

--EUFRA--

USER MANUAL

This manual introduces the “European *Up-Front Risk Assessment Tool*”. *EUFRA* was developed for researchers and policymakers to allow quantification of the risk of transmission of an emerging infectious disease by blood transfusion. The tool estimates the number of transfusion recipients that become infected through transfused blood, either during a local outbreak of an infectious disease, or because donors visited an outbreak area.

Before using *EUFRA*, we recommend users to read **PART I** of this manual which provides an overview of the structure and the main features of the tool. **PART II** provides a definition of all parameters used in the model as well as a list of pre-specified model parameter values for a number of diseases. For the more interested reader, **PART III** provides information on the underlying model, modelling assumptions and formulas for calculating various outputs. Finally, **Part IV** contains a list of frequently asked questions.

There is a separate set of worked-out examples for historical outbreaks and slides of a presentation on the *EUFRA* tool in the documentation section of the tool.

If you have any questions or suggestions concerning the tool, this manual or any of the other materials provided, please contact Mart Janssen at m.p.janssen@umcutrecht.nl.

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PART I: General Overview

Introduction

The European Up-Front Risk Assessment Tool (*EUFRAF*) aims to assess and quantify the risk of transmission of an emerging infectious disease by blood transfusion during an ongoing outbreak. The tool allows assessment of the associated risks to transfusion recipients in an outbreak affected region as well as the risk from a donor that has visited an outbreak affected region.

The tool consists of four steps that describe the blood transfusion chain from start to finish: from the risk of blood donors in the exposed population of becoming infected, to the risk of recipients to become infected from contaminated end products. The blood transfusion chain is schematically depicted in **Figure 1** with the corresponding steps that can be found in the tool.

Tool steps:

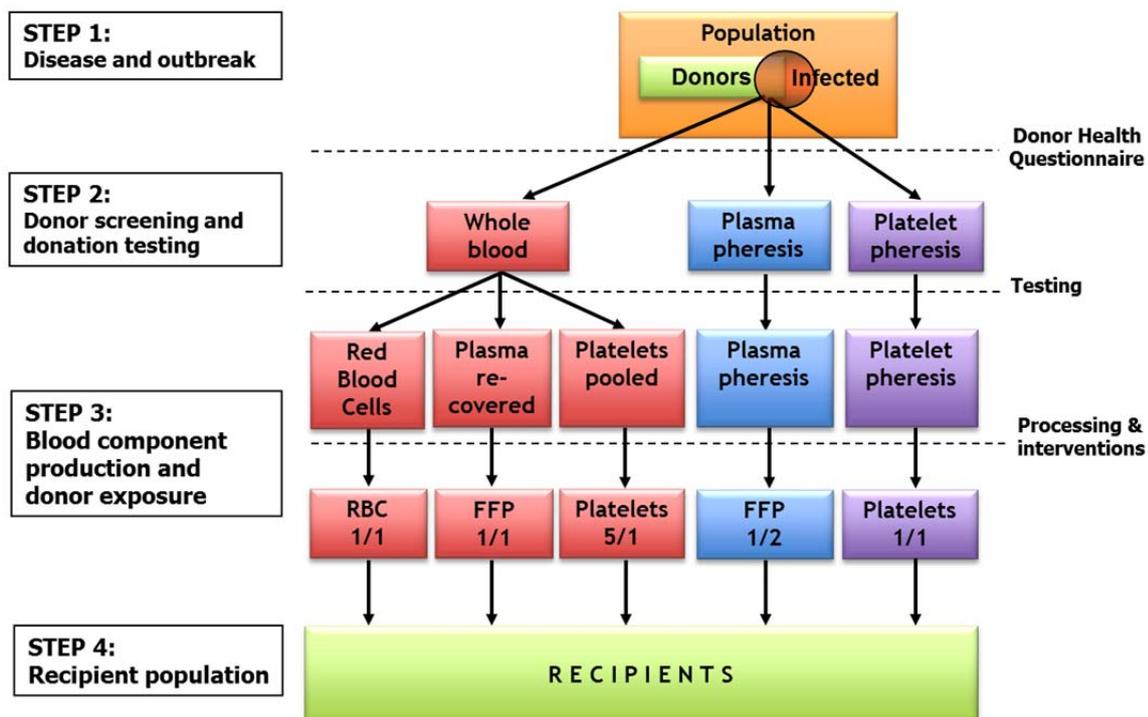


Figure 1: Schematic overview of the blood transfusion chain, showing four steps with potential interventions to prevent transmission of infection.

As part of the general population donors are at risk of infection during a disease outbreak (Step 1). Before donating donors may be excluded for donation by a donor health questionnaire in which donors with risk factors related to exposure or symptoms of infectious diseases are identified. In addition, donations may be tested for infectious

diseases (Step 2). Donors will donate blood with a certain frequency, which is usually dependent on the gender of the donor and on the type of donation, i.e. whole blood (WB) donation, plasmapheresis, and platelet pheresis. Donations are processed into different blood products that are delivered to patients, for instance WB donations are split into red blood cells, plasma and platelets. Platelet products for transfusion are usually obtained by pooling donations from multiple donors. Also, products might undergo further processing to increase safety of the end product (Step 3). Finally the blood products are administered to recipients (Step 4).

The four steps and associated transmission risks and interventions shown in **Figure 1** form the input of the *EUFRAF* tool, and will lead to the output risk estimates indicated in **Figure 2**. The tool will calculate these values using donor, infection and setting-specific information in addition to the result from the previous step, ending in Step 4 with the risk of infection in recipient.

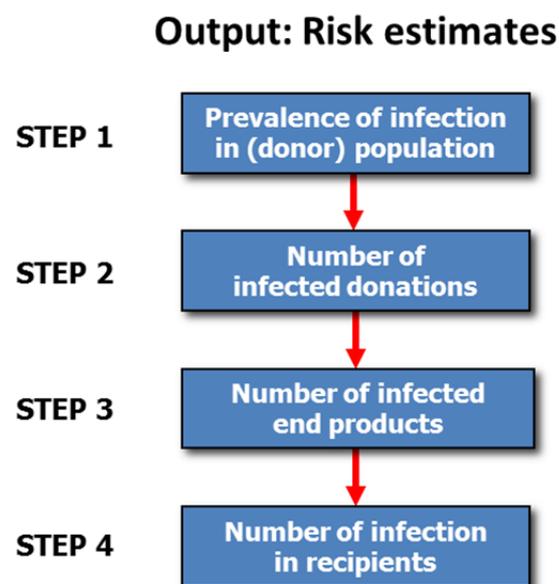


Figure 2: *EUFRAF* output quantifying the risk associated with each step in the transfusion chain.

***EUFRAF*'s Main features**

The tool has two main features: a set of questions that determine the setting of the risk (what is it the user wants to analyse?), and depending on its setting various inputs and outputs will be shown or hidden from the user. The inputs and outputs are grouped per step and initially all hidden from the user (see **Figure 3**).

Specification questions

With the specification questions the user controls the analysis to be performed. The specification question settings tailor the model to the needs of the user. First, the name of the infectious disease of concern can be selected from a dropdown list (see **Figure 3**). By selecting a specific disease the built in disease parameters are loaded. Note that these values should be considered as an indication only. The user is expected to select appropriate

values for the assessment by reviewing and interpreting most recent literature on a particular disease available. If the particular disease of interest is not in the list, the ‘*Not specified*’ selection can be used and disease parameters specified by the user. Next, a set of six yes/no questions need to be answered. These specify whether the risk of a local outbreak or travelling donor risk needs to be assessed, whether data on infected donors is available, whether the disease considered is infectious during a chronic phase, which safety interventions are to be considered, and for which point in time the risk needs to be assessed. Based on the answers to these questions, the tool will provide a relevant set of input fields for each step and adjust the model outputs accordingly.

Model Input and output per step

The model requires input for various model parameters. Values for these model parameters have to be provided by the user. Examples of such parameters are: number of infections observed during the outbreak, duration of the outbreak, duration of infectiousness of an infected donor, effectiveness of screening, number of blood products delivered for transfusion, proportion infections that become chronic. The input and outputs are grouped together per step. In **Figure 3** each of the steps is shown, but not the inputs and outputs (see **Figure 4** for the complete in- and output for Step 1). Whenever these sections are expanded the input fields are shown first, followed by the risk estimates for that step.

The model output consists of calculated risks. These are provided per step in the blood transfusion chain and are presented in the last row(s) of each step. When the calculation checkbox ‘Automatically recalculate...’ is ticked for automatic recalculation the output data will be immediately updated after a change of inputs. Otherwise, click on the blue ‘Calculate’ button (see **Figure 3**) to update the calculation results.

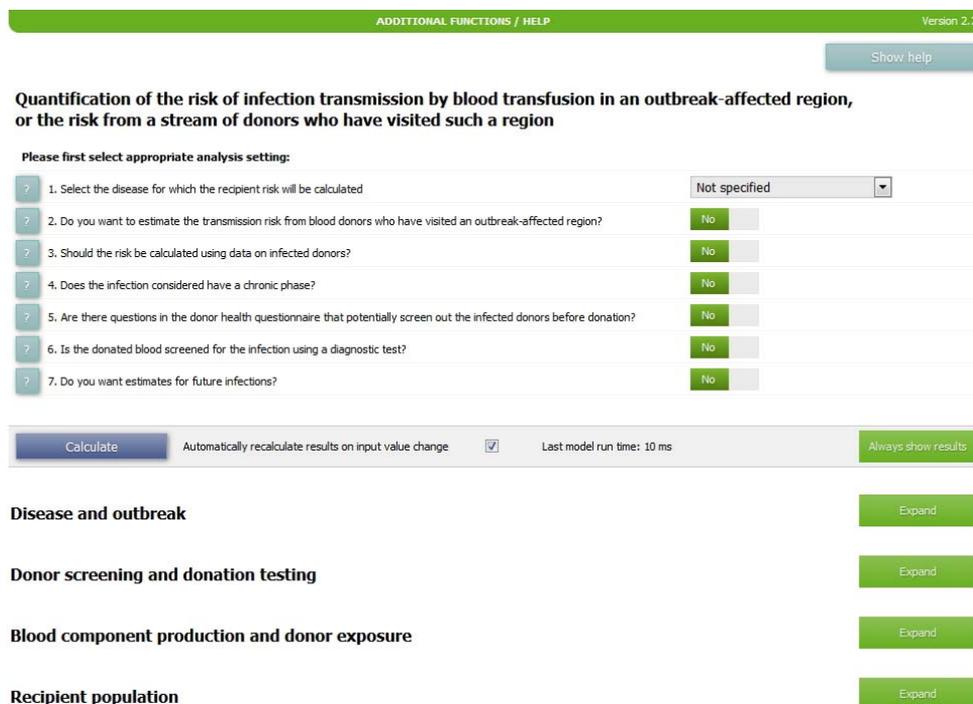


Figure 3: EUFRAT’s opening page displaying its main features.

Expand and Collapse

The ‘Expand/Collapse’ buttons serve to simplify the appearance of the tool by allowing the user to show or hide parts of the input and output fields. The majority of fields are hidden from the user by default. They appear when the ‘Expand’ button for a particular step is clicked. For instance, in **Figure 4** Step 1: ‘Disease and outbreak’ is expanded, now showing the parameter values for its sub-sections ‘Population exposure & susceptibility’ and ‘Disease characteristics’. The other steps remain hidden from the user. Clicking the ‘Always show results’ button will make the tool display results for each of the steps at any time, irrespective of the step being collapsed or not.

ADDITIONAL FUNCTIONS / HELP
Version 2.2

? 5. Are there questions in the donor health questionnaire that potentially screen out the infected donors before donation? No

? 6. Is the donated blood screened for the infection using a diagnostic test? No

? 7. Do you want estimates for future infections? No

Calculate
Automatically recalculate results on input value change
Last model run time: 21 ms
Always show results

Disease and outbreak
Collapse

Population exposure & susceptibility	Value	Unit	Type
Cumulative infections reported (Ip)	<input type="text" value="10"/>	[-]	Const.
Duration of epidemic (D0)	<input type="text" value="100"/>	days	Const.
Population size (N)	<input type="text" value="100000"/>	[-]	Const.
Donor relative risk (RR)	<input type="text" value="100"/>	%	Const.
Disease characteristics	Value	Unit	Type
Proportion of undetected cases (pu)	<input type="text" value="50"/>	%	Const.
Duration of infectivity for acute infection (Da)	<input type="text" value="365"/>	days	Const.
Duration of latent period of acute infection (Dia)	<input type="text" value="0"/>	days	Const.
	Value	Unit	Type
Estimated incidence rate in the donor population (I)	2.00e-6	per day	Const.
Prevalence of infectious donors at the time of last observed infection (Pr)	2.00e-4	[-]	Const.

Donor screening and donation testing
Expand

Blood component production and donor exposure
Expand

Recipient population
Expand

Figure 4: Step 1 ‘Disease and outbreak’ expanded.

Model Input and Output

Model parameters

Depending on the specification questions relevant model parameters will be requested from the user. For each of the model parameters a more elaborate description is provided in **PART II** of this user manual. These can also be accessed by clicking on the parameter definitions in the tool as well. The majority of these definitions however should be self-explanatory.

Using default values

Model inputs, shown with their associated reference symbols, are the parameters used in the risk calculations. Some inputs must be filled in by the user and should reflect observations made during the disease outbreak. Their values are blank by default. This mandatory input represents the minimum of information necessary to calculate risks. For some model parameters for which references are available from the literature (e.g. disease characteristics), default values are provided (also refer to the section ‘Outbreak characteristics of 18 diseases’ in **Part II** of the manual). The user can change these values, but the default values will reappear whenever the self-entered values are removed or the disease is reselected.

Constant versus Range parameters

The tool offers two options for defining an input parameter: the user can enter a fixed value (‘Constant’) or, a range of values (‘Distribution’). A distribution should be used when the user is uncertain about the exact value of an input parameter. Most input fields can be selected by the user to be either constant (point values) or a range (distribution) of values. This is done by pressing the ‘Const.’ button which will turn to ‘Distr.’ or reverse when clicking it again (see **Figure 5**). In case of a ‘Distr.’ input, the user provides the most likely value (the mode) of the input parameter, as well as the minimum and maximum values perceived plausible.

Disease and outbreak Collapse					
Population exposure & susceptibility	Min (input) 2.5% (output)	Mode (input) Mean (output)	Max (input) 97.5% (output)	Unit	Type
Cumulative infections reported (Ip)		<input type="text" value="10"/>		[]	Distr.
Duration of epidemic (D0)	<input type="text" value="90"/>	<input type="text" value="100"/>	<input type="text" value="110"/>	days	<input type="button" value="Distr."/>
Population size (N)		<input type="text" value="100000"/>		[]	Const.
Donor relative risk (RR)		<input type="text" value="100"/>		%	<input type="button" value="Const."/>
Disease characteristics	Min (input) 2.5% (output)	Mode (input) Mean (output)	Max (input) 97.5% (output)	Unit	Type
Proportion of undetected cases (pu)		<input type="text" value="50"/>		%	<input type="button" value="Const."/>
Duration of infectivity for acute infection (Da)		<input type="text" value="365"/>		days	<input type="button" value="Const."/>
Duration of latent period of acute infection (Dia)		<input type="text" value="0"/>		days	<input type="button" value="Const."/>
	Min (input) 2.5% (output)	Mode (input) Mean (output)	Max (input) 97.5% (output)	Unit	Type
Estimated incidence rate in the donor population (I)	9.18e-7	2.00e-6	3.44e-6	per day	Distr.
Prevalence of infectious donors at the time of last observed infection (Pr)	9.15e-5	2.00e-4	3.46e-4	[]	Distr.

Figure 5: Constant versus range parameters. For range parameters the most likely value and a range (minimum and maximum value) are specified. Pressing the type button will change the number of input cells (one or three) and toggle its description between ‘Const’ (orange) and ‘Dist’ (blue).

Accordingly, the output will not be a single calculated value but rather a range of values which will reflect the uncertainty in the estimated output. The tool shows the mean (expected) risk and a 95% credibility interval for the risk estimates in the output field. The credibility interval will indicate an interval of values which is expected to contain the true estimate with 95% probability. The user can view input and output distributions by clicking on the name of the desired parameter and next selecting the ‘Chart’ tab.

If any input parameter is switched to Type 'Distr.', a distribution of output values will be generated for all output parameters from that step onwards.

Not all model parameters can be drawn from distributions. The number of cumulative infections reported (I_p) and the population size (N) are presumed known, as are the number of donors and donations. The remaining risk of transmission after processing (pit), and the specific immunity in recipient population (pim) which are specified per type of product are implemented as non-range parameters.

Model outputs

At the end of each step the calculated output is shown in a light grey / pink background colour (for inputs the background colour is white, see in **Figure 5**). It is possible to show the output irrespective of whether the step inputs are hidden or not by clicking the 'Always show results' button on the right hand side of the bar with the 'Calculation' button (see in **Figure 4**). This enables easy review of model outputs when changing particular input values.

Next to the total number of transmissions by blood transfusion, the *EUFRAF* model allows calculating the number of transmissions expected to occur after a specified time point. As such transmissions may occur after the end of the current outbreak we refer to these as future transmissions. If the user answers the specification question 'Do you want estimates for future infections?' positive, output estimates for transmissions after the specified time point will be shown in addition to the total number of infections with a light blue background colour. In case this specification question is set to 'Yes', Step 1 will contain an additional input field where the user can specify the point in time that distinguishes past from future risks (**Figure 3**).

Note that in case the travellers' risk is calculated, the outputs from Step 1 and Step 2 are not calculated immediately. This is because these calculations require the number of donors in the donor population which are entered in Step 3 ('Blood component production and donor exposure').

Warning messages

A warning message may appear in the right upper corner when an input value is entered that falls outside the range of values allowed for entry. Moreover, an 'x' sign will be shown next to the field concerned with an indication of the cause of the error. The step header will turn red as well to indicate that there is an error in the input in that step. This allows users to note errors even when input and outputs are not visible.

Information and Charts

A brief description and/or comment on what each of the input/output fields refer to appears in a separate window when a user clicks on the input/output item and selects the 'Info' tab. For inputs or outputs derived from range inputs the probability distribution of the parameter can be found under the 'Chart' tab (see **Figure 6**). The chart tab also displays distribution statistics. The dialog box can be moved with the mouse by clicking on the top grey bar and can be closed by clicking on the 'x' in the upper right corner.

Change parameter descriptions

Some input fields can be renamed by the user. This can be for example the case for donation types and blood product descriptions. The descriptions can be changed by pressing the <SHIFT> key whilst clicking on the parameter name. The text will next appear in an editable cell and can be changed as desired.



Figure 6: Probability distribution of the Prevalence of infection as calculated by the EUFRAT model.

Additional functions / Help

The ‘Additional functions / Help’ panel, which is hidden behind the green bar at the top of the screen (see **Figure 3**), can be shown or hidden by clicking the bar. The panel consists of four tabs: Simulation, Print, Save/Load, and Documentation (see **Figure 7**).

Simulation

As explained in the section ‘Constant versus range parameters’, the tool offers the option to specify an uncertainty range for input parameters (minimum, maximum and most likely value, the ‘mode’). The model will incorporate the parameter uncertainty by calculating the outputs using Monte-Carlo simulation. This means that for each parameter for which a plausible range was entered, its parameter value will be determined by a random draw from a triangular distribution defined by its range parameters. Model outputs are next calculated for a large set of such model inputs (the ‘samples’), which will result in a distribution of model output values as shown in **Figure 6**.

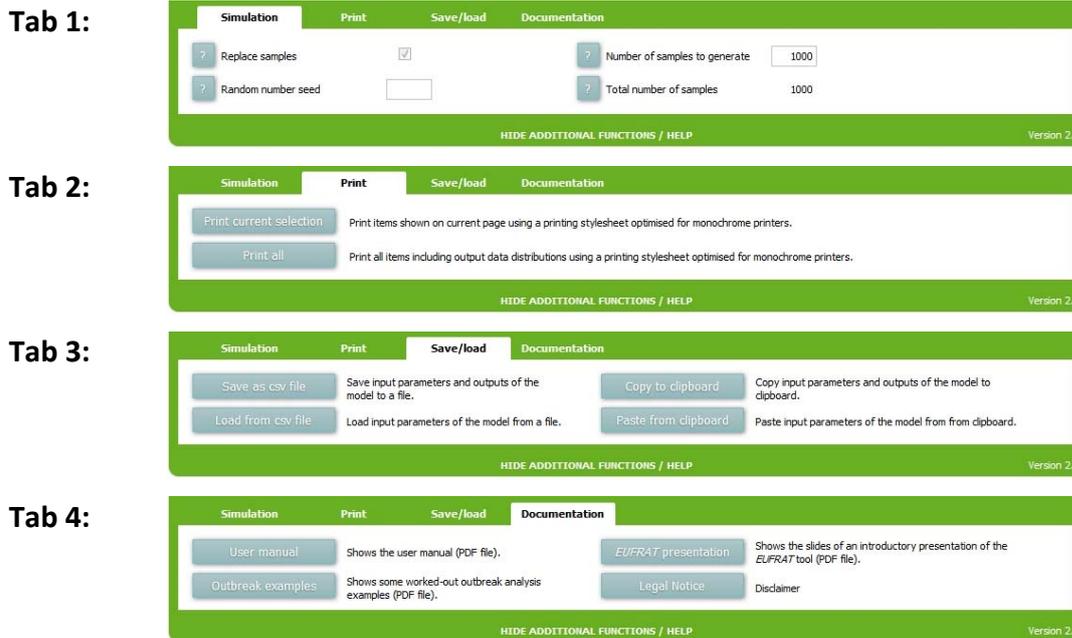


Figure 7: The four tabs of the ‘Additional functions / Help’ panel.

In the ‘Simulation’ tab, users can define how many samples the model will generate per calculation. Increasing the number of samples will produce more precise estimates (smoother histograms for the simulated outputs). However, as increasing the number of samples will also increase calculation time it is advised to leave initial analyses at 1000 samples. ‘Replace samples’ should be ticked to indicate that the currently generated samples are replaced, but unticked when newly drawn samples should be added to the previously generated samples whenever the user presses the ‘Calculate’ button. This allows the user to monitor the change in output estimates when increasing the number of samples. Note that the checkbox for ‘Automatically recalculate results on input value change’ to the right of the ‘Calculate’ button needs to be unticked to enable changing the ‘Replace samples’ checkbox setting. The right hand side of the panel shows the ‘Number of samples to generate’ per run as well as the ‘Total number of samples generated’ which is updated after every calculation. Make sure that none of the model parameters or analysis settings are changed between simulation updates as this will lead to invalid results.

Entering a value in the ‘Random number seed’ entry field ensures that the same ‘random’ calculations are performed to determine the outputs for every run. This ensures reproducibility of the results obtained. Every seed number however will generate its own (reproducible) output, so the actual value of the seed is not important.

The three probabilistic input parameters (minimum, maximum and most likely values) serve to define a triangular distribution from which values are sampled to calculate the model output. Output values will be presented as distributions whenever at least one input parameter is set to ‘Distr.’. The tool will automatically evaluate the uncertainty in incidence and prevalence estimates, which is calculated as a ratio of two fixed numbers (e.g. the cumulative infections reported divided by population size, or the number of infected donors divided by donor population size) and sampled from a beta distribution.¹ The α and β parameters of this beta distribution will be the number of infected and the number of non-

infected individuals respectively. The use of the beta distribution allows obtaining risk estimates that incorporate the uncertainty associated with the amount of data available for incidence or prevalence estimation.

Print

The 'Print' tab allows printing of the current analysis. To print all model input and calculation results press 'Print all', or make a selection and press 'Print current selection' for a particular selection of results. Any graphs opened are printed at the end of the print. Note that the quality of printing is very dependent on the browser used. If this doesn't work well with your browser, please use the computer's print screen option keep a record of your results.

Save/load input and output

All model input values and settings as well as model output can be stored in a text file by clicking on the 'Save as csv file' button. The data from a saved text file can be loaded for reuse by clicking the 'Load from csv file' button. Some systems do not allow saving files directly from a web browser for security reasons. In that case use the 'Copy to clipboard' function. A window will open containing all model input and settings data which can be copied to a text file for storage. For loading saved input data, copy the data stored in the text file and paste these in the window that appears when clicking 'Paste from clipboard' button. Next, click on the 'Load' button to load the data.

A separate MS-Excel spreadsheet is provided to facilitate post-processing of the output data saved in a CSV file. The spreadsheet can be downloaded from the home directory of the tool ('http://eufrrattool.ecdc.europa.eu/Read_EUFRRAT_CSV_output.xlsm'). How this spreadsheet is used is explained in the file itself. Basically all the user has to do is specify the name of the CSV output-file.

Documentation

The documentation consists of this user manual, worked-out outbreak analysis examples, and slides of a presentation on the *EUFRRAT* tool. In addition, a disclaimer is included in the documentation section. Each item can be accessed by clicking the corresponding button.

PART II: Model Parameter Definitions and Values

This section provides definitions of all input, output, and specification questions incorporated in the *EUFRAF* tool. When using the tool it is important to remember that different sets of input and output parameters may be displayed depending on the combination of answers to the specification questions.

Specification Questions

EUFRAF contains a set of questions that specify which risk(s) will be calculated. Based on the answers to these questions, the tool will provide a set of input fields for each step and the corresponding model outputs.

1. Select the disease for which the recipient risk will be calculated.

If you select a specific disease, disease parameters are automatically provided whenever these were available from literature. You can also leave this field unchanged ('Not specified') if you don't want to use pre-specified values. All input values can be specified by the user.

2. Do you want to estimate the transmission risk from blood donors who have visited an outbreak-affected region? (instead of the risk from donors residing in the outbreak area)

If 'Yes' is selected, the number of recipients getting infected by donors who visited an outbreak region is calculated. Apart from outbreak and disease specific data additional information will be requested on travel (number of donors per year and duration of visit). If 'No' is selected, the number of recipients in the outbreak area getting infected by donors who reside in the outbreak-affected region is calculated.

3. Should the risk be calculated using data on infected donors? / Do you have data on the number of infected donors?

Information on either infected individuals in the general population or on infected donors can be used as input. If 'Yes' is selected, the requested input is the number of donors identified as infected. Identification of infected donors is possible either by testing donations or from the notification/surveillance system. If 'No' is selected, the requested input is the number of infections reported in the population of the outbreak-affected region.

4. Does the infection considered have a chronic phase?

For some diseases, acute infected individuals might progress into an infectious chronic phase in which the infection remains transmissible by blood transfusion.

- Are there questions in the donor health questionnaire that potentially screen out the infected donors before donation?

This refers to the questions in the donor health questionnaire, which can either be introduced during the outbreak or be an existing questionnaire that potentially screens out donors with certain risk factors or symptoms related to the disease of concern before they donate blood. If the questions are not specific for the disease of concern but may partly work because of similar symptoms or exposures as other diseases included in the existing questionnaire, users should select 'Yes' and partial effectiveness should be considered.

- Is the donated blood screened for the infection using a diagnostic test?

This refers to the test(s) implemented to screen the donated blood for the infection, in order to exclude donations that are reactive in the test. This test can either be introduced during the outbreak or be part of the existing safety measures.

- Do you want estimates for future infections?

The user can choose obtain estimates for the total number of infections expected beyond a certain point in time. If selected 'Yes', for each step future infections will be shown in addition to the total number of infections with a light blue background colour. In Step 1 'Disease and outbreak' the user can specify the point in time that distinguishes past from future risks.

Model Inputs

In the table below the input parameters for each step in the blood transfusion chain are shown. The first column contains the parameter definition, the second a more detailed description, and the last column the abbreviation of the parameter as used in the formulas for calculating model outputs (see 'Formulas' section).

STEP 1: DISEASE AND OUTBREAK

Population exposure & susceptibility

Cumulative infections reported	The number of individuals in the population of the outbreak-affected region (or donors) who are reported/notified as cases during the epidemic.	<i>Ip</i>
Duration of epidemic	The length of time between the first and the last day of reported cases (end of the observation period).	<i>D0</i>

Population size	The number of individuals in the outbreak-affected region (smallest authority boundary) where the notified cases were observed.	N
Number of donors tested	Refers to those donors whose donations were tested for the presence of the disease considered.	Ndt
Donor relative risk	This is related to donor predisposition (e.g. age, gender, cultural aspects) and behaviour that increases/decreases the risk of getting infected compared with the population risk. Relative risk of 100% should be considered for diseases that are transmitted ubiquitously in the general population (e.g. through mosquito bite).	RR
Donor visits per day	The average number of donors visiting the outbreak area per day.	τ
Duration of stay	The average length of stay of the donors visiting the outbreak area.	Dv

Disease characteristics

Proportion of undetected cases	Estimate of the proportion (in %) of infected individuals who were not identified as cases.	pu
Duration of infectivity for acute infection	The length of the infectious period for acute infections (in days).	Da
Duration of latent period of acute infection	Time interval (in days) between the donor getting infected and being able to transmit the infection.	Dia
Proportion of chronic infection	Proportion (in %) of acute infected individuals who progress into a chronic infection.	pc
Duration of infectivity for chronic infection	The length of the infectious period for chronic infections (in days).	Dc
Duration of latent period of chronic infection	Time interval (in days) between the moment that the donor is no longer infectious from the acute infection and that the donor becomes infectious from the chronic infection.	Dic

Alternative time point for risk evaluation

Time point for evaluation of the future risk	This is the point in time (number of days since the start of the outbreak) for which the model will calculate the number of infected donations/products to expect beyond this time point, or the prevalence at this time point.	Tx
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STEP 2: DONOR SCREENING AND DONATION TESTING***Donor screening***

Proportion of symptomatic acute infections	Out of all infected donors, the proportion of donors who develop symptoms throughout the course of infection, likely to be picked up by the screening questionnaire.	pIa
Proportion of symptomatic chronic infections	Out of all chronically infected donors, the proportion of donors who develop symptoms throughout the course of their chronic infection, likely to be picked up by the screening questionnaire.	pIc
Effectiveness of donor health questionnaire	Out of all symptomatically infected donors, the proportion of donors that is detected by the questionnaire. If the questions are not specific but may still work due to similar symptoms or exposures with other diseases included in the existing questionnaire, partial effectiveness should be considered.	pQe

Donation testing

Test coverage	Percentage of donations being tested for the infection.	pTc
Test effectiveness (test sensitivity)	The proportion of infected donations that are correctly detected by the test.	pTe

STEP 3: BLOOD COMPONENT PRODUCTION AND DONOR EXPOSURE***Donors and products***

Number of donors	The number of donors who donate per year. The number of donors should be entered for each donation type: whole blood donation, plateletpheresis, plasmapheresis, or any other donation type.	Nd
Number of products obtained from individual donations per year	The number of products from individual donations that have contributed to the production of end products for transfusion per year: for pooled products the number of donations that contribute should be counted here, not the number of end products administered to patients; for products that are split, the number of end products need to be counted, not the number of individual donations. <i>Note that the description of donation and product types can be changed by the user by pressing the <SHIFT> key whilst clicking on the name to be changed.</i>	Np

Number of donors exposed

Total number of donors	All donors in donor/product specification are exposed.	<i>tNdo</i>
Proportion of the total number of donors	Proportion of all donors in donor/product specification that are exposed.	<i>pNdo</i>
Specified number of donors exposed	User specified number of donors that are exposed.	<i>Ndo</i>

Risk reduction

Remaining risk of transmission after processing	Proportion of the initial risk of transmission that remains per particular end product. The remaining risk might differ per type of product due to particular biological properties or risk reducing effects during production.	<i>pit</i>
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STEP 4: RECIPIENT POPULATION**Recipient susceptibility**

Specific immunity in recipient population	Probability of recipients not getting infected when receiving the infected end product because of specific immunity, specified per product type.	<i>pim</i>
Proportion of other complications	Proportion of infected recipients who will develop complications other than severe infection or death.	<i>poc</i>
Proportion of severe infections	Proportion of infected recipients who have a severe manifestation of the infection.	<i>pocs</i>
Proportion of deaths	Proportion of infected recipients who will die from the infection.	<i>pocm</i>

Note that the description of various proportions can be changed by the user by pressing <SHIFT> whilst clicking on the parameter name.

Model Output

In the table below the output parameters for each step in the blood transfusion chain are shown. The first column contains the parameter definition, the second a more detailed description, and the last column the abbreviation of the parameter as used in the formulas for calculating model outputs (see 'Formulas' section).

STEP 1: Disease and outbreak

Estimated incidence rate in the donor population	The number of new infectious donors per donor per day.	<i>I</i>
Prevalence of infectious donors at the time of last observed infection	The proportion of infectious donors at the end of the observation period (so at time point <i>DO</i>).	<i>Pr</i>
Prevalence of infectious donors at time point <i>Tx</i>	The proportion of infectious donors at the specified time point <i>Tx</i> .	<i>Prx</i>

STEP 2: Donor screening and donation testing

Prevalence of infectious donors after screening and/or testing	The proportion of infectious donors who are not detected by the donor health questionnaire or screening tests.	<i>pRis</i>
Prevalence of infectious donors after screening and/or testing at time point <i>Tx</i>	The proportion of infectious donors who are not detected by the donor health questionnaire or screening tests at the specified time point.	<i>pRisx</i>

STEP 3: Blood component production and donor exposure

Total number of donors/products per year	Total number of donors or total number of products per product type per year.	<i>sNd/</i> <i>sNp</i>
Number of donors exposed	Total number of donors exposed during the outbreak.	<i>Ndx</i>
Number of infected products	The number of infected end products per product type released during the observation period.	<i>Nip</i>
Number of infected products expected after time point <i>Tx</i>	The number of infected end products per product type released after the specified time point.	<i>Nipx</i>

STEP 4: Recipient population

Total number of infections in recipients due to infected end products	The total number of recipients that become infected after receiving infected blood products.	N_i
Number of chronic infections	The number of recipients who develop a chronic infection after receiving an infected blood product.	N_c
Number of severe infections	The number of recipients who develop a severe infection after receiving an infected blood product.	N_s
Number of deaths	The number of recipients who died after receiving an infected blood product.	N_x
Total number of infections in recipients due to infected end products expected after time point T_x	The total number of recipients that become infected after the specified time point.	N_{ix}

Modelling characteristics of 18 diseases

In the specification questions the user can select one of 18 diseases that are implemented in the tool. With the selection of a disease, a set of disease specific parameters are loaded. The table below shows the values for various input parameters that are set when a particular disease is selected. The proportion of symptomatic infections is used to estimate the proportion of undetected cases (this is presumed to be 1 minus this proportion). The “High” values refer to worst case estimates found, “Low” to best case estimates. “Mean” values may refer to the average of High and Low values or to a specific value found in the literature.

Note that these values should be considered as an indication only. The user is expected to select appropriate values for the assessment by reviewing and interpreting most recent literature on a particular disease available.

No	Disease	Length of the infectious period (days)						Proportion of chronic infections (%)			Proportion of symptomatic infections (%)			Proportion of severe infections (%)			Case fatality rate (%)			
		Acute			Chronic			Low	Mean	High	Low	Mean	High	Low	Mean	High	Low	Mean	High	
		Low	Mean	High	Low	Mean	High													
1.	Babesiosis ^{2,6}	17	33	49	90	210**	366		52.2		60	70	81					5	42	
2.	Chagas disease ^{2,7,8}	20	38	56	10950	14600	18250**		90		15	20	30		10			5	7.5	10
3.	Chikungunya ^{2,9,10}	1	5	12	90	120	1825	10	12.5	15		34.3			0.2				0.1	
4.	Dengue ²	2	5	12	-	-	-		0		1	5	10	1	10**	20		0.2	10	20
5.	Epidemic Typhus ²	5	14	23			14600											2	21	40
6.	Hantavirus infection ^{2,11}	7	14	56								37			5			1	8	15
7.	Hepatitis A ²	7	14	50	-	-	-		0		60	70	99.9		1.5			0.01	0.2	1.7
8.	Hepatitis E ²	28	70	112	120	150	180		0.01			90		2	11	20		0.2	4	20
9.	Leishmaniasis ²	28	90	180	90	210	365	0.02	0.05	0.1					25			5	50	95
10.	Leptospirosis ²	7	9	10	14	365	730					30			5			1	10	20
11.	Malaria ²	7	90	180	365	1500	15000		2.5			84.6			9			0.43	6	11
12.	Q fever ^{2,12}	10	15	20	90	210	365		1			40		0.5	1	2		1	1.5	2
13.	St. Louis encephalitis ²	14	21	28	50	200	365		0		0.12	0.5	1	2	12	22		2	12	22
14.	Tick-borne encephalitis ²	2	14	28							0.01	12.5	25	1	10.5	20		1	10	20
15.	Toxoplasmosis ²	7	10	14					50									1	6	10.8
16.	vCJD ^{2,13,14}	180	420	1200								0.02							98.5	
17.	West Nile Viral infection ¹⁵⁻¹⁷	1	6	11	-	-	-		0			20			1				0.1	
18.	Yersiniosis ²	1	3	5	28	180	366												50	

** Presumed value.

PART III: Modelling Assumptions and Formulas

Model Assumptions

This section provides a brief introduction to the underlying model that is implemented in the *EUFRAF* tool. The modelling concepts and assumptions will be discussed which should help the user to understand the applicability and limitations of the *EUFRAF* tool.

Incidence rate estimation

Starting point for the assessment of the transfusion transmission risk is the incidence rate, the number of new infections per unit time in the exposed population. We presume that there is a constant incidence rate in the time interval $[0, D_o]$. This means that if in this time interval I_p infections have occurred in a population of size N , the estimated incidence rate would be I_p/ND_o . Similarly, in case data are obtained from within a sub-population of (monitored) donors, the incidence rate would be $I_p/N_{dt}D_o$ (where N_{dt} is the number of donors tested). Next the proportion of undetected infections (pu) is required from the user in order to correct for unobserved infections. These can be due to the fact that only part of the population has been tested, only symptomatic infections are observed which only form part of all infections, or because the timing of the observations is such that only part of the infected population have yet shown symptoms. The figure below shows a graph of the proportion of infectious donors (the prevalence) as a result of the outbreak in case the infectious period (D_a) is less than the duration of the outbreak (D_o).

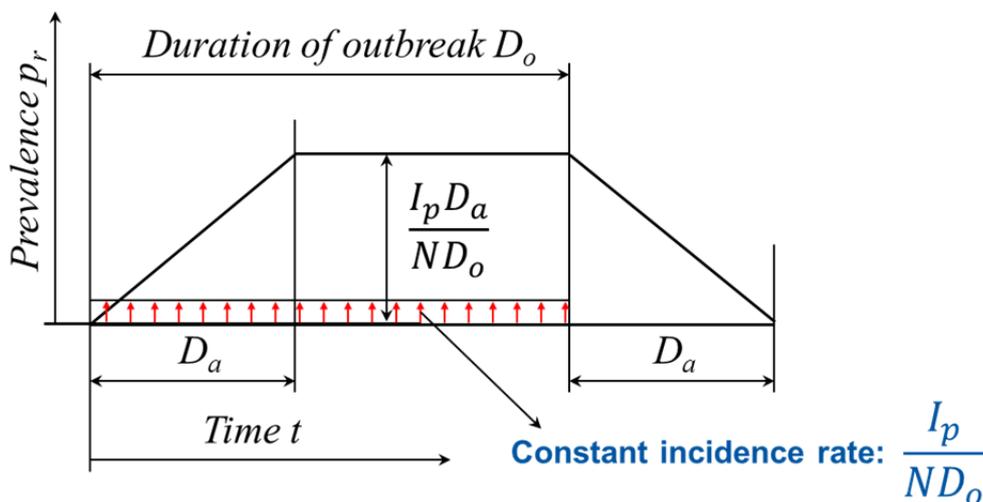


Figure 7: Prevalence of infectious donors (p_r). Note that there is a linear increase in prevalence until the initially infected donors will stop being infectious. From that point in time there will be as many donors stopping to be infectious as there are new donors who become infectious. This means that the number of prevalent cases will remain constant. This will remain so until the end of the outbreak when there are no longer new infectious cases. From there on the prevalence will decline at the same rate as it was increasing at the start of the outbreak.

Donor infectivity

Donors are presumed to be able to transmit the infection after a pre-defined incubation time (D_{ia}). The infectious period of acute infection will last for D_a days after which the donor will no longer be infectious. If a chronic infectious phase exists, a pre-specified proportion of all infected donors (pc) are presumed to develop a chronic infection. The infectiousness of the chronic phase starts D_{ic} days after the acute infection and lasts for D_c days, after which the donor is no longer infectious.

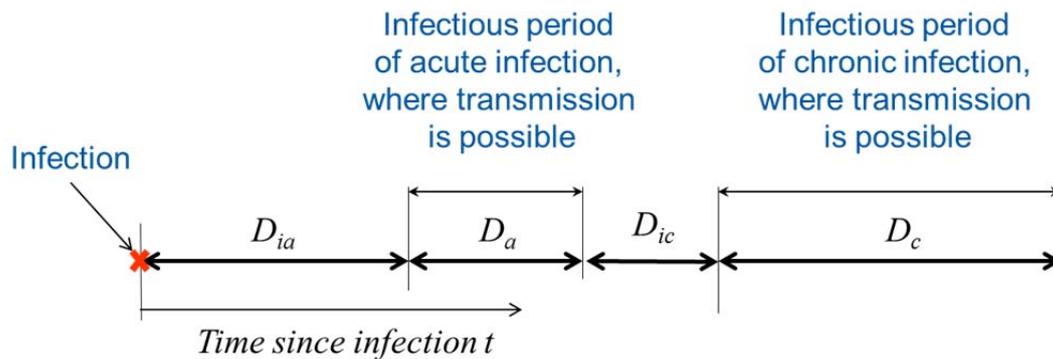


Figure 8: Donor infectivity over time: The donor incubates the infection during interval D_{ia} after which the donor becomes infectious. The donor remains infectious during interval D_a . If a chronic infectious phase exists, a proportion pc of all infected donors are presumed to develop a chronic infection which starts being infectious D_{ic} days after the acute infection, and which will remain infectious for D_c days.

Donor screening and donation testing

If donor screening is applied, the user can specify the proportion of donors who develop symptoms throughout the course of infection that are likely to be picked up by the screening questionnaire. Next to the probability of detectable symptoms, the user has to specify the proportion of donors with such symptoms that are likely to be detected by the questionnaire (the effectiveness of the questionnaire).

Similarly, if donation testing is applied, the user can specify the proportion of donations that are tested (test coverage) and the proportion of donations that are likely to be detected by the screening test (the test sensitivity).

Calculating the number of infected donations

Once the number of infected donors and the duration of the infectivity of an infected donor are known, the donation frequency will determine the likelihood that a donor will actually donate while being infectious, or, in case of a very long infectious period, the number of infected donations one infected donor on average will deliver. The donation frequency is determined by the number of blood products transfused per year and the number of donors that have contributed to these products.

Calculating the impact of infected blood products on donors

The risk of infection transmission may vary per type of blood product and can be reduced by processing of various blood components. Therefore, the tool allows specification of a risk reduction factor per type of end product (remaining risk of transmission after processing). In addition, the recipient population may have (partial) immunity against the infection considered. Thus does the tool also allow specification of the probability of recipients not getting infected when receiving an infected end product.

To allow for differentiation of the impact of disease transmission in patients, three different patient outcomes are defined: 'Deaths', 'Severe infections' and 'Other complications'. Each of these outcomes are assigned a probability, the total of which adds up to one. The user can change both the assigned probabilities and the description of the disease categories.

Summary of main modelling assumptions

- Incidence rate of the infection is constant over the outbreak period, despite the timing of individual infections.
- There is a fixed proportion of undetected (asymptomatic) infectious cases.
- All donors have the same risk of infection, however there is a relative risk to the general population for donors to become infected.
- The risk from travelling donors is determined on basis of their exposure. Travelling donors are presumed to have the same exposure as local inhabitants.
- A donor has potentially two subsequent infectious periods (acute and chronic). The proportion of donors that develop chronic (infectious) infections is constant.
- The length of the infectious period(s) of donors is known and the infectivity of a donor is constant during this period.
- There is no effect of the infection on the donation behaviour of donors.
- The likelihood of detection of infectious donations by the screening questionnaire is constant, regardless of the level of pathogenemia throughout the infectious period.
- The risk of getting infected may be reduced by the risk reduction capacity during processing of blood products or by the specific immunity in recipients
- The proportion of recipients that develop a particular disease outcome is the same chronic as for acute infections.

Formulas

This section contains the formulas implemented to calculate various model outputs. A more extensive description of the model and the derivation of various formulas can be found in the paper to be published on the *EUFRAT* model.¹⁸

Risk estimates for local outbreaks

Estimated incidence rate in the donor population (I)

The incidence is calculated as:

$$I = \frac{I_p * RR}{(N * D_0) * (1 - pu)}$$

Prevalence of infectious donors at the time of last observed infection (P_r)

The prevalence at the time of last observation is dependent on the relative lengths of D_a and D_0 :

$$\begin{aligned} \text{If } (D_a \geq D_0) : & \quad P_r = I * D_0 \\ \text{If } (D_a < D_0) : & \quad P_r = I * D_a \end{aligned}$$

In case of chronic infections the prevalence of chronic infections at time point D_0 need to be added (see next section).

Prevalence of infectious donors at time point T_x (P_{rx})

Prevalence of *acute* infection $p_{ra}(t)$ as a function of the time point of evaluation (t) is calculated as:

$$\begin{aligned} \text{If } (D_a \geq D_0) : & \\ \quad \text{If } (t < D_{ia} \text{ or } t > D_{ia} + D_0 + D_a) : & \quad P_{ra} = 0 \\ \quad \text{Else If } (t < D_{ia} + D_0) : & \quad P_{ra} = I * (t - D_{ia}) \\ \quad \text{Else If } (t < D_{ia} + D_a) : & \quad P_{ra} = I * D_0 \\ \quad \text{Else :} & \quad P_{ra} = I * D_0 * \left(1 - \frac{t - D_{ia} - D_0}{D_0}\right) \\ \text{Else } (D_a < D_0) : & \\ \quad \text{If } (t < D_{ia} \text{ or } t > D_{ia} + D_0 + D_a) : & \quad P_{ra} = 0 \\ \quad \text{Else If } (t < D_{ia} + D_a) : & \quad P_{ra} = I * (t - D_{ia}) \\ \quad \text{Else If } (t < D_{ia} + D_0) : & \quad P_{ra} = I * D_a \\ \quad \text{Else :} & \quad P_{ra} = I * D_a * \left(1 - \frac{t - D_{ia} - D_0}{D_a}\right) \end{aligned}$$

For chronic infections (P_{rc}) replace D_a by D_c , and D_{ia} by $(D_{ia} + D_a + D_{ic})$ in the above equations, and the prevalence of infection at time point t is equal to:

$$P_r(t) = P_{ra}(t) + P_{rc}(t)$$

Prevalence of infectious donors after screening and/or testing ($pRis$)

The prevalence of infectious donors after screening and/or testing is dependent on the implementation of safety measures and the degree of symptomatic (detectable) donors, the degree of screening applied, and effectiveness of screening. For donor screening the prevalence of infectious donors after screening is calculated as:

$$pRis = \left(P_{ra} * (1 - pQ_e * pI_a) + P_{rc} * (1 - pQ_e * pI_c) \right) * (1 - pT_c * pT_e)$$

Number of infected products (Nip)

The number of transmitted infections is equal to:

$$\begin{aligned} N_{ip} &= (\text{Number of infected donors}) \times (\text{Number of donations per infected donor}) \\ &= (\text{Number of infected donors}) \times (\text{Duration of infectivity}) / (\text{Inter-donation interval}) \\ &= (\text{Number of infected donors}) \times (\text{Duration of the infectivity}) \times (\text{Donation frequency}) \end{aligned}$$

The number of transmissions is summed over the acute and chronic per infectious states and therefore can be calculated as:

$$\begin{aligned} N_{ip} &= \sum_{p_x} \frac{I_p * RR}{(1 - pu)} * \frac{N_{do}}{N} * p_x * (1 - pQ_e * pI_a) * (1 - pT_c * pT_e) * D_a * fr_x * p_{it} * p_{im} * n_x \\ &+ \frac{I_p * RR}{(1 - pu)} * \frac{N_{do}}{N} * p_c * p_x * (1 - pQ_e * pI_c) * (1 - pT_c * pT_e) * D_c * fr_x * p_{it} * p_{im} * n_x \end{aligned}$$

Where p_x is a particular fraction of donors with a donation frequency fr_x of a particular blood donation type. Also, n_x represents the number of products derived from a single donation.

Number of recipient complications

The number of complications is calculated by multiplying the number of infections per product type with the respective proportion of recipients that are expected to obtain various complications and the specific immunity (p_{im}) per type of blood product.

Traveller's risk

When calculating the risk from travelling donors, some formulae are different. The deviating formulas are given below.

Because the prevalence and incidence rates caused by travelling donors require data from a later stage of the model (donation and product types) these are hidden from the user. In a next update of the model we will show these conditional on the presence of these data.

Estimated incidence rate in the donor population (I)

The incidence rate among travelling donors is equal to the incidence rate in the outbreak region multiplied by the proportion of travelling donors present in this region. To calculate the incidence in the local donor population this number needs to be multiplied by the size of the population in the outbreak area and divided by the size of the local donor population. The formula to calculate the incidence in the local donor population therefore becomes:

$$I = \frac{I_p * RR}{N * D_0 * (1 - pu)} * \frac{(\tau * D_v)}{N} * \frac{N}{N_{do}}$$

The number of infected travelling donors is equal to:

$$n_i = \frac{I_p * RR}{(1 - pu)} * \frac{(\tau * D_v)}{N}$$

All further calculations concerning the number of infections transmitted by travelling donors is similar to those of transmissions by local outbreaks as described above. One thing that needs to be corrected for however is the fact that travelling donors will not be able to donate when being infectious while travelling. The length of infectivity D_a should therefore be replaced by D'_a which depends on the relative lengths of stay and infectivity:

$$D'_a = \begin{cases} D_a < D_v: & D_i^2 / (2D_v) \\ D_a \geq D_v: & (D_i - D_v / 2) \end{cases}$$

Calculating risks using data on infected donors

This option merely implies a direct estimate of the incidence rate using data of infections as observed in donors. The incidence rate is therefore calculated as:

$$I = \frac{I_p}{(N_{dt} * D_0)}$$

The number of infected donors is equal to:

$$n_i = \frac{I_p N_{do}}{N_{dt}}$$

All further calculations concerning the number of infections transmitted are similar to those of transmissions by local outbreaks as described above.

Future risks

The tool allows calculating the number of transmissions after a user specified point in time (T_x). These are referred to as ‘future’ transmissions. Future transmissions are (per definition) a proportion of all transmissions.

Future risk proportions for local outbreak risks

The proportion of future outbreaks (so after time point D_0) is dependent on the duration of the outbreak and the duration of the acute infection:

$$pI_f(D_0, D_a) = \begin{cases} \forall (D_0 \geq D_a): & \frac{1/2 D_a}{D_0} \\ \forall (D_a < D_0): & 1 - \frac{1/2 D_0}{D_a} \end{cases}$$

With this definition the proportion of infections after any point in time t can be calculated as follows:

$$pI_{ft}(D_0, D_a, t) = \begin{cases} \forall (t < 0): & 1 \\ \forall (0 \leq t \leq D_0): & (1 - t/D_0) + t/D_0 * pI_f(t, D_a) \\ \forall (D_0 < t): & t/D_0 * pI_f(t, D_a) - (1 - t/D_0) * pI_f(t - D_0, D_a) \end{cases}$$

In case transmission of infection is delayed by an interval of length D_{ia} , Infections after time point t can again be calculated by first calculating the number of transmission after time point t from a similar outbreak that would last over length $D_0 + D_{ia}$ and then subtracting transmission after time point t from an outbreak over a time interval of length D_0 .

$$pI_{ftd}(D_0, D_a, D_{ia}, t) = pI_{ft}(D_0, D_a + D_{ia}, t) - pI_{ft}(D_0, D_{ia}, t)$$

Future risk proportions for travelling donor risks

The proportion of future outbreaks (so after time point D_0) from travelling donors is dependent on the duration of the outbreak, the duration of the acute infection and the duration of stay in the outbreak area:

$$pI_{tf}(D_0, D_a, D_v) = \begin{cases} \forall (D_0 \geq D_a \geq D_v) : & \frac{(1/2 D_a^2 - 1/6 D_v^2)}{D_0(D_a - 1/2 D_v)} \\ \forall (D_a \geq D_0 \geq D_v) : & \frac{(D_0(D_a - 1/2 D_0) - 1/6 D_v^2)}{D_0(D_a - 1/2 D_v)} \\ \forall (D_a \geq D_v \geq D_0) : & 1 - \frac{1/6 D_0^2}{D_v(D_a - 1/2 D_v)} \end{cases}$$

Similar to above, the proportion of infections after any point in time t can be calculated as:

$$pI_{tft}(D_0, D_a, D_v, t) = \begin{cases} \forall (t < 0): & 1 \\ \forall (0 \leq t \leq D_0): & (1 - t/D_0) + t/D_0 * pI_{tf}(t, D_a, D_v) \\ \forall (D_0 < t): & t/D_0 * pI_{tf}(t, D_a, D_v) - (1 - t/D_0) * pI_{tf}(t - D_0, D_a, D_v) \end{cases}$$

And similarly, infections after time point t in case transmission of infection is delayed by time D_{ia} can be calculated as:

$$pI_{tftd}(D_0, D_a, D_v, D_{ia}, t) = pI_{tft}(D_0, D_a + D_{ia}, D_v, t) - pI_{ft}(D_0, D_{ia}, D_v, t)$$

PART IV: Frequently Asked Questions

In this part of the manual a list of frequently asked questions is provided, together with answers in order to provide guidance for the user. If you have any queries or comments when (starting) to use the *EUFRAF* tool, forwarding these to m.p.janssen@umcutrecht.nl will allow us to keep this FAQ list up-to-date and relevant. Also, providing feedback will allow us to further improve *EUFRAF* over time.

1. Is assuming a constant incidence rate during the course of the outbreak realistic?

A constant incidence rate during the outbreak is very unlikely. However, this assumption will not impact the estimated total number of infection transmissions through blood transfusion. It will however impact the timing of these transmissions, and therefore affect the estimated number of future transmissions. In case more specific information on the timing of observed infections is available, an assessment can be made where the *EUFRAF* model is used to estimate future infections but where the outbreak is modelled as a sequence of smaller outbreaks with constant incidence rates. Tools for such analyses are available and can be provided on request. An example of such an application is given in our paper on the travellers' risk model.¹⁸

2. Which donors (first time, repeat and/or regular donors) should I include when determining the number of donors for a particular donation type?

Include all products from all donors, but only include regular donors for the size of the donor population. The number of regular donors in a year will be the best reflection of the average size of your donor population. You can calculate the number of regular donors by subtracting the total number of donors in one year by the number of donors who started donating in that year.

3. Why are the outputs for Steps 1 and 2 ('Disease and outbreak' and 'Donor screening and donation testing') not provided?

In case the tool is set to calculate the travellers' risk, the outputs from Step 1 and Step 2 are not shown until information on donor and donations is provided. This info is requested from the user in Step 3 ('Blood component production and donor exposure').

4. How can I reset EUFRAT?

If for any reason you want to reset the tool, this can be done by simply reloading your internet browser. For most windows applications this is done by pressing the <SHIFT> key whilst clicking on the browser refresh button or by pressing <CTRL>+<F5>; For Mac/Apple this is Apple + R or Command + R; for Linux it's simply F5.

5. The recipient risk (number of complications due to infected end products) does not change when I change the number of donors. Is there an error somewhere?

If you do the maths you can show that the expected number of infected recipients is not affected by the number of donors but only by the number of end products. Apart from that, this risk is affected by the number of infections, the population size and the length of the infectious period. This does makes sense because the donor is only the medium to transport the infection to the end product, the number of end products determine the extent of recipient exposure. Note that when calculating the risk from travelling donors the number of donors does affect the number of infected recipients. This is because now the donation frequency determines the recipient's exposure in combination with the number of donors per day travelling to the outbreak area.

6. I have set a random seed number but I am still unable to reproduce the output from the EUFRAT tool. What is going wrong here?

Setting a seed value for the random number generation when calculating outputs that involve model parameters that are represented by distributions is intended to allow exact reproduction of earlier obtained results. However, as the random number generation engine may differ between computers, identical results can only be guaranteed when running the model is run on the same computer using the same browser.

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