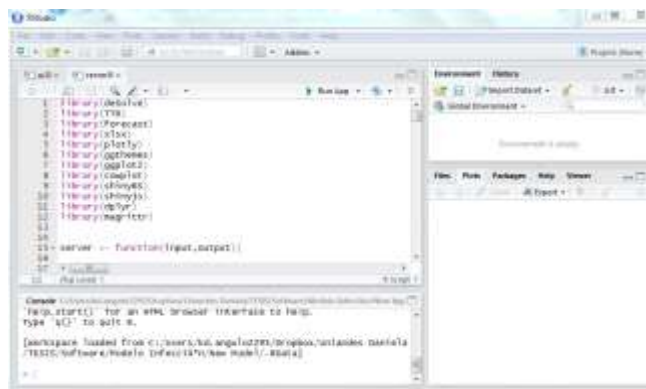


Figure 1. "server.R" and "ui.R"

The first time you use the tool, it will take longer to open, since it will start to install the necessary packages for its operation that are not previously installed on the computer. The other times when the user uses the tool will take a considerably less time to load.

Quick view

Once the tool is installed we proceed to run it. To do this, in any of the two files, "server.R" or "ui.R", click the "Run App" button.



Figure 2. Run App

Once we run the application will appear a popup tab, which will look like this:

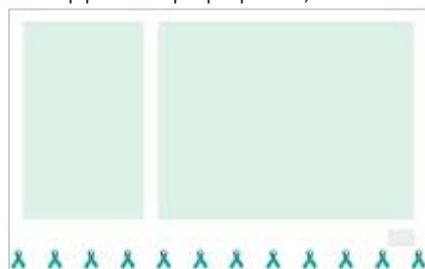


Figure 3. First pop up tab

After the first pop-up tab appears, two progress bars will appear indicating the percentage of data, death rate, and fertility that the tool has generated. The user shouldn't manipulate the application until all the data has been processed.

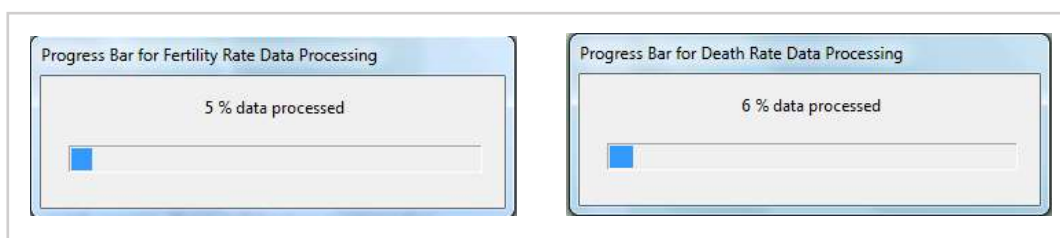


Figure 4. Progress bars

Once the application has finished processing the data a popup tab like the one shown in Figure 5 will appear. From that moment the user will be able to manipulate the tool.



Figure 5. Cos-effectiveness introduction panel

In this tab is explained how the different compartments, in which the population is divided, are generated. The population is divided into 3 different types of compartments: (1) population is divided into two genders, (2) into age ranges and (3) into biological compartments. For the age group it is necessary that the user specified the minimum, the maximum and the step of the age ranges. For the

biological compartments the user must select which of the biological compartments that he previously created in the parameters wants to see in the results. After all the compartments parametrization is completed, click on the “Next” button. After this, two things can happened, either there is showed the tan as in Figure 7 or a model parametrization error tab showed. The error can occurred because the user did not fill all the necessary field (min, max, step and at least one biological compartment should have been selected), or because the filled fields do not agree with respect to the parameters that the tool received. Until these errors are corrected, the tool will not allow you to advance to the results/prediction tab.

The results tab is shown as in Figure 7.

This tab presents the introduction to the application, what is the purpose and purpose of the tool, and what types of models can be solved with it. It also presents a short biography of the authors. Inside the tab is also display the "Next" button in the lower left. Click on that button and the application will show the parameterization tab, as shown in Figure 6.

Figure 6. Parametrization panel



Figure 7. Results tab

Input Parameters

The tool is highly parametrizable. In order to do this, the tool receives two different input parameter files. These files must be in the same folder in which the R executable is stored. For all the files that will be described below, keep in mind that the decimal separator is the comma (",") and that they cannot be changed the name and the format. These files are:

General Parameters:

This file is named "generales.txt". The final form of this data file should be as in Figure 8 (the order of the parameters in the file must be the same as it's presented here). The file contain the following 7 parameters:

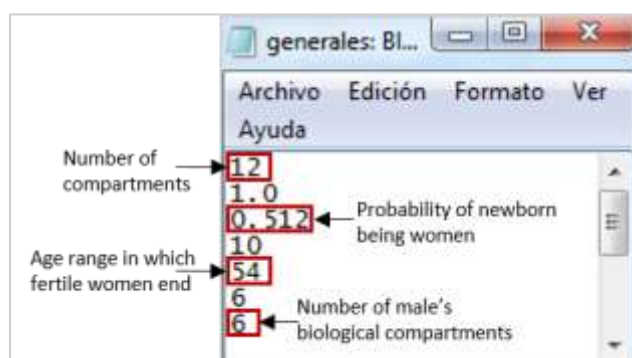


Figure 8. File "generales.txt"

1. **Number of compartments:** This parameter indicates the number of compartments (different to the age) in which the population was divided. For example: population was divided into 2 genders and 3 biological compartments (the number of biological compartments for men and women should be the same, in case they are not equal put all the necessary values in 0) so in total there are 6 compartments ($2 \cdot 3 = 6$).
2. **Aging Rate:** This parameter indicates the rate at which the population moves between age ranges per year. For example: 0.2
3. **Probability of a newborn being a female:** This parameter indicates the probability of a newborn being a female. For example: 0.5

4. **Age range in which fertile women start:** This parameter indicates the age range in at which fertile women start. For example, if the population is divided into age ranges of 5 years -{[0,4]; [5,9]; [9,14]; ...; [64,69]; [70+]}- this parameter will take the value of 3 if fertile women start between the ages of 9 and 14 or take the value of 4 if a woman is considered to be fertile from [15, 19].
5. **Age range in which fertile women end:** This parameter indicates the age range in which women are not considered fertile. For example, if the population is divided into age ranges of 5 years [0,4]; [5,9]; [9,14]; ...; [64,69]; [70+] this parameter will take the value of 10 if women end up being fertile between ages 44 and 49.
6. **Number of female's biological compartments:** This parameter indicates the number of biological compartments for women.
7. **Number of male's biological compartments:** This parameter indicates the number of biological compartments for males.

Rate and Transition Parameters:

This file is an Excel file named "ParametrosGenerales.xlsx". In this file is important to note that all cells must be values (do not put formulas). The file is organized within 8 sheets:

1. **Sheet 1:** This sheet contains death rates and the initial number of entities in every compartment in which the population is divided. To illustrate how to generate this sheet, suppose that we divide the population into 3 age ranges, 2 genders and 2 biological compartments. The organization of the data is shown below:

Males				Females			
M_S_AR1	M_S_AR1	M_I_AR1	M_I_AR2	F_S_AR1	F_S_AR2	F_I_AR1	F_I_AR2
1250	1100	1531	1839	1434	19951	464	976
0,03	0,03	0,03	0,03	0,03	0,03	0,03	0,03
0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01
0,02	0,02	0,02	0,02	0,02	0,02	0,02	0,02
0,05	0,05	0,05	0,05	0,05	0,05	0,05	0,05
0,05	0,05	0,05	0,05	0,05	0,05	0,05	0,05
0,06	0,06	0,06	0,06	0,06	0,06	0,06	0,06
0,00	0,00	0,00	0,00	0,00	0,00	0,00	0,00
0,01	0,01	0,01	0,01	0,01	0,01	0,01	0,01
infected males in the age range 1.				infected Females			

Figure 9. Mortality rate and initial population

As shown in Figure 9, each column of the data file represents a combination of all compartments (including age), for example: Susceptible Men in the age range 1 (M_S_AR1). Note that all combinations of men comes first and then all combination for women. In that order, the columns of women must follow the same order as that of men. So if the first

column of men is M_S_AR1 the first column of the women should be F_S_AR1. Finally, keep in mind that the first value of each column corresponds to the name of the column (M_S_AR2), the second value corresponds to the initial number of entities (purple boxes) and the other values (green boxes) correspond to the death rates. This same order must be used in the data file.

2. **Sheet 2:** This sheet contains the fertility rates of the population. These rates vary according to any compartment, i.e. if your model contemplates divisions in sex, biological stages and age, fertility rates will vary by biological stage and age. You must specify each of them in the data file. Each column in the text file represents the fertility rates for each compartment (for example: by biological compartment and age). The order of the columns should be the same as that used in the file of deaths, except that it is only necessary to specify the age ranges for in which women are fertile. The organization of the data is shown below:

F_S_AR1	F_S_AR2	F_I_AR1	F_I_AR2
0,03	0,03	0,03	0,03
0,01	0,01	0,01	0,01
0,02	0,02	0,02	0,02
0,05	0,05	0,05	0,05
0,05	0,05	0,05	0,05
0,06	0,06	0,06	0,06
0,00	0,00	0,00	0,00
0,01	0,01	0,01	0,01

Infected women

Figure 10. Fertility rate

3. **Sheet 3/4:** These sheets contains the transition probability matrices between biological compartments for women and men (sheet 3 and 4), respectively. Matrices should be square, were each entry of the matrix indicate the transition probability between two biological compartments. The format of the transition probability should be as shown in Figure 11.

	A	B	C	D	E	F	G	H
1		t+1						
2		S	I	PI	CIN1	CIN23	C	
3	S	0,1	0,1	0,1	0,1	0,1	0,5	
4	I	0,1	0,2	0,3	0,4	0	0	
5	PI	0	0	0	0,5	0,5	0	
6	CIN1	0	0	0,2	0,4	0	0,4	
7	CIN23	0,1	0,2	0,3	0,2	0,2	0	
8	C	0	0,3	0,7	0	0	0	
9		S	I	PI	CIN1	CIN23	C	
10	S	0,1	0,1	0,1	0,1	0,1	0,5	
11	I	0,1	0,2	0,3	0,4	0	0	
12	PI	0	0	0	0,5	0,5	0	
13	CIN1	0	0	0,2	0,4	0	0,4	
14	CIN23	0,1	0,2	0,3	0,2	0,2	0	
15	C	0	0,3	0,7	0	0	0	
16		S	I	PI	CIN1	CIN23	C	
17	S	0,1	0,1	0,1	0,1	0,1	0,5	
18	I	0,1	0,2	0,3	0,4	0	0	
19	PI	0	0	0	0,5	0,5	0	
20	CIN1	0	0	0,2	0,4	0	0,4	
21	CIN23	0,1	0,2	0,3	0,2	0,2	0	
22	C	0	0,3	0,7	0	0	0	
23								

Figure 11 Transition Probability matrices

There are as many transition matrices as age ranges. The first matrix indicates the transition between age range 1 and age range 2. The second matrix indicates the transition between age range 2 and 3, so on and so forth. It is important to always conserve the row and column names (as shown in Figure 11).

4. Sheet 5:

This sheet contains 5 columns. Each column has a name that cannot be replace. In column 1 ("Biological") you should write the names of the biological compartments you used to divide the population. In column 2 and 3 you should write the death rate due to that biological state for men and women, respectively. An example is shown in Figure 12, the death rate due to cervical cancer is 0 for men and 0.52 for women.

	A	B	C	D	E
1	Biological	Men	Female	Code	Pinfection
2	Susceptible	0	0	S	0.410
3	Infected	0	0	I	
4	P.Immune	0	0	S	0.205
5	CIN1	0	0	P	
6	CIN23	0	0	P	
7	Cancer	0	0.52	P	

Figure 12. Sheet 5(ParametrosGenerales.xlsx)

In order to generate the transition rates to infected compartments, the application uses a convention box to know which compartment are of certain type. Table 1 shows the convention the user should use to fill column 4 ("Code").

Table 1. Convection box for biological compartments

Biological Compartment Type	Description	Convention
Susceptible	Individuals in this compartment do not have the infection but they are susceptible to get it.	S

Infected	Individuals in this compartments are infected.	I
Partially Immune	Individuals in this compartment had the infection, and now they have less probability of acquiring.	PI
Progress	Individuals in this compartment have a progression from the infection but that haven't reach cancer.	PL
Cancer	Individuals at any stage of cervical cancer-	C

Finally in column 5 ("Pinfection") for all Susceptible ("S") compartments the user must provide the probability of acquiring the infection in one sexual relationship.

5. Sheet 6:

This sheet contains the average number of sexual partners in a year that have males (column 2) and females (column 3), for each age range that applies, as is shown in Figure 13. For example, the average number of sexual partners that women have in the age range 19 is 0,785 per year.

	A	B	C
1	Age Range	Male	Female
2	16	0,45578	0,27388
3	17	0,77058	0,41803
4	18	1,10531	0,57154
5	19	1,37455	0,78560
6	20	1,63382	0,86831
7	21	1,71156	0,90336
8	22	1,80892	0,94801
9	23	1,82043	1,02811
10	24	1,70498	0,99658

Figure 13. Average number of sexual couples

Probability of infection formula:

Many of the parameters that were previously requested will be used to calculate the likelihood that an individual who is susceptible will acquire the infection within a year. The formula used to calculate this probability is:

- For men:

$$P(S \rightarrow I) = 1 - e^{-\left(\left(\frac{\text{total Infected women}}{\text{total women}} * \# \text{Sexual Partners} * P_{\text{Infected}_s}\right) \cdot 1\right)}$$

- For women:

$$P(S \rightarrow I) = 1 - e^{-\left(\left(\frac{\text{total Infected men}}{\text{total men}} * \text{\#Sexual Partners} * P_{\text{Infected}_s}\right) \cdot 1\right)}$$

6. Sheet 7:

This sheet contains the list of screening tests for women with their respective sensitivity. In the first column the user must provide all the possible screening test that women can have and in the second column the respective sensibility to that screening test, as is shown in Figure 14.

	A	B
1	Test	Sensibility
2	Citology	0.78
3	HPV-DNA	0.9

Figure 14. Screening tests

7. Sheet 8:

This sheet contains the average screening coverage of the country for each age range. As is shown in Figure 15 the first column (“Age Range”) should have all the age ranges that are considered in the model. The second column (“Coverage”) should have the average screening coverage for each age range.

	A	B
1	Age Range	Coverage
2	1	0
3	2	0
4	3	0
5	4	0
6	5	0.66726619
7	6	0.68199234
8	7	0.67926357
9	8	0.74455446
10	9	0.73822976

Figure 15. Screening coverage

Results

The results will be displayed in graphical form, with tables or downloading the results. To do this, the tool will have four tabs (explanation for the tabs are shown in order according to the order that they appear in the application):

1. Prevention Policy tab:

This first tab, does not show any results, on the contrary it is use to parametrize the vaccination and screening policies.) In this tab the user must enter the vaccination and

screening policy that he wants to apply to the population. In order to do this, within this panel the tool has two separate boxes for vaccination and screening.

Figure 16. Vaccination policy box

The vaccination box is the first one to appear. The user must select first to which gender(s) will apply the vaccination policy. In case there is not vaccination policy, do not select any gender. Once the user has chosen the genders, you can select the age ranges, the vaccination percentage (percentage of people to whom the vaccine will be given), and the years in which the policy will be applied. Once the user enter all

the specifications for the vaccination policy, he should click on the “Add Vaccination Policy” button, once he clicks on that button a message box should appear indicating the specifications of the vaccination policy. If the policy has an error (i.e. the age ranges selected for the vaccination policy are not in accordance with the data entered in the parameters) the message box will show the error found, if any error is found, **NO** policy will be applied.

Figure 17. Screening policy box

In the second box of this panel the user can enter the parameters to define a screening policy, as is shown in Figure 17. The screening structures that can be evaluated with the model consist of 3 different stages, as shown in Figure 18. The user can choose whether to use each stage within the screening tests or not.

The first stage is a primary screening test. A woman to whom the primary screening policy is applied, precancerous lesions will be detected with a probability equivalent to the screening coverage for that age range and to the sensitivity of the test applied. If the lesion is detected the model assumes that the woman will start a treatment and therefore will pass the stages of Partial Immune (“PI” according to our convention). Otherwise, (if the lesion is not detected) the disease will continue its natural course.

The second stage is the triage test. If the primary test is positive and the user decides to apply a triage test then the first positive result will be confirm with another test (triage). The triage or second test will detect the lesion with a probability equivalent to the sensibility of the test applied. If the lesion is detected the model assumes that the woman will start a treatment.

Otherwise (if the lesion is not detected) two things can happen (1) if the user decides to have a tracking policy (third stage) then the woman will perform another test (follow-up test) after n months of having performed the triage test, or (2) if the user decides to not have a tracking policy (third stage) then the disease will continue its natural course. Figure 18 shows the three stages within the screening policies evaluated by the model.

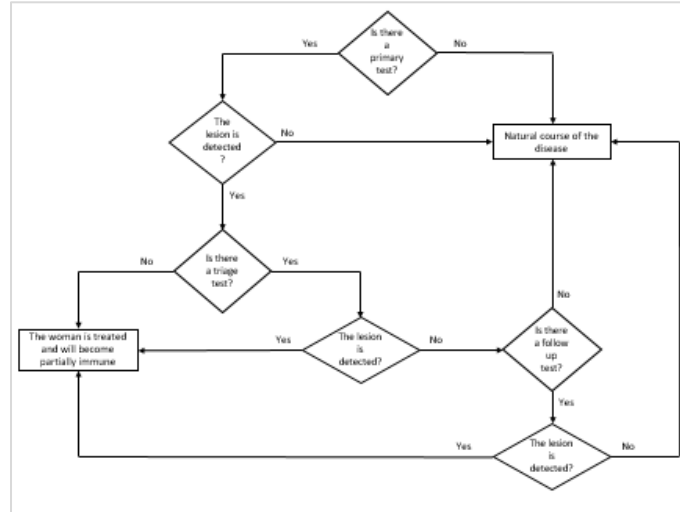


Figure 18. Possible screening policies for the model

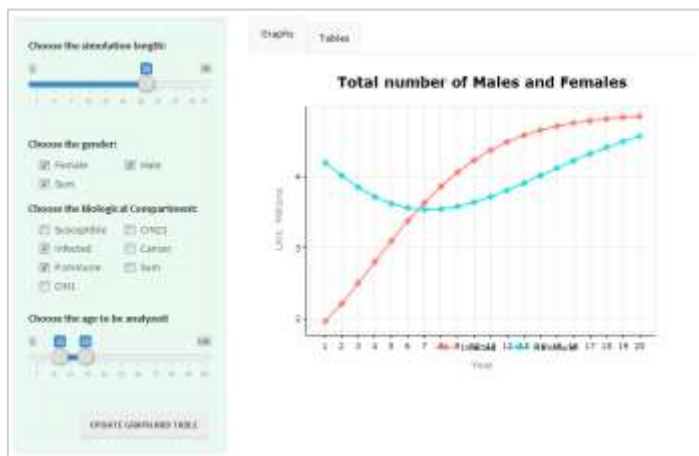
In the screening policy box there are the three types of test: primary, triage and follow up. The blue boxes in Figure 17 allow the user to choose which test applies, the option “None” will be taking as no policy for that stage. In the red boxes the user must provide the age range at which the screening policy for that test will apply. In the green boxes the user must enter the last age range at which women are into the screening policy. In the purple boxes the user must enter the number of years (in terms of age ranges) that a woman should expect to re-test. In the yellow boxes the user must provide the time, in months, to take the follow up test after a positive result in the primary test and a negative result in the triage test.

Once the user enters all the specifications for the screening policy, he should click on the “Add Screening Policy” button, once he clicks on that button a message box should appear indicating the specifications of the screening policy. If the policy has an error (i.e. the age ranges selected are not in accordance with the data entered in the parameters) the message box will show the error found, if any error is found, **NO** policy will be applied.

2. Population Prediction tab:

The objective of this tab is to present the population results of the model. For that, the tab has a left panel (green) in which the user can choose the length of the simulation and the population that wants to visualize. Once the user has chosen the gender, the biological compartment and the age range he can update the graph and table with the button “Update graph and table”. A Progress bar (“Progress Bar for Differential Equations”) will appear indicating the percentage of differential equations that have been solved. Once the

application finishes all the equations, the graph and the table will appear in the "Graph" and "Table" panel, respectively.



The sum checkbox in the field of gender and biological compartments means that the sum of the other selected fields will be displayed in the graph. For example in Figure 14 "Female", "Male" and "Sum" were selected for the gender field and "Infected" and "P.Immune" were selected for the Biological Compartment field. The graph will display two curves, each one is showing the sum of males

and females in one biological compartment. As there are two biological compartments selected there will be two curves displayed. Also each curve is showing the sum of males and females in "Infected, i.e." from the 15 to 30 age range (sum).

Figure 19. Population Prediction Graph

In Figure 15 "Female" and "Male" were selected for the gender field and "Susceptible", "Infected" and "Sum" for the biological compartment field. The graph will display two curves, one for females and the other one for males. Each curve is showing the total number of males/females in each biological compartment for the 52 age range.

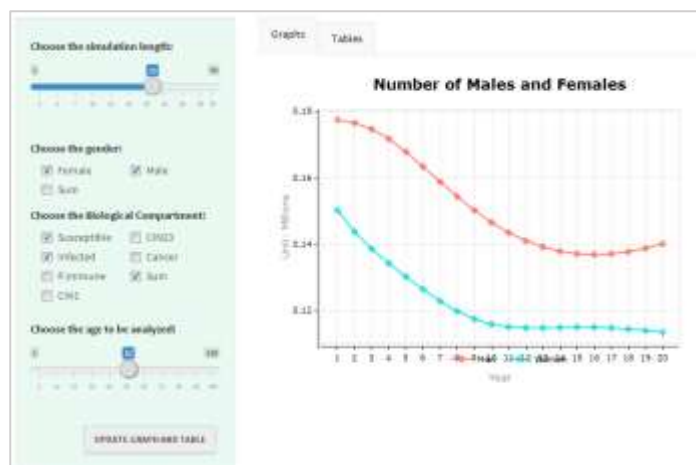


Figure 20. Population Prediction Graph

In the Table panel the results are display in a table form. Also you can also download the result of the differential equations with the "Download" button.

3. Public Health Indicators tab:

The objective of this tab is to present the Public Health indicators of the model. In order to do so, the tab has a left panel (blue) were the user can choose the simulation length, the biological compartments and the health indicators to show. The results are display in two forms: graphically and in a table.

In the biological compartments field the user can choose any of the Progression type biological compartments (the ones with a “LP or a C” in the parameters). Also there are five types of health indicators: (1) Number of cases, (2) Number of deaths, (3) Incidence, (4) Deaths per million and, (5) Death rate.

The results of the Health Indicators Panel as are shown in Figure 16. Also the user can download the results or save the figure with the “Save Figure” and “Download Data” buttons.

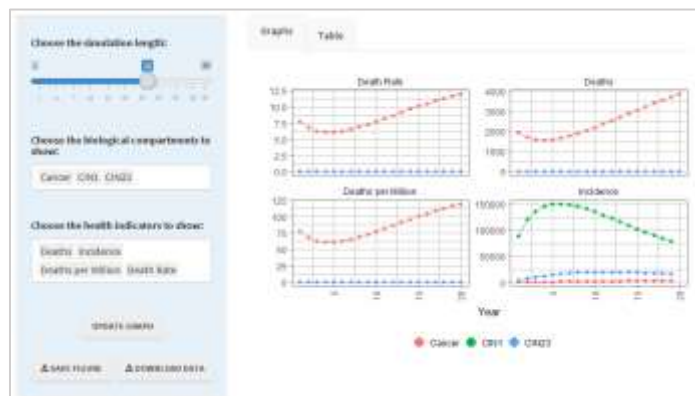


Figure 21. Health Indicators panel

4. Policy comparison tab:

The objective of this tab is to compare different policies. In order to do so the tab let you select three “.csv” files that have the solution for the differential equations. In particular, the files you may select can be the same as the one the user can download in the Population Prediction Tab.

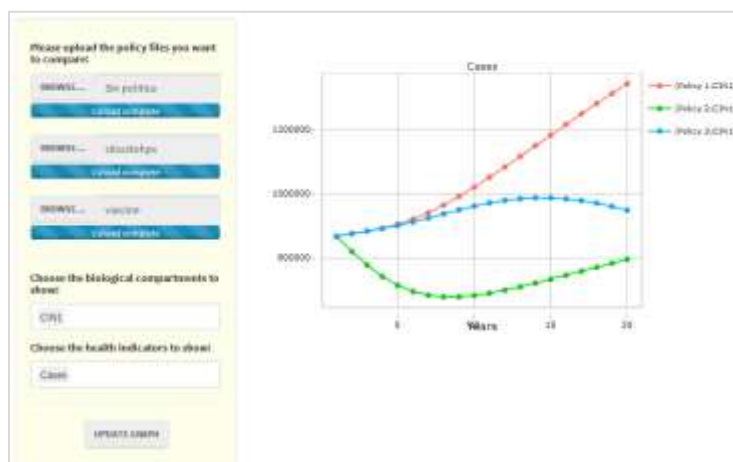


Figure 22. Policy prevention tab

To show the results of the comparison the application will display graphs according to what is selected in the “Biological Compartment” and in the “Health indicators” fields. In the biological compartments field the user can choose any of the Progression type biological compartments (the ones with a “LP or a C” in the parameters). Also there are five types of

health indicators: (1) Number of cases, (2) Number of deaths, (3) Incidence, (4) Deaths per million and, (5) Death rate. Once the user have selected all the files and the biological compartment(s) and the health indicator(s) to show, it should click on the “Update Graph” button. The results are shown as in Figure 22.